Nitric Oxide and Peroxynitrite in Health and Disease

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Abstract

The discovery that mammalian cells have the ability to synthesize the free radical nitric oxide (NO) has stimulated an extraordinary impetus for scientific research in all the fields of biology and medicine. Since its early description as an endothelial-derived relaxing factor, NO has emerged as a fundamental signaling device regulating virtually every critical cellular function, as well as a potent mediator of cellular damage in a wide range of conditions. Recent evidence indicates that most of the cytotoxicity attributed to NO is rather due to peroxynitrite, produced from the diffusion-controlled reaction between NO and another free radical, the superoxide anion. Peroxynitrite interacts with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms. These reactions trigger cellular responses ranging from subtle modulations of cell signaling to overwhelming oxidative injury, committing cells to necrosis or apoptosis. In vivo, peroxynitrite generation represents a crucial pathogenic mechanism in conditions such as stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer, and neurodegenerative disorders. Hence, novel pharmacological strategies aimed at removing peroxynitrite might represent powerful therapeutic tools in the future. Evidence supporting these novel roles of NO and peroxynitrite is presented in detail in this review.

I. INTRODUCTION

Nitric oxide (NO) is an omnipresent intercellular messenger in all vertebrates, modulating blood flow, thrombosis, and neural activity. The biological production of NO is also important for nonspecific host defense, but NO itself is unlikely directly to kill intracellular pathogens and tumors. Although NO is often described as highly toxic and reactive, it is not. Inhaling low concentrations of gaseous NO is approved by the Food and Drug Administration for the treatment of persistent pulmonary hypertension of the newborn (**53**, **411**, **412**, **593**, **680**, **681**, **1143**). In addition, NO can be produced for 80 years by neurons in human brain without overt toxicity. Paradoxically, the production of the same molecule can

become highly damaging to the same neurons within a few minutes during pathological challenges as occur after cerebral ischemia. How is this possible? The reaction of NO with superoxide ($O_2^{\cdot -}$) to form the much more powerful oxidant peroxynitrite ($ONOO^-$) is a key element in resolving the contrasting roles of NO in physiology and pathology.

Neither superoxide nor NO is particularly toxic in vivo because there are efficient means to minimize their accumulation (72, 74). Superoxide is rapidly removed by high concentrations of scavenging enzymes called superoxide dismutases (SOD) with distinct isoenzymes located in the mitochondria, cytoplasm, and extracellular compartments. NO is rapidly removed by its rapid diffusion through tissues into red blood cells (161, 639), where it is rapidly converted to nitrate by reaction with oxyhemoglobin (Fig. 1). This limits the biological half-life of NO in vivo to less than a second, whereas the concentrations of NO relevant for cellular signaling can persist in phosphate-buffered saline for an hour (79). However, when both superoxide and NO are synthesized within a few cell diameters of each other, they will combine spontaneously to form peroxynitrite by a diffusion-limited reaction (583). In essence, every time NO and superoxide collide, they form peroxynitrite. No enzyme is required to form peroxynitrite because no enzyme can possibly catalyze any reaction as fast. NO is the only known biological molecule that reacts faster with superoxide and is produced in high enough concentrations to outcompete endogenous levels of superoxide dismutase. Consequently, the kinetics and thermodynamics of the reaction of superoxide with NO make the formation of peroxynitrite inevitable in vivo.

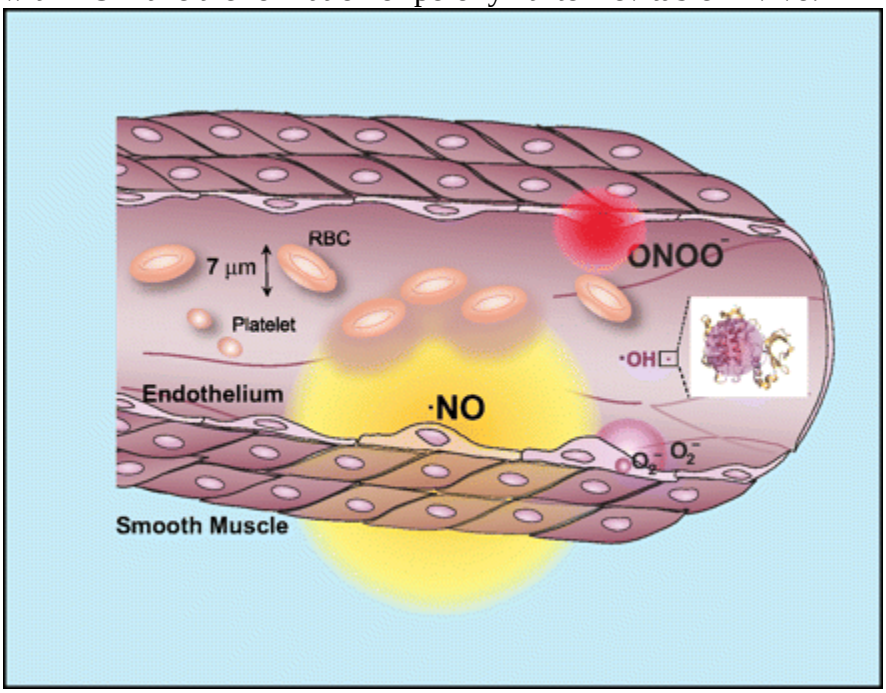

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FIG. 1.

Cellular diffusion of superoxide, peroxynitrite, and hydroxyl radical within their estimated first half-lives. These circles indicate the extent to where the concentration of each species from a point source would decrease by 50%. The diffusion of peroxynitrite accounts for its rapid reaction with carbon dioxide and with

intracellular thiols. The diffusion distance for nitric oxide is calculated based on its half-life of 1 s in vivo, which results mostly from its diffusion into red blood cells. The diffusion distance for hydroxyl radical is about the same diameter as a small protein, or 10,000 times smaller than peroxynitrite. All of these estimates involve many approximations, but varying the estimated half-lives by 10-fold would only alter the diameters by the square root of 10 or by 3.2-fold.

Generally, the physiological literature is content with discussing NO as a physiological signaling agent without considering its complex and controversial chemistry. A lot of biology is masked in the fog of the nebulous description reactive nitrogen species. Many of the biological effects attributed to NO are in fact mediated by peroxynitrite. While requiring some knowledge of the underlying convoluted chemistry of free radicals and nitrogen oxides, recognition of these reactions in vivo will produce a deeper understanding of the underlying biology and help resolve many puzzling controversies. In this review, we describe the substantial progress made in understanding the biological chemistry of peroxynitrite and its many roles in virtually all disease processes affecting humans. New tools enabling the imaging of superoxide formation in vivo (**1446**, **1455**) combined with the careful interpretation of nitration and the use of scavengers for peroxynitrite can allow these processes to be experimentally dissected (**370**, **371**).

The formation of reactive nitrogen species is not an inescapable consequence of synthesizing NO. NO is efficiently removed by reacting with oxyhemoglobin to form nitrate, which prevents even the highest rates of NO synthesis from directly reacting with oxygen to form significant amounts of nitrogen dioxide. However, the simultaneous activation of superoxide synthesis along with NO will completely transform the biological actions of NO by forming peroxynitrite. Several enzyme complexes, such as NADPH oxidases (NADPHox) and xanthine oxidase, can be activated in many cellular systems to actively produce large amounts of superoxide. What happens when superoxide and NO are produced simultaneously in close proximity? Modestly increasing superoxide and NO each at a 10-fold greater rate will increase peroxynitrite formation by 100-fold. Under proinflammatory conditions, simultaneous production of superoxide and NO can be strongly activated to increase production 1,000-fold, which will increase the formation of peroxynitrite by a 1,000,000-fold (**Fig. 2**). Without superoxide, the formation of nitrogen dioxide by the reaction of NO with oxygen is miniscule by comparison. NO and superoxide do not even have to be produced within the same cell to form peroxynitrite, because NO can so readily move through membranes and between cells (**Fig. 1**).

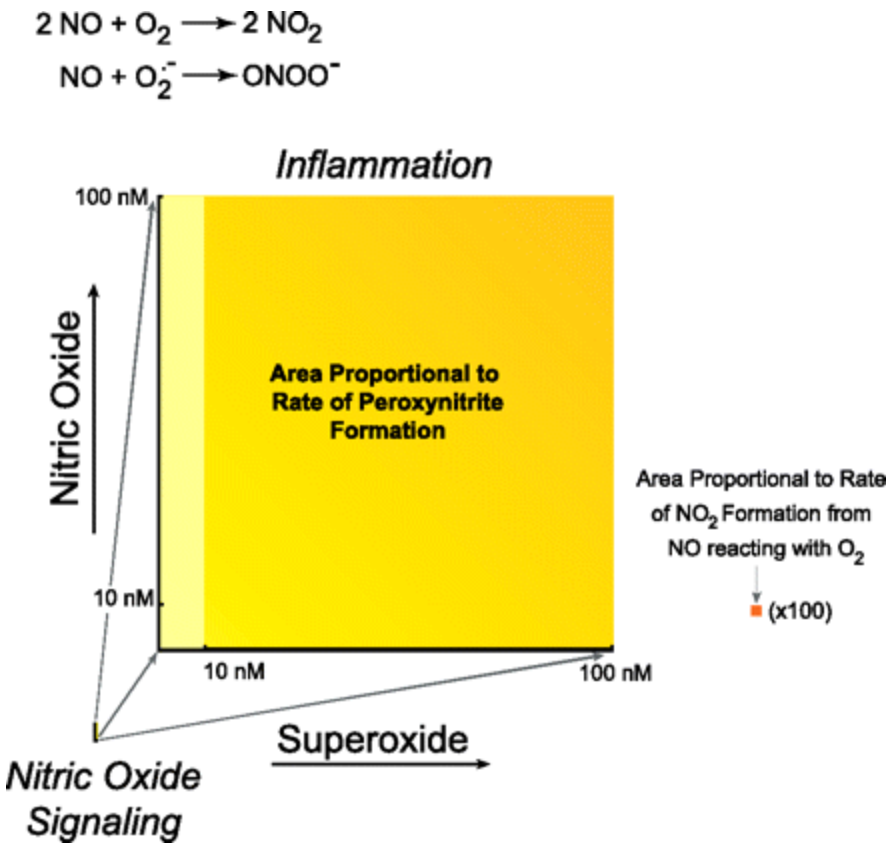

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FIG. 2.

Comparison of oxidant production by the reaction of nitric oxide with superoxide versus oxygen. Both reactions are generally given equal weight, but this obscures the vast difference in oxidant productions because of the vast difference in rates. Because the formation of peroxynitrite depends on the product of the concentration of nitric oxide and superoxide, the rate of formation is proportional to the area. *Left*: estimate of peroxynitrite formation in the cytosol if a cell produces 10 nM nitric oxide, sufficient to activate guanylate cyclase enough to cause at least 10% relaxation of vessels, using 0.1 nM superoxide as an estimate of the basal steady-state concentration of superoxide (777).*Right*: increase in peroxynitrite formation if the formation of superoxide production increased either 100-fold (yellow) or 1,000-fold (yellow-orange), increases that can reasonably occur with the activation of NADPH oxidase. Nitric oxide is shown to increase only 10-fold and could rise to ~1 μM in highly inflamed states. *Far right* (orange square): proportional area of nitrogen dioxide formation from 100 nM nitric oxide reacting with oxygen (estimated to be 50 μM in cells), which is magnified 100-fold. This rate is the faster rate occurring in hydrophobic membranes and would be 300-fold smaller in solution (784). Pathways that stimulate the synthesis of superoxide vastly increase oxidant production compared with the reaction of nitric oxide with oxygen.

Although peroxynitrite is a strong oxidant, it reacts at a relatively slow rate with most biological molecules. With its reaction with carbon dioxide and other major reactions in cells taken into account, peroxynitrite can still diffuse quite far on a cellular scale (**Fig. 1**). Peroxynitrite is able to traverse cell membranes in part through anion channels (**312**, **824**). The contrast with hydroxyl radical is dramatic (**73**, **78**). Hydroxyl radical is formed by a rather slow reaction via the reaction of ferrous iron with hydrogen peroxide, but is so reactive that it can only diffuse about the diameter of a typical protein (**586**). In contrast, peroxynitrite is formed each time superoxide and NO collide, but reacts slowly enough to react more selectively throughout the cell. That makes the biological and pathological implications of peroxynitrite far more interesting because it can have more subtle and specific actions on cells. The implications of biological oxidants having more specific actions in vivo have been described by Nathan in his essay on biological specificity of a third kind (**933**).

II. NITRIC OXIDE

A. Discovery of Nitric Oxide as a Biological Molecule

The regulation and synthesis of NO by mammalian cells has been the focus of many excellent reviews (**935**), as have many of its physiological and pathological actions (**595**, **890**, **893**, **895**,**1201**). With around 80,000 references invoking NO listed in PubMed, it may be difficult to remember how controversial was the initial proposal that NO was a biological molecule. There were early indications that were ignored for many decades. Haldane and co-workers (**56**) reported in the 1920s of a man found dead of apparent carbon monoxide poisoning. However, analysis of the blood showed that the stable red color persisting in hemoglobin at autopsy was due to nitroso-hemoglobin rather than carboxy-hemoglobin (**56**). There was no evidence for the consumption of nitrite that might account for the nitroso-hemoglobin. Commoner and co-workers (**1387**) in the 1960s demonstrated the nitroso-heme signals could be detected by EPR spectroscopy. Tannenbaum's group (**475**), while investigating the role of nitrite and nitrosamines in food in the induction of carcinogenesis, characterized nitrite and nitrate metabolism in healthy student volunteers. Curiously, more nitrate was being secreted than could be accounted for by ingestion. When one of the students became ill with the flu, nitrate levels in urine increased enormously.

For a century, nitrovasodilators had been used clinically without understanding their mechanism of action. Alfred Nobel lamented the irony that he was taking nitroglycerin to treat angina after making his fortune developing dynamite. Increased levels of cGMP produced by guanylate cyclase within vascular smooth muscle were discovered to allow blood vessels to relax and thus increase blood flow (**596**). The endogenous agents responsible for activating guanylate cyclase remained mysterious, although nitrovasodilators were able to activate the enzyme. The enzyme contained a heme group that was essential for this activation. Murad's group (**130**) found that NO itself, as well as a variety of oxidants, was able to activate guanylate cyclase. However, the possibility that NO might be synthesized in mammals was considered to be too far fetched for another decade. The more likely candidates for activators of guanylate cyclase were considered to be nitroso thiols and possibility that NO, a major air pollutant, could be the endogenous regulator was generally dismissed.

Major progress came from the curiosity of Furchgott and Zawadzki (422) in understanding how a technician in his laboratory was able to isolate aortas that relaxed in vitro when exposed to acetylcholine. Acetylcholine was a well-known vasodilating agent when injected in vivo, but generally caused isolated blood vessels to constrict in vitro. Furchgott and Zawadzki (422) recognized that the difference was caused by mechanical damage to the vascular rings as they were being cut, which stripped the single layer of endothelial cells off the blood vessels. With the preparation of a spiral cut of blood vessels, the endothelium was preserved and responded by relaxing when acetylcholine was added. Furthermore, Furchgott and Zawadzki (422) established that acetylcholine-treated endothelium was releasing a diffusible factor that would relax endothelium-denuded blood vessels by activating guanylate cyclase. The diffusible factor, termed the endothelium-derived relaxing factor (EDRF), was quickly inactivated by oxyhemoglobin and was inherently unstable in the perfusion cascades used to study the vasorelaxation. EDRF had a half-life of only 6–8 s in Krebs-Henseleit buffer saturated with 100% oxygen and 30–60 s in the same buffer saturated with room air (21% oxygen). Addition of low concentrations of SOD to the perfusion cascade doubled the half-life of EDRF in Krebs-Henseleit buffer, while agents known to generate superoxide diminished its activity (484, 894, 1089). Consequently, the sensitivity to superoxide and oxyhemoglobin became standard criteria to verify the production of EDRF in isolated cells. Moreover, EDRF was proposed to be a protective factor by scavenging superoxide. In 1986, Furchgott proposed that NO was the elusive EDRF produced by endothelium, with Ignarro providing additional evidence supporting the identification (594, 596, 597). Moncada's group (892), adapting a gas-phase chemiluminescent detector used for monitoring NO pollution in the atmosphere, was able to directly measure NO produced in vivo.

The identification of NO as EDRF was greatly facilitated by the independent work of John Hibbs, who was investigating how macrophages kill cancer cells. Hibbs found that different batches of fetal calf serum had widely varying effects on the tumoricidal activity of macrophages in vivo. He observed in the local slaughterhouse that calf serum at the time was prepared from blood collected in buckets and deduced that endotoxin from contaminating bacteria was responsible for activating the macrophages. He also noticed that activated macrophages rapidly depleted the media of some nutrient necessary for their tumoricidal activity (542, 543). By supplementing the depleted media with each component, he discovered that arginine was the major compound that could restore the tumoricidal activity of macrophages. He also showed that the macrophages were producing nitrite and nitrate by oxidizing arginine to citrulline, but did not make the connection that macrophages may be producing NO and peroxynitrite. The production of NO by macrophages was established by Stuehr and Nathan (1208) and peroxynitrite by Ischiropoulos et al. (611). He deduced that arginine derivatives might be useful inhibitors and discovered that methylarginine blocked the tumoricidal activity of macrophages. Thus he provided the background for Moncada's group to show that EDRF was synthesized from arginine and that methylarginine blocked its biological activity.

A major difficulty in the identification of EDRF is the fact that endothelium produces relatively small amounts and is not an abundant cell in vivo. But the identification of EDRF as NO made sense of many puzzling results in the brain, where cGMP was known to be involved in many intracellular functions. Deguchi and Yoshioka (305) painstakingly purified a low-molecular-weight compound from nervous tissue that was required to activate soluble guanylate cyclase and showed that it was unexpectedly arginine. For many years, it had been recognized that the brain had all of the enzymes necessary to convert citrulline to arginine, but curiously lacked

arginase that is necessary for the complete urea cycle to be functional. Although the urea cycle was not functional in the brain, genetic deficiencies in these enzymes often resulted in phenotypes with neurological defects. Garthwaite and co-workers (**433**, **435**) connected the dots and showed that under normal physiological conditions the brain produced ~20 times more NO than the entire vasculature. Since NO synthase produces citrulline from arginine, the presence of the remaining urea cycle enzymes was rationalized. Later, he identified ODQ, 1H-(**1**,**2**,**4**)oxadiazolo(4,3-a)quinoxalin-1-one, as a potent inhibitor that prevented the activation of guanylate cyclase by NO (**436**), which has proven to be a crucial tool for unraveling the physiological action of NO in vitro.

The brain proved to be a rich source of NO synthesis and allowed the first NO synthase (NOS) to be cloned and purified (**133**–**135**). It is called nNOS (neuronal NOS) or NOS1 as it was the first synthase to be cloned. Eventually, it was realized that the histological stain for NADPH diaphorase in brain corresponded to the distribution of nNOS (**292**, **568**). The NOS1 gene has the most complex genomic organization in humans with multiple splice variants being produced (**468**,**1164**). The first knock-out mouse still retained substantial NOS1 activity in muscle and some neuronal populations because of alternative splicing that bypassed the second exon that had been targeted for deletion (**574**, **1394**). Consequently, several studies finding no protection in the knockout of NOS1 do not necessarily prove the lack of involvement of NO (**375**).

The second NOS to be cloned was isolated from macrophages and known as NOS2 or iNOS (inducible NOS) because it is readily induced in many tissues by proinflammatory cytokines. Unlike the neuronal or endothelial NOS isoenzymes, NOS2 is not regulated by changes in intracellular calcium. However, careful examination of purified preparations of iNOS revealed that calmodulin was so tightly bound that it copurified with iNOS (**215**, **1395**). Consequently, the enzyme appeared to be unresponsive to physiologically relevant changes in calcium concentrations. Because NOS2 can be strongly induced by proinflammatory stimuli, it is often called a high-output source of NO. However, the enzyme does not produce NO at a substantially greater rate measured for neuronal or endothelial NOS, just more of the protein can transiently be induced and normal calcium levels are sufficient to fully activate NOS2 (**934**, **935**).

The first source of NO identified, endothelial NO synthase was the last to be cloned and is known as eNOS or NOS3. NOS3 binds to plasma membranes and is typically associated with caveolin (**387**). It is strongly activated by the entry of calcium through membrane-bound receptors and is also regulated by phosphorylation (**1122**). NOS3 is also found in neurons and other tissues in addition to endothelium.

B. The Selective Reactivity of Nitric Oxide

To understand why NO itself is not highly reactive, it is instructive to remember that NO is an intermediate between molecular oxygen (O_2) and nitrogen (N_2) (**Fig. 3**). All three have low solubility and readily diffuse through membranes as easily as through cytoplasm. While molecular oxygen is thermodynamically a strong oxidant, it has a limited kinetic reactivity as evidenced by life being possible in an atmosphere of 21% oxygen without spontaneous combustion. Molecular oxygen has two unpaired electrons in separate orbitals, which prevents this biradical from directly reacting with most biological molecules. However, the unpaired electrons on molecular oxygen allow it to bind strongly with metals such as the iron in hemoglobin and in cytochrome-*c* oxidase. Molecular oxygen will also react quickly with the

unpaired electron on other free radicals, which leaves the second unpaired electron available for further reactions: $R\cdot + \cdot OO\cdot \rightarrow R\text{-}OO\cdot \rightarrow$ further reactions.

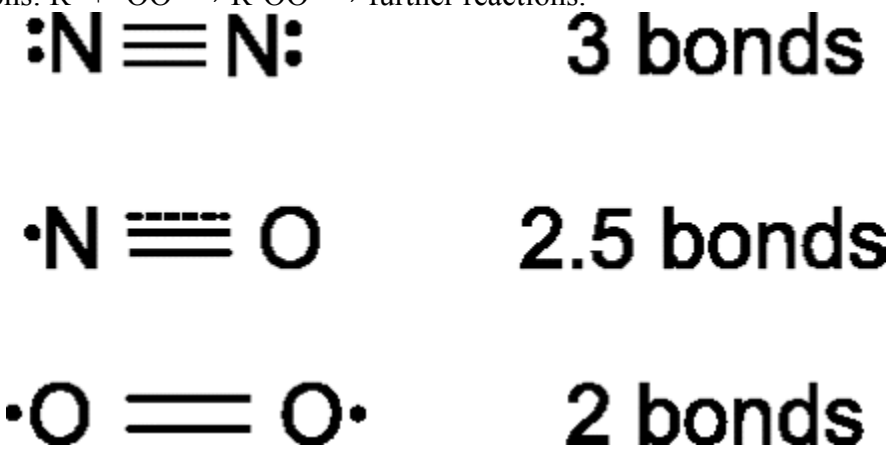

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FIG. 3.

The chemical structure of nitric oxide is intermediate between molecular oxygen and nitrogen. The dot illustrates the unpaired electron on nitric oxide and two unpaired electrons on oxygen. These unpaired electrons are in antibonding orbitals, counteracting the three bonding orbitals characteristic of nitrogen gas. Thus nitric oxide has effectively 2.5 bonds and a slightly longer distance separating the nuclei. Oxygen has only two bonds and an even longer intranuclear distance.

Hence, molecular oxygen propagates free radical damage and has a central role in oxidative stress.

In contrast, nitrogen gas (N_2) is one of the most inert molecules known. Because NO is essentially a hybrid between molecular nitrogen and oxygen, NO is generally less reactive than molecular oxygen. In particular, NO has only one unpaired electron, which allows it to bind strongly to the iron in heme groups, which is crucial to its biological activity of activating guanylate cyclase and slowing mitochondrial respiration by binding to cytochrome-*c* oxidase. Like molecular oxygen, NO also reacts with free radicals quickly, but NO is chain terminating. For example, NO can convert thiyl radicals into nitrosothiols by acting as a chain-terminating agent: $RS\cdot + \cdot NO \rightarrow RS\text{-}NO$.
The chain-terminating reactions account for many of the antioxidant properties attributed to NO, but this is an oversimplification. NO does not directly repair radical damage as does ascorbate, tocopherol, or glutathione, but rather forms transient intermediate products that have distinct biological activities. These intermediate products can often be repaired by antioxidants to regenerate the original compound. Depending on one's point of view, nitrosative stress can also be viewed as an antioxidant activity.

C. Diffusion and Signaling Properties of Nitric Oxide

NO is often considered to be just another signaling molecule. But it is important to consider how NO communicates information to understand why NO has so many physiological roles in vivo. The production of cGMP by guanylate cyclase is the major signal transduction mechanism of NO. Soluble guanylate cyclase contains the same heme protoporphyrin IX as hemoglobin with iron in the ferrous form that binds NO with great affinity. Deoxyhemoglobin binds NO with a 10,000-fold greater affinity than molecular oxygen (**1151**, **1286**). Only 5–10 nM NO is necessary to activate guanylate cyclase. NO can diffuse from where it is synthesized into surrounding cells where it will activate soluble guanylate cyclase in the target tissue to produce cGMP. In turn, cGMP activates cGMP-dependent kinases in the target tissue that modulates intracellular calcium levels to modulate many diverse activities in the target tissues.

However, the unique properties of NO confer an important distinction that allows NO to be used for local signaling in virtually every organ system. For many signaling molecules, receptors in target tissues can distinguish two closely related molecules like norepinephrine or epinephrine because the appropriate receptors can recognize subtle variations in shape. With only two atoms, NO cannot be readily distinguished by its shape. Thus information is reflected by changes in its local concentration. The longer NO is present, the greater the amount of cGMP that will be formed. The system depends on NO being constantly removed or else guanylate cyclase will remain fully activated.

The rapid infusion of NO has major implications for how information is communicated. NO is a small hydrophobic molecule that crosses cell membranes without channels or receptors as readily as molecular oxygen and carbon dioxide. The diffusion coefficient of NO in water at 37°C is slightly faster than oxygen and carbon dioxide (**1377**), which is ideal for quickly transmitting information over short distances. Because NO is freely permeable to membranes, NO will repeatedly diffuse in as well as out of a cell over the time span of a second. The average molecular velocity of a molecule with the mass of NO is ~400 m/s at room temperature. The trajectory of NO in solution is repeatedly changed by making ~10 billion collisions each second. Consequently, the path of a NO molecule will follow long but highly convoluted trails that can repeatedly cross cell membranes during its half-life of ~1 s. A single molecule of NO can readily move between cells many times within this time span.

The hydrophobicity of NO will allow slightly faster diffusion in a lipid membrane than in water so that membranes provide effectively no barrier to NO. Hence, diffusion away from a single cell producing NO contributes far more substantially to the loss of NO than do the reactions of NO within the cell (**728**). When a group of cells simultaneously produces NO, the concentration of NO within a single cell will be much greater than if that cell was producing NO alone. Most of the NO one breathes when stuck in a traffic jam results from the surrounding cars rather than the car itself. An important consequence is that NO can integrate and average the activity of the local group of cells (**728**).

Red blood cells provide a drain for NO that creates a sharp diffusion gradient leading to the vasculature (**161**, **1294**, **1385**). The addition of a red blood cell outside of a cell will capture much of the NO produced inside of this cell, because the hemoglobin will greatly reduce the reentry of NO into the cell (**728**). For example, endothelium can make 10- to 40-fold more NO than needed to activate guanylate cyclase as measured by microelectrodes placed against individual isolated cells. However, red blood cells will be major sinks in vivo, so the majority of the NO will be quickly lost to the vascular compartment (**196**, **1293**). In fact, the packaging of hemoglobin into red blood cells is important to limit the rate of scavenging of NO. Lysis of red blood cells causes vasoconstriction by more efficient scavenging of NO and is a major limitation

of giving hemoglobin-based blood substitutes. Even with hemoglobin packaged into red blood cells, the production of 100 nM NO by endothelium would be necessary to achieve 5–10 nM concentrations in smooth muscle containing guanylate cyclase, because such a large fraction is consumed by red blood cells. NO that has diffused into the smooth muscle can also diffuse back down the diffusion gradient to the red blood cell (**Fig. 1**). In the perfusion cascades used to originally assay EDRF, the excess production of NO in the absence of hemoglobin allowed the dilation of endothelium-denuded artery rings far removed down the perfusion cascade.

Although the biological half-life of NO is only a scant few seconds in vivo, a second is long compared with a simple neural reflex or to the time needed to contract a muscle. A sprinter can run ~10 m within the reported half-life of NO (far shorter than the total distance covered of a molecule of NO as it bounces around inside and between cells in the same time). The relatively short overall distance that NO can diffuse limits its action to only a few cells near the source of production. Thus NO produced in the gut, for example, will not influence its actions in the central nervous system (CNS). On the other hand, the intermediate lifetime of NO coupled with its rapid diffusion through most tissues allows NO to integrate and modulate complex physiological processes (**1293**).

In effect, NO is the equivalent of a shock absorber that dampens the oscillations of a car driving over a bumpy road. By affecting levels of calcium in target tissues through the actions of cGMP, NO can modulate the extent that target tissues respond to stress. When a distal vascular bed dilates to supply more blood flow to an actively working muscle, the upstream blood vessels must also dilate to support the increased blood flow. Exceeding the Reynolds number results in turbulent flow, increasing the local stress on blood vessels (**479**). The stress of turbulent flow is counterpoised by myogenic contraction that would cause a further increase in shear stress in the absence of endothelial production of NO. Left unopposed, further muscle contraction amplifies turbulent flow that in the extreme will cause a catastrophic collapse of blood flow to distal vascular beds. However, turbulence induces endothelium to synthesize NO via shear-induced stress. The resulting local relaxation of the underlying vascular smooth muscle increases the diameter of the blood vessel to restore laminar flow and thereby ensures a laminar distribution of blood between vessels (**479**). With prolonged turbulence, additional mechanisms are activated that can lead to the formation of superoxide and the pathogenic conversion of NO to peroxynitrite as described below.

NO can convey information by more subtle means than just simply its local concentration. The life span of NO is relatively long compared with the firing of nerve or even the activation of a neural network, and thus can help to integrate neuronal activity in small volumes of the brain (**1385**). Gally et al. (**426**) proposed that NO provides an important signal-averaging mechanism to control synaptic plasticity in the brain. The spatial organization of the nervous system is determined by the temporally correlated activation of neurons. A general principle controlling the organization of the developing brain is that groups of neurons activated in synchrony tend to project to similar regions, whereas neurons with uncorrelated activity will project into different regions (**897**). NO appears to be one determinant of this neuronal localization because it is ideally suited to carry information about neuronal activity in a retrograde manner, opposite to the normal mode of an activated neuron passing information down its axon and releasing a neurotransmitter across the synaptic junction. NO produced by dendrites will diffuse radially to surrounding synapses and will not distinguish between synapses in direct contact with that particular dendrite versus those that are localized in the same region (**434**, **1385**, **1391**).

The nNOS (NOS1) is particularly well suited to produce NO in a manner that facilitates synaptic plasticity (**336**, **1188**). The amino terminus of NOS1 contains an additional sequence lacking on NOS2 and NOS3 that anchors the enzyme to the cytoskeleton in postsynaptic boutons beneath the *N*-methyl-D-aspartate (NMDA) receptor (**547**). The NMDA receptor has been implicated in learning and development as well as in many forms of excitotoxic neurodegeneration (**149**) (see sect. VI, *F* and *G*). The NMDA receptor only activates when a neuron has been partially depolarized, as occurs when a neuron has been firing frequently. In addition, the receptor must bind glutamate and glycine to the extracellular surface for the channel to open. A local group of neurons that are firing repeatedly for a few milliseconds is sufficient to cause local increase in NO. The synthesis of NO is initiated by extracellular calcium entering the neuron through the NMDA receptor. NO plays an important role in long-term potentiation, the most widely studied neuronal equivalent of learning in vitro (**126**, **1137**).

Local neuronal activity can be temporally integrated because NO will only be synthesized by localized groups of neurons that had been depolarized through repeated activation that is necessary to open NMDA receptors (**426**). NO can help enhance the synaptic efficiency of surrounding axonal arbors of neurons that have been active, whereas the axonal arbors from neurons that have not been activated will be weakened. The ability to modulate local groups of neurons on a moderate time scale is one in the reasons why the CNS is a major source of NOS and why it undergoes radical changes in expression throughout development (**154**, **462**, **647**,**1188**).

D. Cytotoxic Effects of Nitric Oxide

Although NO is reported to have many potentially toxic effects, many of them are more likely mediated by its oxidation products rather than NO itself. Thus NO does not directly attack DNA, as was initially believed, but this effect instead depends on its conversion into higher nitrogen oxides (**1375**). It also does not directly cause the ribosylation of glyceraldehyde-3-phosphate dehydrogenase (**323**), but rather reacts with a sulfhydryl anion in the active site of the enzyme (**888**). Furthermore, the early consideration that NO produced by activated macrophages would inactivate the iron/sulfur centers in tumor cell mitochondria (**329**, **542**) has been reevaluated by a series of experiments indicating that the NO-dependent inactivation of iron/sulfur centers was in fact mediated by peroxynitrite (**182**, **523**). Indeed, activated macrophages produce both NO and superoxide, so the inactivation of mitochondria in tumor cells could well have been mediated by peroxynitrite (**1062**).

NO may reversibly inhibit enzymes with transition metals or with free radical intermediates in their catalytic cycle. NO in micromolar concentrations will reversibly inhibit catalase and cytochrome *P*-450 (**153**, **1376**). It also can inhibit ribonucleotide reductase, the enzyme responsible for DNA synthesis that contains a tyrosine radical. Subsequent inhibition of DNA may inhibit viral replication. However, the inhibition of ribonucleotide reductase is rapidly reversible and lost when NO is less than a few micromolar in concentration. Large continuous fluxes of NO are necessary to keep ribonucleotide reductase inhibited, which would occur only under major inflammatory conditions or in the neighborhood of an activated macrophage. Enormous amounts of oxygen are required to maintain synthesis of NO in micromolar concentrations. Since it takes two oxygens per NO produced, and if the half-life of NO in vivo was as long as 7 s, then 120 nmol O_2 would be needed per gram tissue per minute to maintain NO at a steady-state concentration of 1 μM! NO in the submicromolar range can also reversibly

inhibit cytochrome-*c* oxidase (**141**, **220**, **1161**), which may transiently increase the leakage of superoxide from the electron transport chain. The superoxide so formed could then react with NO to generate peroxynitrite, which would cause irreversible injury to the mitochondria.

E. Superoxide and the Hydroxyl Radical Theory of Radical Damage

The recognition that superoxide could be a biologically significant molecule was at one time viewed as unlikely as NO. Many thought superoxide was chemically far too reactive to be produced in vivo. Inorganic chemists produce superoxide by burning molten potassium metal with pure molecular oxygen. As a solid, potassium superoxide ($KO_2\cdot$) is a powerful oxidant that reacts vigorously when added to water. Originally, chemists wrote the structure as K_2O_4. In 1934, Pauling and Neuman (**1013**) deduced from quantum mechanics that $2KO_2\cdot$ would be more stable than a molecule with four oxygen atoms and proposed the name superoxide for this one-electron reduced state of molecular oxygen.

In the mid 1960s, Fridovich (**410**) investigated the oxygen-dependent reduction of cytochrome *c*by the flavin-containing xanthine oxidase. Oxygen would be expected to oxidize cytochrome *c*rather than to facilitate reduction. A protein was found in blood cells that would inhibit the reduction of cytochrome *c*, which was purified by McCord and Fridovich in 1969 (**859**). This protein had previously been purified as a copper binding protein, but McCord and Fridovich (**688**) showed this protein was an efficient scavenger of superoxide. Fridovich's group soon isolated a manganese-containing version from bacteria and also present in mitochondria (**1026**). The ability of SOD to scavenge superoxide provided strong evidence that superoxide was a biologically relevant molecule. This provided strong impetus to the theory that the univalent reduction of molecular oxygen to produce the free radicals superoxide, hydrogen peroxide, and hydroxyl radical were responsible for the toxicity of oxygen in biological systems. Oxygen has been known since the 1950s to greatly amplify the toxicity resulting from radiation by amplifying radical damage.

While the name superoxide implies that superoxide should be a powerful oxidant, superoxide more generally behaves as a mild reductant under physiological conditions rather than a “super”-oxidizing agent. This is because superoxide exists naturally as a small anion ($O_2^{\cdot -}$), which is more likely to surrender its electron than to accept a second electron from another biological molecule. Hence, the reduction potential for superoxide is about −0.1 V at physiological oxygen concentrations. Superoxide is a strong oxidant when it is protein mated, but its pK_a is ∼4.3 so that it will directly oxidize positively charged chemical moieties such as iron/sulfur centers. The destruction of iron/sulfur centers in mitochondria has been well described in SOD knockout mice (**761**, **910**). Aconitase is another iron/sulfur protein that is particularly susceptible to inactivation by superoxide (**523**).

The limited chemical reactivity of superoxide created considerable controversy about the role of superoxide in cellular toxicity (**1125**). To explain how a more potent oxidant might be generated by superoxide, the iron-catalyzed formation of hydroxyl radical from hydrogen peroxide was proposed. Because hydroxyl radical was well known to be a potent oxidant and important in radiation-induced damage to biological molecules, it became widely accepted as the major toxin produced in vivo. While widely described in many pathology textbooks, there are many limitations to the hydroxyl radical theory. In particular, the formation of hydroxyl radical requires the presence of an appropriately chelated iron atom reacting first with superoxide to become reduced and then with hydrogen peroxide to form hydroxyl radical. Scavengers of either

superoxide or hydrogen peroxide such as SOD can effectively inhibit this reaction. The reaction of iron with hydrogen peroxide tends to have rather slow rate constants. Finally, hydroxyl radical is so reactive that it will react with virtually every biological molecule within a very short diffusion distance. Hydroxyl radical will diffuse on average less than the diameter of the typical protein. Thus the biological relevance of hydroxyl radical is limited because it is formed by a slow reaction while being so highly reactive that its toxicity becomes limited by reacting with too many irrelevant biological targets.

Still administration of SOD to experimental animals subjected to ischemia and other inflammatory stresses could provide substantial benefits. At the same time that McCord and Fridovich had purified SOD, another group purified an anti-inflammatory compound from cow blood that turned out to be identical to SOD (**578**). By the mid 1980s, 6,000,000 doses of SOD had been administered as an anti-inflammatory agent to patients in Europe. These studies clearly implicated superoxide as having a major role in promoting tissue pathology. However, the biological targets of superoxide remained obscure. The protection of EDRF by SOD suggested that it might be a major target of superoxide in vivo. When EDRF was identified as NO, it raised the possibility that its product, peroxynitrite, could be a significant and unrecognized oxidant in vivo.

III. PEROXYNITRITE

A. Historical Perspectives

At the time when NO was discovered, the controversy about the reactivity of superoxide and its significance to pathology was at its nadir. A few publications concerning peroxynitrite were scattered in the older chemical literature or found in studies of atmospheric pollution. The diffusion-limited reaction of NO with $HO_2\cdot$ was recognized to be the major source of nitrogen dioxide and hydroxyl radical in the atmosphere and strongly implicated in the formation of smog.

The historical perspective of the discovery of peroxynitrite has been nicely reviewed by Koppenol (**708**). As early as 1901, the unusual oxidizing power of acidified nitrite mixed with hydrogen peroxide was noted. As an oxidant, peroxynitrite attracted little attention because it produced a bewildering array of products even with fairly simple starting substrates such as phenol. In 1970, several investigators more thoroughly characterized the chemistry of peroxynitrite showing that it decomposed to form hydroxyl radical and nitrogen dioxide (**85**, **401**, **580**, **581**, **832**). Hughes and Nicklin (**580**) established the most commonly used extinction coefficient (1.67 $mM^{-1} \cdot cm^{-1}$) through indirect measurements. Later, Bohle et al. (**108**) prepared pure peroxynitrite and determined the extinction coefficient as 1.70 $mM^{-1} \cdot cm^{-1}$.

Peroxynitrite can also be formed through the ultraviolet radiation of solid crystals of nitrate, turning clear crystals yellow (**678**). This is potentially more than a laboratory curiosity. The attempts by the Viking missions to Mars in 1976 to detect life may have been confronted by ultraviolet-induced peroxynitrite formation in nitrate found in the Martian soil (**1031**).

Peroxynitrite may also prove useful to solubilize chromium III by oxidizing it to chromium VI from the radioactive sludge found in the Hanford nuclear storage facilities in Washington state (**808**). Solid chromium III causes glass to weaken more quickly and requires more glass to be used for vitrification of radioactive waste. Treatment with peroxynitrite can reduce the amount of

glass needed to entrapp trans-uranium elements by a factor of two, which has huge economic benefits to reduce the cost of permanent storage of radioactive waste.
In studies of the fate of NO in the ocean, Zafirou and co-workers (**104**, **1428**) showed that superoxide reacts with NO to form peroxynitrite. The most commonly cited rate constant for this reaction was measured as $6.7 \times 10^9\ M^{-1} \cdot s^{-1}$ (**583**). Koppenol et al. (**937**) found using three different flash photolysis methods that the rate was slightly faster ($16–20 \times 10^9\ M^{-1} \cdot s^{-1}$), while others report slightly slower rate constants as determined by pulse radiolysis ($3–4 \times 10^9\ M^{-1} \cdot s^{-1}$). The rate of superoxide reacting with SOD is $\sim 2 \times 10^9\ M^{-1} \cdot s^{-1}$. Hence, NO is the one molecule produced in high enough concentrations and reacts fast enough to outcompete endogenous SOD for superoxide. As described below, the interactions of superoxide, NO, and peroxynitrite with SOD are more complex than this simple analysis indicates.

B. Biological Chemistry

In 1990, the first papers suggesting that peroxynitrite could be a biological oxidant were published (**71**, **75**). At the time, much of the literature suggested that NO was a scavenger of superoxide and thus acting as an antioxidant (**379**, **855**). However, Beckman et al. (**75**) showed peroxynitrite was a far more effective means of producing hydroxyl radical than the widely accepted reaction of reduced iron with hydrogen peroxide (known as the Fenton reaction or the iron-catalyzed Haber-Weiss reaction). These results were confirmed by Hogg et al. using systems to cogenerate superoxide and NO (**287**, **559**). In addition, peroxynitrite produced nitrogen dioxide, which could lead to novel oxidation products that were previously only suspected to occur after exposure to cigarette smoke or to air pollution.
Peroxynitrite itself is also a strong oxidant and can react directly with electron-rich groups, such as sulfhydryls (**1056**), iron-sulfur centers (**182**), zinc-thiolates (**245**), and the active site sulfhydryl in tyrosine phosphatases (**1254**). Curiously, the reaction rate constants are relatively slow for these second-order reactions, ranging from 10^3 to $10^6\ M^{-1} \cdot s^{-1}$. Peroxynitrite is surprisingly stable in solution, considering its strong oxidizing potential and that it is 36 kcal/mol higher in energy than its isomer nitrate. The unusual stability of peroxynitrite results in part because it folds into a stable*cis*-conformation where the negative charge is localized over the entire molecule (**1291**). The molecules are further stabilized by forming strong hydrogen bonds with two or three waters (**1290**). The limited reactivity of peroxynitrite with most molecules makes it unusually selective as an oxidant, which increases its influence over biological processes.
Although peroxynitrite is a strong oxidant, the anion ($ONOO^-$) also reacts directly with nucleophiles, molecules with a partial positive charge. One example of major importance is carbon dioxide. The carbon is surrounded by two oxygens, which effectively pull electron density away. Hence, carbon dioxide reacts with hydroxyl anion to form bicarbonate. In the same way, carbon dioxide reacts with peroxynitrite to form a transient intermediate nitrosoperoxycarbonate that rapidly decomposes homolytically to nitrogen dioxide and carbonate radical. Because carbon dioxide is nearly 1 mM in cells (~10,000 times greater than hydrogen ions), the formation of carbonate radicals is more likely to occur in vivo than the formation of hydroxyl radical per se from HOONO (peroxynitrous acid, the conjugated acid of peroxynitrite). Carbonate radical is more selective than hydroxyl radical but will initiate many of the damaging reactions commonly attributed to hydroxyl radical in the biological literature and is perhaps more significant as a biological oxidant (**873**).

Multiple oxidative pathways can form both hydroxyl and carbonate radical independently of peroxynitrite or NO. However, peroxynitrite can also produce novel products such as nitrotyrosine, nitrotryptophan, and nitrated lipids that serve as important biological markers in vivo. Ohshima et al. (**967**) developed a mass spectrometric method to measure nitrotyrosine of smokers, but was surprised to find significant amounts in the urine of nonsmoking humans as well. At the same time, Ischiropoulos and co-workers found that peroxynitrite caused bovine SOD to turn yellow, which was eventually traced to the nitration of the sole tyrosine at position 108 (**609**, **612**, **1174**).

A major limitation to the acceptance of peroxynitrite or any reactive nitrogen species as a significant player in disease was whether enough could be produced to be damaging. Significant questions were raised as to whether human "macrophages" produced NO and whether its synthesis was mostly a rodent-specific phenomenon. However, in subsequent studies, it became clear that the regulation of inducible NOS was under tighter control in humans (**936**, **1196**, **1353**).

The development of antibodies that recognize nitrotyrosine also provided a major impetus to the study of peroxynitrite (**80**). Nitrotyrosine can easily be detected in Formalin-fixed tissue, and the antibodies are not species specific. This allowed the antibodies to be broadly applicable (**1327**,**1414**). Nitrotyrosine was first shown to be localized in human atherosclerotic lesions and vascular muscle (**80**). Later, it was found in a huge number of most disease-affected tissues (see⇓⇓⇓**Tables 4** and **5** and sect. VI) and its presence confirmed by mass spectrometric analyses (**244**, **1098**, **1397**). One of the major values of nitrotyrosine is that it provided strong evidence that the production of NO was sufficient to produce observable products in virtually every human disease (**606**).

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TABLE 1.

Peroxynitrite-induced protein modifications

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TABLE 2.

Major signaling pathways shown to be influenced by peroxynitrite in vitro

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TABLE 3.

Selected effects of peroxynitrite with potential relevance to cardiovascular pathophysiology

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TABLE 4.

Evidence implicating endogenous peroxynitrite formation and/or protein nitration in cardiac and vascular diseases

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TABLE 5.

Evidence implicating endogenous peroxynitrite formation and/or protein nitration in diabetes and diabetic complications

In recent years, it has become common to use nitrotyrosine as a marker of nitrosative stress, although this is a serious misrepresentation of the underlying processes. Incubating large amounts of NO (1–2 mM) aerobically with proteins, tissue homogenates, or cell cultures does not yield significant amounts of nitrotyrosine (**80**). However, peroxynitrite readily yields nitrotyrosine in yields of 3–14%. Although a high concentration of NO forms nitrogen dioxide, the concentration of nitrogen dioxide is thousands of times more dilute than NO. Consequently, the nitrogen dioxide reacts rapidly with the NO to form N_2O_3, which is a nitrosating agent that is far more likely to react with thiols as well as primary and secondary amines than with tyrosine. Nitrotyrosine readily decomposes to tyrosine and nitrite. Hence, nitrosative stress produces products such as nitrosothiols and nitrosamines, but nitrotyrosine and nitrotryptophan are more stable products and indicative of a more intense oxidative stress. This stress is better characterized as nitrative stress.

Nitrotyrosine is extremely useful for measuring the formation of peroxynitrite, but this requires additional experimental validation. The first evidence for peroxynitrite formation came from SOD as a catalyst of tyrosine nitration to detect peroxynitrite being formed from freshly isolated rat alveolar macrophages (**611**). As isolated, these macrophages produced NO, but not superoxide. No nitration of a tyrosine analog could be observed under these basal conditions. When superoxide synthesis by NADPH oxidase was activated with a phorbol ester, nitration could be visually observed by the tyrosine analog turning a faint yellow color. The amount of nitration could be increased paradoxically by adding SOD (**Fig. 4**). SOD catalyzes tyrosine nitration by peroxynitrite, but would generally be expected to reduce peroxynitrite formation by scavenging superoxide. To parse these conflicting actions, SOD was chemically treated by a combination of two well-established methods to reduce its superoxide scavenging activity by >99%. The copper remained bound to the SOD after these treatments, and the ability to catalyze tyrosine nitration was unaffected. Unexpectedly, unmodified SOD was equally effective at catalyzing nitration as the inactivated SOD, suggesting that nitration was enhanced by metal-dependent catalysis (copper) at the active site of the enzyme. This also argued that NO was reacting so quickly with superoxide produced on the cell surface by NADPH oxidase that SOD added to the extracellular media could not effectively remove superoxide under these identical conditions. What was particularly important about this study was that oxygen consumption, NO production, superoxide formation, and nitration were all quantified as well as the effects of NOS inhibition on these quantities. When superoxide formation was stimulated to a threefold greater rate than NO synthesis, all of these data showed that NO was being quantitatively converted to peroxynitrite.

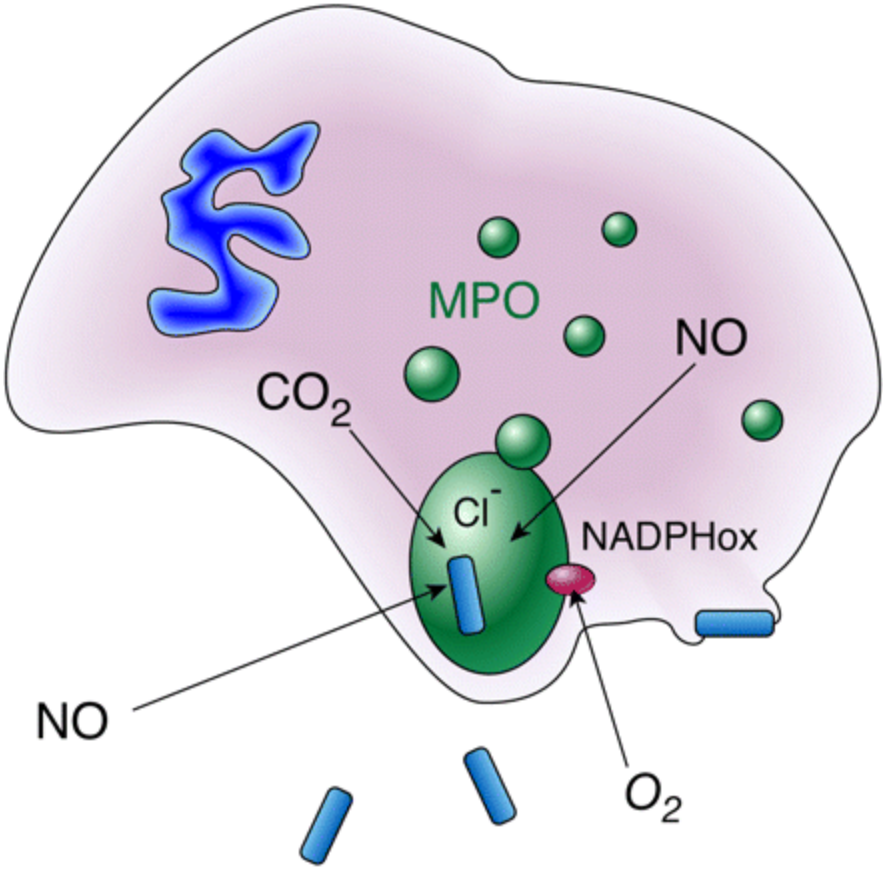

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FIG. 4.

Diffusion of nitric oxide into the phagolysosome and the recycling of peroxynitrite-derived nitrite. Only a miniscule volume of extracellular fluid is engulfed into phagocytic vacuoles, which provides a limited amount of chloride as a substrate for myeloperoxidase. In contrast, nitric oxide can readily diffuse into the phagolysosome. Neutrophils produce superoxide by NADPH oxidases, but superoxide is unlikely to penetrate cell membranes or cell walls of pathogens, and can reversibly inactivate myeloperoxidase. Peroxynitrite is a substrate for myeloperoxidase and can reverse this inhibition. In addition, nitrite formed from peroxynitrite decomposition is entrapped within the phagolysosome and serves as an additional substrate for myeloperoxidase. Myeloperoxidase is not a predominant protein in macrophages, where formation of peroxynitrite from superoxide and nitric oxide appears to be a major mechanism of cytotoxicity.

The production of oxidants is a crucial mechanism for neutrophils and macrophages to damage or kill microorganisms (Fig. 5). One of the major limitations is the minuscule volume of fluid present in these phagocytotic vacuoles. Neutrophils release large quantities of myeloperoxidase into these vacuoles, while eosinophils release eosinophil peroxidases. Chlorine and bromine are well-established substrates for these enzymes, being oxidized to hypohalous acids. Even though chloride is 100 mM in extracellular fluids, the minuscule volume absorbed into these vacuoles

implies that chlorine can be a major limitation in the myeloperoxidase reaction. It has also long been puzzling why the NADPH oxidase of neutrophils produces superoxide rather than hydrogen peroxide directly. The ability of NO to rapidly diffuse across cellular membranes greatly expands the armamentarium of phagocytic inflammatory cells. The large localized production of superoxide will form a major sink to trap NO produced by any cell in the region and the peroxynitrite will react quickly in the immediate region because of the large local concentrations of carbon dioxide produced by activation of the hexose monophosphate shunt activated to supply NADPH needed for superoxide formation and NO synthesis. Myeloperoxidase reacts rapidly and directly with peroxynitrite to produce nitrogen dioxide and efficiently catalyzes tyrosine nitration (**400**, **1112**).

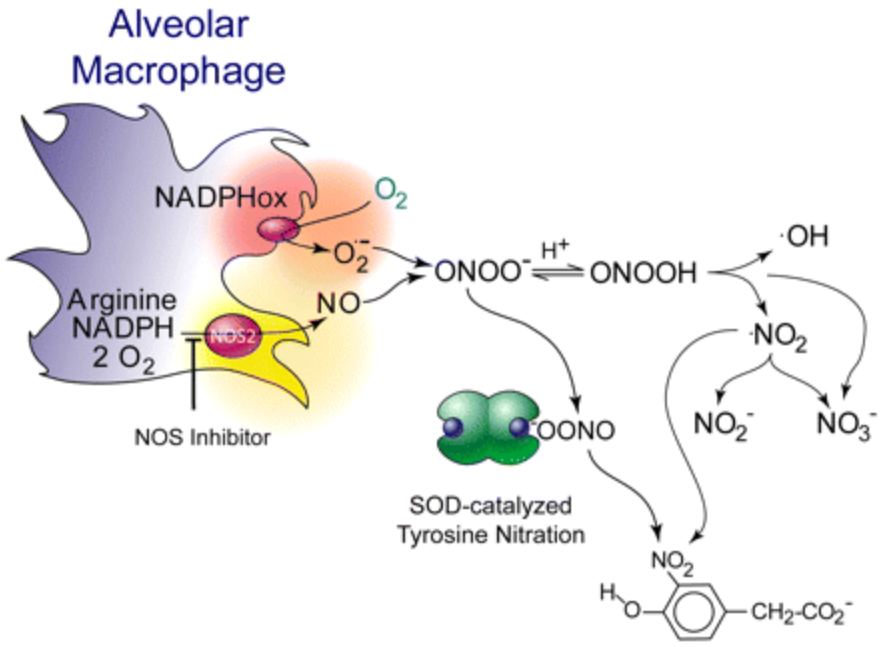

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FIG. 5.

Alveolar macrophages produce peroxynitrite. When alveolar macrophages are stimulated to produce both superoxide and nitric oxide, peroxynitrite is quantitatively produced (**611**) as evidenced by the amount of nitric oxide and superoxide produced and the amount of oxygen consumed. Extracellular addition of superoxide dismutase (SOD) in high concentrations does not significantly reduce the amount of peroxynitrite formed and instead serves as a catalyst of tyrosine nitration. This suggests that superoxide produced at the membrane surface and nitric oxide diffusing through the membrane react at the membrane interface so quickly that SOD in the bulk phase cannot compete.

When peroxynitrite acts as an oxidant, it produces nitrite and hydroxide ion rather than isomerizing to nitrate. Consequently, the major decomposition products of superoxide and peroxynitrite formation in the phagosome are ultimately hydrogen peroxide and nitrite. These are also substrates for myeloperoxidase and can be a significant source of tyrosine nitration (**158**,**668**, **1113**). Using mass spectrometry to quantify nitrotyrosine formation in knockout mice

for myeloperoxidase and eosinophil peroxidase, Brennan et al. (**136**) found that nitrotyrosine was reduced by a maximum of 50% in some models of severe acute inflammatory but nitration was hardly affected in other models. Nitration catalyzed by peroxidases from nitrite has been frequently interpreted as implying nitrotyrosine does not necessarily result from peroxynitrite. In many cases, peroxidases from inflammatory cells are not found in regions showing tyrosine nitration. Furthermore, a major issue is where does nitrite come from in vivo. NO is mostly removed by reacting with oxyhemoglobin to form nitrate, with only a small fraction being oxidized by heme proteins. Even the highest fluxes of NO proposed to be present in vivo will form minor amounts of nitrogen dioxide by the reaction with oxygen (**Fig. 2**). By cogenerating superoxide, NO is rapidly redirected to the initial formation of peroxynitrite. Within a neutrophil or macrophage phagolysosome, this serves as a recycling mechanism to reutilize nitrite and hydrogen peroxide to generate more reactive species. It will be the rare exception to find nitrotyrosine being formed without peroxynitrite being a major intermediate.

C. The Reverse Reaction of Peroxynitrite to Form Superoxide and Nitric Oxide

Although the back reaction is ~100,000,000,000 times slower than the formation of peroxynitrite, the reverse reaction of peroxynitrite forming superoxide and NO can be significant when working with bolus additions. When the production of superoxide and NO are both occurring at very low levels, the back reaction can be significant. However, the rapid reaction of peroxynitrite with carbon dioxide will pull the overall reaction to form carbonate radical and nitrogen dioxide. Thus carbon dioxide increases the amount of radical damage produced from NO plus superoxide cogeneration and ensures that peroxynitrite decomposes to form radicals even at very low fluxes of superoxide and NO.

The reverse reaction to form superoxide and NO also explains many of the puzzling aspects of peroxynitrite chemistry at alkaline pH (**Fig. 6**). The apparent radical generation from peroxynitrite decomposition decreases at alkaline pH (**75**). The details have been worked out by Goldstein, Meyreni, Lymar, Hurst, and co-workers (**224**, **452**, **812**, **868**). In brief, the superoxide produced during the reverse reaction reacts with nitrogen dioxide to form peroxynitrate anion (O_2NOO^-), which decomposes to give nitrite and oxygen. The NO produced reacts with additional nitrogen dioxide to form dinitrogen trioxide, which is a well-known nitrosating agent. Peroxynitrite reacts quickly with dinitrogen trioxide to form two nitrogen dioxides plus nitrite. This catalytically increases the formation of nitrogen dioxide and accelerates the decomposition of peroxynitrite. This complex interplay of reactive intermediates illustrates how a slight excess of NO can interact with peroxynitrite to increase the formation of nitrosothiols and other unexpected products that greatly complicate the biological chemistry of peroxynitrite.

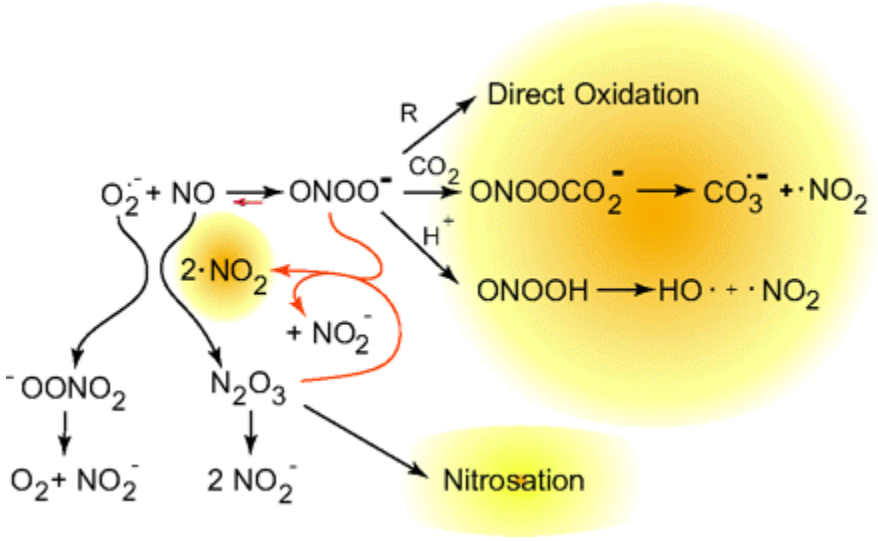

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FIG. 6.

The interplay of nitric oxide, superoxide, peroxynitrite, and nitrogen dioxide. When nitric oxide and superoxide are both present, they may also react with nitrogen dioxide to form N_2O_3 and peroxynitrate. Peroxynitrate decomposes to give nitrite and oxygen, while N_2O_3 can react with thiols to give nitrosothiols or with hydroxide anion to give nitrite. Goldstein et al. (**452**) showed that it also reacts at a diffusion-limited rate with peroxynitrite to yield two molecules of nitrogen dioxide and one of nitrite. This creates a cycle to generate more nitrogen dioxide when bolus additions of peroxynitrite are added at neutral pH and substantially increases the number of potential reactions occurring. These same reactions will also occur in vivo, particularly when nitric oxide is produced faster than superoxide.

IV. PEROXYNITRITE-INDUCED CYTOTOXICITY

Under physiological conditions, the production of peroxynitrite will be low and oxidative damage minimized by endogenous antioxidant defenses (**1058**, **1059**). Even modest increases in the simultaneous production of superoxide and NO will greatly stimulate the formation of peroxynitrite; a 10-fold increase in superoxide and NO production will increase peroxynitrite formation 100-fold. Consequently, pathological conditions can greatly increase the production of peroxynitrite. Even the generation of a moderate flux of peroxynitrite over long periods of time will result in substantial oxidation and potential destruction of host cellular constituents, leading to the dysfunction of critical cellular processes, disruption of cell signaling pathways, and the induction of cell death through both apoptosis and necrosis (**1334**). Hence, the production of peroxynitrite can be instrumental in the development of many pathological processes in vivo.

A. Mechanisms of Peroxynitrite-Mediated Oxidations

Although not a free radical in nature, peroxynitrite is much more reactive than its parent molecules NO and $O_2^{\cdot-}$ (71, 75, 78). The half-life of peroxynitrite is short (~10–20 ms), but sufficient to cross biological membranes, diffuse one to two cell diameters (312), and allow significant interactions with most critical biomolecules (1041). Kinetic studies have indicated that peroxynitrite oxidizes target molecules through two distinct mechanisms. First, peroxynitrite and its protonated form peroxynitrous acid (ONOOH) can exert direct oxidative modifications through one- or two-electron oxidation processes (78). Only a few chemical groups directly react with peroxynitrite, which favors selective reactions with key moieties in proteins, such as thiols, iron/sulfur centers, and zinc fingers (78). The second mechanism involves peroxynitrite indirectly mediating oxidation by decomposing into highly reactive radicals (16). Peroxynitrite can yield hydroxyl radical and nitrogen dioxide ($NO_2\cdot$) during the homolytic decomposition of peroxynitrous acid (1054). However, the formation of hydroxyl radical by this mechanism probably plays only a minor role in vivo (1054) because of the particularly rapid reaction of peroxynitrite with carbon dioxide (CO_2) (310, 809–811, 1060). The direct reaction of peroxynitrite with CO_2 ($4.6 \times 10^4\ M^{-1} \cdot s^{-1}$ at 37°C) gives rise to an unstable product (nitrosoperoxycarbonate, $ONOOCO_2^-$), which rapidly homolyzes into the $CO_3^{-}\cdot$ (carbonate radical) and $NO_2\cdot$ (34). Carbonate radical is likely to be more toxic than hydroxyl radical and yields many of the same types of oxidation commonly attributed to hydroxyl radical. Thus carbon dioxide redirects much of the peroxynitrite produced in vivo towards radical mechanisms (16).

B. Biological Targets of Peroxynitrite

1. Proteins

A) REACTIONS OF PEROXYNITRITE WITH TRANSITION METAL CENTERS.

The direct reaction of peroxynitrite with transition metal centers is among the fastest known for peroxynitrite (16). Peroxynitrite thus modifies proteins containing a heme prosthetic group, such as hemoglobin (106), myoglobin (540), or cytochrome *c* (1275), oxidizing ferrous heme into the corresponding ferric forms. Similarly, peroxynitrite can inactivate inducible NOS by oxidative modification of its heme group (582), a reaction which might serve as a feedback negative regulation of peroxynitrite generation under inflammatory conditions. Peroxynitrite reacts particularly rapidly with iron-sulfur clusters, inactivating enzymes involved in critical metabolic processes, including mitochondrial aconitase (182) and phoshogluconate dehydratase (669), as well as with Zn^{2+} sulfur motifs, an effect resulting in the inactivation of eNOS (1469) and alcohol dehydrogenase (245).

B) REACTIONS OF PEROXYNITRITE WITH AMINO ACIDS.

I) Cysteine oxidation.

Peroxynitrite may alter protein structure and function by reacting with various amino acids in the peptide chain. The most prevalent reaction is that with cysteine, making thiol oxidation a major modification introduced by peroxynitrite (1056, 1057). The direct second-order reaction of peroxynitrite with thiols (particularly with the anion form, RS^-) results in the formation of an intermediate sulfenic acid (RSOH), which then reacts with another thiol, forming a disulfide

(RSSR) (16). Thiols may also be oxidized by the radicals formed from peroxynitrite, generating thiyl radicals (RS·). Thiyl radicals may react with oxygen and promote oxidative stress by propagating free radical reactions (334). They will also react with NO to form nitrosothiols.
The oxidation of critical cysteine residues by peroxynitrite inactivates many enzymes involved in cellular energetic processes, including glyceraldehyde-3-phosphate deshydrogenase (157, 1192), creatine kinase (703), complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), and complex III (cytochrome *c* reductase) as well as complex V (ATP synthase) from the mitochondrial respiratory chain (1058, 1059, 1062). These enzymes are also inactivated by nitration of tyrosine residues (see below), indicating that they may be particularly vulnerable targets of peroxynitrite. Cysteine oxidation also inactivates several protein tyrosine phosphatases, which may enhance phosphotyrosine-dependent signaling (791, 1254). In addition to protein-bound thiol, peroxynitrite can directly oxidize low-molecular-weight thiols, most notably reduced glutathione (GSH). GSH thereby serves as an efficient endogenous scavenger of peroxynitrite and plays a major role in the cellular defense against this species (31). Accordingly, the susceptibility of cells to peroxynitrite toxicity largely depends on the amount of intracellular GSH. GSH depletion enhances peroxynitrite toxicity and tissue injury during circulatory shock (258,278), and a relationship between GSH depletion and enhanced peroxynitrite toxicity has also been proposed as contributing to the development of some neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis (847, 1321).
In some instances, cysteine oxidation by peroxynitrite may result in enzyme activation instead of inhibition, as demonstrated for matrix metalloproteinases (MMPs), which have been recently implicated as an important mechanism of peroxynitrite-dependent toxicity in heart disease (994,1085, 1345) and stroke (495). Peroxynitrite activates the proenzyme (proMMPs) via thiol oxidation and *S*-glutathiolation of its autoinhibitory domain (971). Similarly, cysteine oxidation by peroxynitrite has been associated with the activation of the src kinase *hck* in erythrocytes, inducing the amplification of tyrosine-dependent signaling in these cells, as detailed in section V(838, 840).

II) Tyrosine nitration.

Protein tyrosine nitration is a covalent protein modification resulting from the addition of a nitro ($-NO_2$) group adjacent to the hydroxyl group on the aromatic ring of tyrosine residues (464). Tyrosine nitration affects protein structure and function, resulting in the generation of antigenic epitopes, changes in the catalytic activity of enzymes, altered cytoskeletal organization, and impaired cell signal transduction (1132), and is thus increasingly considered as a central aspect of peroxynitrite-mediated cytotoxicity.
Tyrosine does not react directly with peroxynitrite. Instead, tyrosine nitration occurs through a radical mechanism in which a hydrogen atom is first abstracted from tyrosine to form a tyrosyl radical that quickly combines with $NO_2\cdot$ to produce 3-nitrotyrosine. This competes with a secondary reaction where combining with another tyrosyl radical to form dityrosine (72, 78, 605,1053). Although the radicals involved in the reaction may come from peroxynitrite homolysis ($HO\cdot$ and $NO_2\cdot$), they most likely result from the reaction between peroxynitrite and CO_2 (producing $CO_3^{-}\cdot$ and $NO_2\cdot$ radicals) (16, 1053, 1300). Nitration is also enhanced in the presence of transition metals due to the formation of secondary radicals at the metal center plus $NO_2\cdot$ (16). Metalloproteins such as heme-containing proteins (e.g., prostacyclin synthase) or Cu,Zn- and Mn-SOD may thus catalyze peroxynitrite-mediated tyrosine nitration (1053). A second mechanism of tyrosine nitration relies on the generation of the $NO_2\cdot$ radical by various

heme-peroxidases (mainly myeloperoxidase and eosinophil peroxidase) in the presence of hydrogen peroxide (**438**,**1314**, **1390**). This may serve as a recycling mechanism to reuse products formed from superoxide and NO production. Therefore, nitrotyrosine formation technically must be considered a marker of "nitrative" stress. Additional control experiments are needed before concluding tyrosine nitration resulted from the generation of peroxynitrite (**606**).

The advent of proteomic analyses has confirmed that nitration is a highly selective process, limited to specific tyrosine residues on a surprisingly small number of proteins (**35**, **464**, **654**, **655**). Nitration on specific tyrosine residues is promoted by the exposure of the aromatic ring to the surface of the protein, the location of the tyrosine on a loop structure, its association with a neighboring negative charge, and absence of proximal cysteines (**1190**). Tyrosine nitration may also be favored in hydrophobic environment, which is a relevant issue, considering that peroxynitrous acid can readily pass through lipid membranes (**64**, **1300**).

A) Selected cytotoxic processes related to protein tyrosine nitration.

The list of proteins being nitrated in cellular models, as well as in various pathologies in vivo, is rapidly growing. Tyrosine nitration has been identified in at least 50 human diseases and more than 80 conditions modeled in animals, as reviewed recently (**476**), and these figures are continuously increasing. However, finding of nitrated proteins in a given condition does not necessarily imply a direct pathogenic role, but at least it indicates an increased formation of peroxynitrite along with other nitrogen reactive species during the disease process. Novel proteomic approaches are being used to identify which proteins are nitrated in vivo, and such studies will help to define the potential pathogenic role of tyrosine nitration in diseases.

In most reported studies, nitration of tyrosine has been associated with a significant loss of function of the nitrated protein, as summarized in **Table 1**. An important example of loss of enzyme activity is that of mitochondrial Mn-SOD, which was the first protein found to be nitrated in vivo. Nitration of a single tyrosine residue (Tyr-34) leads to complete enzyme inactivation (**830**), with the possible consequence to favor peroxynitrite generation in this organelle, due to the impaired dismutation of $O_2^{\bullet-}$. In vivo, nitration of Mn-SOD has been detected in rodent (**828**) and human (**826**) rejected kidney allographs, in cerebrospinal fluid of patients with amyothrophic lateral sclerosis as well as Alzheimer's and Parkinson's diseases (**27**), and in hearts from humans with diabetes (**1397**) and from mice exposed to cigarette smoke (**691**), and it has also been associated with vascular aging (**1311**).

Prostacyclin synthase (PGI_2 synthase) is another important target of peroxynitrite that is inactivated by a specific nitration of Tyr-430 (**1130**). PGI_2 synthase is rapidly nitrated in arterial walls during inflammatory processes (**39**), through a mechanism involving CD40 ligand-dependent increases in vascular peroxynitrite generation (**290**). The consecutive loss of PGI_2 synthesis may be a significant contributor to endothelial dysfunction in many pathological conditions, e.g., diabetes (**1473**), atherosclerosis (**290**), and ischemia-reperfusion (**1468**) and may play an important role in the phenomenon of nitrate tolerance (**549**).

In the heart, nitration of several critical proteins has been proposed as a major mechanism of cardiac dysfunction (**995**, **1300**). Thus both creatine kinase (**740**, **877**, **878**, **883**), a critical energetic controller of cardiomyocyte contractility, and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2A) (**789**, **1397**) are rapidly inactivated by tyrosine nitration. Peroxynitrite also nitrates and inactivates the voltage-gated K^+ channels in the coronary endothelium, which may foster cardiac dysfunction by imparing coronary flow reserve (**754**), and nitrates several important

structural protein in cardiomyocytes such as desmin, myosin heavy chain, and α-actinin with potential deleterious effects on contractility (**117**, **878**, **881**).
Tyrosine nitration represents a major cytotoxic pathway in the nervous system, possibly contributing to neurodegenerative disorders. α-Synuclein, a neuronal presynaptic protein, undergoes oligomerization upon peroxynitrite-mediated nitration, forming Lewy bodies, the hallmark of Parkinson's disease (**22**), and nitrated α-synuclein has been detected both in experimental and human Parkinson's disease (**443**, **1042**). Peroxynitrite further contributes to Parkinson's disease through nitration (and cysteine oxidation) of tyrosine-hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (**103**, **720**, **721**, **1005**). Peroxynitrite nitrates the microtubule-associated tau protein, inducing tau aggregation, a critical mechanism of Alzheimer's disease (**1073**, **1074**), while peroxynitrite-mediated nitration of neurofilament L may be involved in the alterations of motor neurons in amyotrophic lateral sclerosis (**247**).
Disabling of several cytoskeletal proteins by nitration represents a further major cytotoxic effect attributed to peroxynitrite. Tubulin nitration by peroxynitrite or by direct incorporation of free nitrotyrosine has been reported in cell lines derived from intestine (**54**), neurons (**1269**), and muscle (**199**), resulting in the loss of normal physiological functions. Peroxynitrite also disorganizes actin polymerization through actin nitration, and via the nitration of profilin (**658**,**659**), an important actin-binding protein. These effects have been associated with platelet dysfunction (**659**), disruption of both intestinal (**55**) and endothelial barrier function (**940**), as well as impaired migration and phagocytosis of activated polymorphonuclear cells (**221**).
Two additional important aspects of tyrosine nitration include the modulation of tyrosine kinase-dependent signaling, which will be exposed in detail in the specific section on peroxynitrite and cell signaling, and the generation of new epitopes on proteins, to which T and B lymphocytes are not rendered tolerant. A number of nitrotyrosine-carrying proteins have thus been shown to elicit both humoral and cellular immune responses in mice (**102**, **966**), and recent findings indicate that nitrated proteins may be involved in the development of autoimmune diseases such as systemic lupus erythematosus, arthritis, and glomerulonephritis (**571**, **671**).

III) Tryptophan, methionine, and histidine oxidation.

Peroxynitrite directly oxidizes methionine, forming methionine sulfoxide, and to a lesser extent, ethylene and dimethyldisulfide (**16**). These modifications may participate in immune defenses by inactivating glutamine synthetase (**90**) and the molecular chaperone GroEL (**673**) in bacteria. Met oxidation also inhibits α1-antiproteinase, which then loses its ability to inactivate proteases, most notably elastase (**1368**). Methionine oxidation is reversed by methionine sulfoxide reductase, an enzyme whose reduced expression in the brain is associated with the development of Alzheimer's disease (**1199**). Peroxynitrite can also oxidize tryptophan (**16**), yielding *N*-formylkynurenine, oxindole, hydropyrroloindole, and nitrotryptophan, but the relevance of these effects remains to be established (**16**, **1403**). Finally, peroxynitrite modifies histidine through a radical mechanism, forming a histidinyl radical, a mechanism involved in the inactivation of Cu,Zn-SOD by peroxynitrite (**15**, **1403**, **1404**).

2. Lipids

A major aspect of peroxynitrite-dependent cytotoxicity relies on its ability to trigger lipid peroxidation in membranes (**1055**), liposomes, and lipoproteins by abstracting a hydrogen atom from polyunsatturated fatty acids (PUFA). Resulting products include lipid hydroperoxyradicals,

conjugated dienes, and aldehydes (311). Such radicals in turn attack neighboring PUFAs, generating additional radicals which propagate free radical reactions and the degeneration of membrane lipids (560, 1055), causing membrane permeability and fluidity changes with significant biological consequences (1075). Peroxynitrite may play a critical role in inflammatory diseases of the nervous system by initiating peroxidation of myelin lipids, leading to demyelination (1155,1175, 1313). It also acts as a potent oxidizing agent towards low-density lipoprotein (LDL) (742,1287). Peroxynitrite-modified LDL binds with high affinity to scavenger receptors leading to the accumulation of oxidized cholesteryl esters and foam cell formation, which represent a key early event in atherogenesis (465, 498, 558). Finally, the interactions of peroxynitrite with membrane lipids may lead to the formation of various nitrated lipids, with potential biological properties as mediators of signal transduction both under physiological and pathological conditions (50), and of several intermediates products, including isoprostanes and 4-hydroxynonenal that can further trigger secondary oxidative insults (311).

3. Nucleic acids

Peroxynitrite can damage DNA by introducing oxidative modifications in both nucleobases and sugar-phosphate backbone (for review, see Refs. 160, 945). Among the four nucleobases, guanine is the most reactive with peroxynitrite due to its low reduction potential (1422). The major product of guanine oxidation is 8-oxoguanine, which further reacts with peroxynitrite, yielding cyanuric acid and oxazolone (945). Ultimately, guanine oxidation by peroxynitrite results in guanine fragmentation, a critical step towards mutagenesis and carcinogenesis (160, 945). Peroxynitrite can nitrate guanine, yielding 8-nitro-guanine, which leads to the formation of abasic sites that can be cleaved by endonucleases in vivo to give DNA single-strand breaks (160, 945,1422). Peroxynitrite may also attack the sugar phosphate backbone by abstracting a hydrogen atom from the deoxyribose moiety, resulting in the opening of the sugar ring and the generation of DNA strand breaks (160, 945). The formation of DNA single-strand breaks represents a critical aspect of peroxynitrite-mediated cytotoxicity, since they represent the obligatory trigger for the activation of the nuclear enzyme poly(ADP-ribose) polymerase (PARP) (1243), a pathway ultimately related to the induction of cell death and tissue inflammation, as developed in detail in the next section.

C. Peroxynitrite, Mitochondria, and Cell Death

Mitochondria are involved in many vital processes, e.g., energy production, calcium homeostasis, and the control of various biosynthetic pathways. They also play essential roles in cell death mechanisms. Disruption of mitochondrial functions is implicated in a great number of disease processes, such as diabetes, atherosclerosis, ischemic heart diseases, stroke, aging, and neurodegenerative diseases. The pivotal role of peroxynitrite in such derangements is increasingly recognized, as it can react with key components of mitochondria and thus may affect virtually every critical function of these organelles. Peroxynitrite may reach mitochondria either from extramitochondrial compartments or may be directly produced within the mitochondria. Indeed, mitochondria can produce both NO, by the activity of a Ca^{2+}-sensitive mitochondrial NOS (mtNOS) (140, 528), and superoxide, following the partial reduction of oxygen within the mitochondrial matrix due to the natural leak of electron from the respiratory chain. A major physiological function of NO in the mitochondria is to regulate oxygen

consumption by reversibly inhibiting cytochrome-*c* oxidase (complex IV of the electron transport chain) via competition with oxygen for the binuclear binding site (**1001**). In conditions of high NO production (e.g., during inflammation, reperfusion injury, or neuronal hyperactivation), the interruption of electron transfer at cytochrome oxidase markedly increases the leakage of electrons from the respiratory chain, resulting in enhanced formation of superoxide within the mitochondrial matrix and generation of significant amounts of peroxynitrite (**143**, **147**, **533**). In turn, peroxynitrite nitrates and inhibits Mn-SOD (**830**), thereby preventing the breakdown of locally produced superoxide, which further fuels the formation of peroxynitrite. The mitochondrial toxicity of peroxynitrite results both from direct oxidative reactions and from free radical-mediated damage (**1058**, **1059**), secondary to peroxynitrite reacting with CO_2, giving rise to $CO_3^{-}\cdot$ and $NO_2\cdot$ radicals. The latter reaction is particularly favored within mitochondria, which are the main organelles where CO_2 is produced during decarboxylation reactions (**1058**, **1059**).
With the use of both cultured cells and isolated submitochondrial fractions, peroxynitrite has been shown to exert significant inhibition to most components of the electron transport chain, including complex I (NADH dehydrogenase) (**146**, **919**, **1016**), complex II (succinate dehydrogenase) (**111**,**1092**), complex III (cytochrome *c* reductase) (**489**, **1016**), and complex V (ATP synthetase) (**177**,**1058**, **1059**), through mechanisms involving, to various extents, cysteine oxidation, tyrosine nitration, and damage of iron sulfur centers, as extensively reviewed in References **1058** and**1059**. In contrast, cytochrome-*c* oxidase (complex IV), which is readily inhibited by NO, appears remarkably resistant to peroxynitrite, and may even serve, in its reduced form, as an endogenous catalyst of the two-electron reduction of peroxynitrite into nitrite (**1015**, **1017**). Another target of peroxynitrite is cytochrome *c*, the nitration of which significantly impairs its redox properties. Notably, cytochrome *c* nitration increases its peroxidatic activity, leading to the generation of hydrogen peroxide and exacerbation of oxidative damage to mitochondrial proteins (**178**, **627**). Peroxynitrite further impairs energy metabolism by inhibiting the tricarboxylic acid cycle enzyme aconitase, located in the mitochondrial matrix, via oxidative disruption of the 4Fe-4S center of the enzyme (**182**, **511**), as well as mitochondrial creatine kinase, which is present in the intermembrane space (**1197**). Nicotinamide nucleotide transhydrogenase, which allows formation of NADPH from NADH and $NADP^+$, is another important mitochondrial protein oxidized, nitrated, and inactivated by peroxynitrite (**403**). The ensuing depletion of NADPH reduces the mitochondrial ability to regenerate GSH, contributing to the amplification of oxidative stress within the organelle.

1. Peroxynitrite and apoptosis

Once the level of cellular damage inflicted by peroxynitrite supercedes any possibility of repair, the cell eventually dies via one of the two main pathways of cell demise, necrosis or apoptosis. Necrosis is associated with loss of cellular ATP, leading to membrane disruption, release of noxious cellular debris, and the development of secondary inflammation. In contrast, apoptosis occurs in a well-choreographed sequence of morphological events characterized by nuclear and cytoplasmic condensation with blebbing of the plasma membrane. The dying cell eventually breaks up into membrane-enclosed particles termed apoptotic bodies, which are rapidly ingested and degraded by professional phagocytes or neighboring cells, without inducing any inflammatory response. Apoptosis is orchestrated by the proteolytic activation of cysteine proteases known as caspases, that requires preserved ATP levels to proceed properly, and which

may be triggered either by the activation of death receptors (extrinsic pathway) or by the permeabilization of the outer membrane of mitochondria (intrinsic pathway) (see Refs. 121, 942 for recent reviews on the topics of apoptosis). The mechanisms of peroxynitrite-mediated apoptotic and necrotic cell death are presented in Figure 7.

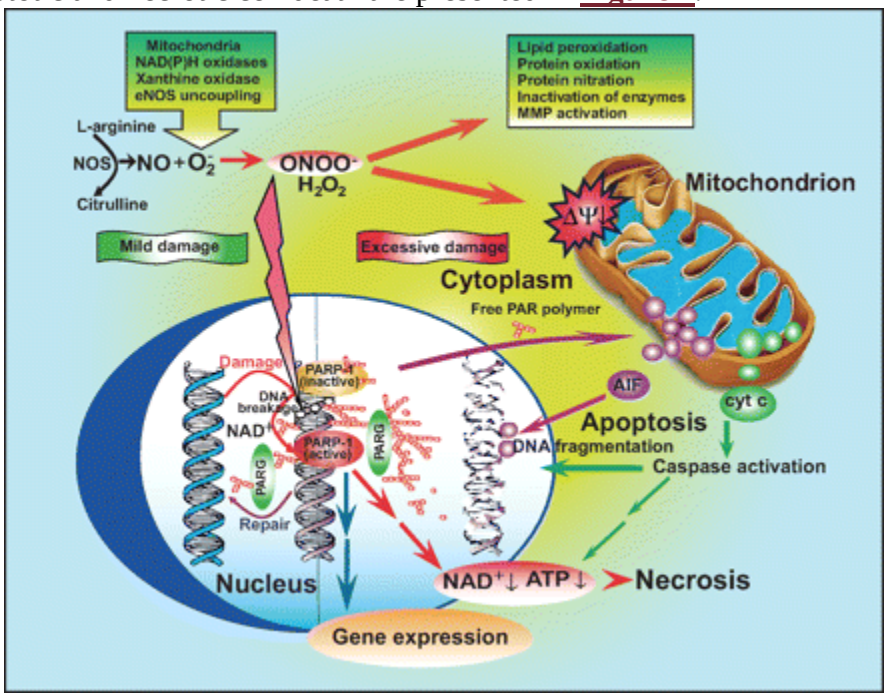

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FIG. 7.

Molecular mechanisms of peroxynitrite-mediated cell death. A number of pathological conditions are associated with the simultaneous generation of nitric oxide (NO) and $O_2^{\cdot-}$. NO sources are restricted to the activity of the various NO synthases, whereas $O_2^{\cdot-}$ arises from multiple sources, including electron leak from the mitochondria, NADPH oxidase, xanthine oxidase, and uncoupling of NO synthases. Once a flux of NO and $O_2^{\cdot-}$ is produced simultaeously in close proximity, the generation of peroxynitrite is considerably enhanced. Peroxynitrite-dependent cytotoxicity is then mediated by a myriad of effects including lipid peroxidation, protein nitration and oxidation, DNA oxidative damage, activation of matrix metalloproteinases (MMP), and inactivation of a series of enzymes. Mitochondrial enzymes are particularly vulnerable to attacks by peroxynitrite, leading to reduced ATP formation and induction of mitochondrial permeability transition by opening of the permeability transition pore, which dissipates the mitochondrial membrane potential ($\Delta\psi_m$). These events result in cessation of electron transport and ATP formation, mitochondrial swelling, and permeabilization of the outer mitochondrial membrane, allowing the efflux of several proapoptotic molecules, including cytochrome *c* and apoptosis-inducing factor (AIF). In turn, cytochrome *c* and AIF activate a series of downstream effectors that eventually lead to the fragmentation of nuclear DNA. In addition to its damaging effects on mitochondria, peroxynitrite inflicts more or less severe oxidative injury to DNA, resulting in DNA

strand breakage which in turn activates the nuclear enzyme poly(ADP-ribose) polymerase (PARP). Activated PARP consumes NAD to build-up poly(ADP-ribose) polymers (PAR), which are themselves rapidly metabolized by the activity of poly(ADP-ribose) glycohydrolase (PARG). Some free PAR may exit the nucleus and travel to the mitochondria, where they amplify the mitochondrial efflux of AIF (nuclear to mitochondria cross-talk). Mild damage of DNA activates the DNA repair machinery. On the contrary, once excessive oxidative and nitrosative stress-induced DNA damage occurs, like in various forms of reperfusion injury and other pathophysiological conditions, the cell may be executed by apoptosis in case of moderate PTP opening and PARP activation with preservation of cellular ATP, or by necrosis in the case of widespread PTP opening and PARP overactivation, leading to massive NAD consumption and collapse of cellular ATP. [Derived from Pacher et al. (**995**) with permission from Elsevier.]

While initial studies looking at peroxynitrite-mediated cell death pointed to necrosis as the main death pathway triggered by this species, it soon became evident that apoptosis was also a characteristic consequence of peroxynitrite exposure (**115**). An early study by Salgo et al. (**1105**), indicating peroxynitrite's ability to trigger apoptosis in cultured thymocytes, was rapidly followed by numerous reports confirming similar results in virtually every cell type examined. For example, peroxynitrite has been associated with apoptosis in HL-60 cells (**773**), PC12 cells (**367**), fibroblasts (**1064**), SN 4741 dopaminergic neurons (**1148**), SH-SY5Y neuroblastoma cells (**1101**), primary neurons (**115**, **370**, **664**, **665**), astrocytes (**1452**) and oligodendrocytes (**1439**), endothelial cells (**319**, **1339**), beta islet cells (**309**, **1210**), neutrophils (**408**, **1267**), chondrocytes (**1366**), cardiomyocytes (**30**, **750**), and renal tubular cells (**13**).

Several mechanisms have been proposed to explain the activation of the apoptotic program by peroxynitrite, which appear largely dependent on the cell type studied and the experimental conditions (**1334**). However, a common pathway involving the mitochondria and permeabilization of their outer membrane is emerging as a key feature of peroxynitrite-mediated apoptosis. Mitochondrial outer membrane permeabilization (MOMP) allows the efflux of various proapoptotic signaling molecules, which promote cell death via both caspase-dependent (e.g., cytochrome *c*, APAF-1, Smac/DIABLO) and caspase-independent (especially apoptosis-inducing factor) mechanisms (**121**, **533**). MOMP may either be triggered by the formation of pores within the outer membrane by proapoptotic proteins (e.g., Bid, Bax, and Bak), a process inhibited by antiapoptotic Bcl-2 and bcl-XL proteins, or by a phenomenon termed mitochondrial permeability transition (MPT) (**29**), which is a prominent feature of peroxynitrite-mediated cell death. MPT describes the permeabilization of the inner mitochondrial membrane by a multiprotein complex termed the permeability transition pore, which is composed of the adenine nucleotide translocase (ANT), cyclophilin D (CyP-D) and the voltage-dependent anion channel (VDAC). Formation of the permeability transition pore is triggered by calcium overload or by oxidative modifications of critical thiol groups within the ANT, allowing its interaction with CyP-D. The permeability transition pore results in the dissipation of mitochondrial membrane potential ($\Delta\psi_m$), cessation of electron transfer and ATP production, and the secondary production of reactive oxygen species within the mitochondria, which further amplify the phenomenon. Finally, the permeability transition pore induces mitochondrial swelling and rupture of the outer membrane with subsequent efflux of the above-mentioned proapoptotic molecules. Depending on the degree of MPT, cells may either recover (minimal MPT) or die by apoptosis (moderate or transient MPT, with maintained ATP production) or necrosis (widespread and irreversible MPT, leading to severe ATP depletion) (**982**,**984**, **1356**).

Permeability transition pore opening in response to peroxynitrite has been documented in isolated mitochondria (**118**, **142**, **1127**, **1326**), where it is likely to occur as a consequence of peroxynitrite-mediated oxidation of cysteine-bound thiols in the ANT (**1326**). Recent indications that calcium overload enhances PTP opening by peroxynitrite suggest that calcium-dependent sensitization of certain mitochondrial proteins to oxidative/nitrative damage is critical for apoptosis to proceed following peroxynitrite exposure (**142**). At the cellular level, dissipation of mitochondrial potential (**216**, **758**, **1148**, **1332**, **1339**), mitochondrial efflux of cytochrome *c* (**758**, **1339**), and caspase activation (**1148**, **1339**) occurred to various extents in different cells exposed to endogenously produced or exogenously added peroxynitrite, for example, PC12 cells (**758**), astrocytes (**216**), thymocytes (**1332**), and cardiomyocytes (**30**) (**750**). The finding that these events can be prevented by the upregulation of the antiapoptotic protein Bcl-2 (**1148**, **1326**, **1332**) further emphasizes the essential role of mitochondria in peroxynitrite-triggered apoptosis. According to recent results, permeability transition pore opening secondary to peroxynitrite can also elicit AIF efflux and caspase-independent cell death (**1436**, **1451**). Gabor Szabo's group (**82**) has proposed that this mechanism might participate to the phenomenon of vascular restenosis, a serious complication of arterial endarterectomy that is due to neointima proliferation.

In addition to directly targeting the mitochondria, peroxynitrite can also activate cell death mechanisms through the modulation of various cell signal transduction processes. The role of mitogen-activated protein kinases (MAPKs) and Akt (protein kinase B) deserves some comment here, though more details on these cascades are given in section V. MAPKs comprise three distinct members, ERK, JNK, and p38, whose activation regulates many critical cellular functions, notably apoptosis, and which are strongly activated by peroxynitrite in vitro. The peroxynitrite-mediated activation of ERK committed bronchial (**922**) and neural cells (**645**, **1099**, **1420**) to apoptotic cell death, while activation of JNK, p38, or both triggered a similar outcome in murine alveolar cells (**1162**), cerebrocortical neurons (**120**), and PC12 cells (**1148**), respectively. Recent reports have shown that the release of free Zn^{2+} by peroxynitrite, possibly due to oxidation of Zn^{2+}-sulfur bridges in mitochondrial and cytosolic proteins (**120**, **245**, **1469**), could play an essential role in initiating these responses (**120**, **1439**, **1440**). Indeed, treatment with zinc chelators impaired ERK (**1439**) and p38 (**120**, **1439**, **1440**) activation and attenuated peroxynitrite-mediated apoptosis in cells from glial (**1439**) and neuronal (**120**, **1440**) origin. In contrast to the activation of MAPKs, peroxynitrite has been associated with significant inhibition of protein kinase B (Akt), a serine-threonine protein kinase whose activation represents a powerful protective mechanism to limit apoptosis in various stress conditions, including oxidative stress (**848**). Peroxynitrite blocked the activation of Akt in macrophages (**536**), adipocytes (**949**), PC12 cells (**1148**, **1193**), and endothelial cells (**353**, **485**–**487**, **1471**), through a mechanism involving nitration and inactivation of phosphatidylinositol 3-kinase, the upstream signaling intermediate in the Akt pathway (**353**, **536**). In several of these cell systems, overexpression of a constitutively active Akt completely masked the proapoptotic effects of peroxynitrite (**353**, **1148**), implicating a direct link between Akt inhibition and apoptosis in these experimental conditions.

2. Peroxynitrite and necrosis: the role of PARP

Whereas apoptosis is a typical consequence of low to moderate concentrations of peroxynitrite, exposure of cells to higher concentrations of the oxidant has been associated with necrosis

(115,1334). Studies investigating this process have established that peroxynitrite-dependent cell necrosis is not a purely passive phenomenon, but instead is mediated by a complex process involving DNA damage and activation of the DNA repair enzyme PARP-1 (1243). PARP-1 is a member of the PARP enzyme family consisting of PARP-1 and many additional poly(ADP-ribosylating) enzymes. PARP-1 detects and signals DNA strand breaks induced by a variety of genotoxic insults, including ionizing radiations, alkylating agents, oxidants (essentially hydrogen peroxide, peroxynitrite, and possibly nitroxyl anion), and free radicals (mainly carbonate or hydroxyl radical) (299, 696, 1230). Upon binding to DNA strand breaks, PARP transfers ADP-ribose units from the respiratory coenzyme nicotinamide adenine dinucleotide (NAD^+) to various nuclear proteins (e.g., DNA polymerase, histones, and an automodification domain of PARP itself), building up large ADP-ribose polymers that may reach up to 200 units (1150). These posttranslational modifications are transient in nature, and the modified proteins are rapidly restored to their native state by the activity of the enzyme poly(ADP-ribose) glycohydrolase (PARG) (288). From a physiological view point, PARP-1 activity and poly(ADP)-ribosylation reactions are implicated in DNA repair processes, the maintenance of genomic stability, the regulation of gene transcription, and DNA replication (539, 1150, 1165).

An important function of PARP-1 is to allow DNA repair and cell recovery in conditions associated with a low degree of DNA damage. Upon severe DNA injury, overactivation of PARP-1 depletes the cellular stores of NAD^+, an essential cofactor of the glycolytic pathway, the tricarboxylic acid cycle, and the mitochondrial electron transport chain (762, 769, 1227, 1243). As a result, the loss of NAD^+ leads to a marked decrease in the cellular pools of ATP, resulting in cellular dysfunction and cell death via the necrotic pathway (503, 765) (Fig. 7). This intriguing mode of cell response to acute genotoxic stress led Berger (86) to propose the "suicide hypothesis" of PARP activation, which can be regarded as a way to eliminate cells after irreversible DNA injury. Evidence has been gathered that both exogenous and endogenously generated peroxynitrite potently induce DNA strand breakage leading to PARP activation in a variety of cell types, including pulmonary (1239) and intestinal epithelial cells (666), vascular endothelial and smooth muscle cells (430,1233), fibroblasts (1240), macrophages (1462), and cardiomyocytes (444, 987, 992), to cite just a few examples. These effects have been correlated with steady reductions of cellular NAD^+ and ATP pools and the induction of necrosis, which could be prevented either by pharmacological inhibition or genetic deletion of PARP-1, as reviewed in Refs. 1227, 1334. A vast amount of experimental studies have then established that the PARP-1 pathway of cell death plays pivotal roles in tissue injury and organ dysfunction in virtually every disease process accompanied by oxidative/nitrosative stress: ischemia-reperfusion, localized and systemic inflammation, diabetes, and circulatory shock to name but a few (for extensive recent reviews on this topics, see Refs.248, 254, 373, 624, 821, 959, 995, 997, 1228, 1245, 1306). An important point to make clear at this stage is the essential distinction between PARP activation, which triggers necrosis by ATP depletion, and PARP cleavage, which is a typical feature of apoptosis. In fact, the caspase-mediated cleavage of PARP into 89- and 24-kDa fragments inactivates the enzyme by destroying its ability to respond to DNA strand breaks, thereby preventing the loss of cellular ATP associated with PARP activation and thereby allowing the maintenance of the cellular energy essential for the execution of apoptosis. As such, PARP cleavage has been proposed to function as a molecular switch between apoptotic and necrotic modes of cell death (122, 750, 792).

Besides its well-described function as an inducer of necrotic cell death, two recently discovered roles of PARP have been described. The first one involves the role of PARP in regulating the mitochondria-to-nucleus translocation of apoptosis-inducing factor (AIF). AIF is a 67-kDa mitochondrial death promoting protein, which induces DNA fragmentation by triggering the activation of a yet unidentified nuclease (**1216**). Recent results have indicated that PARP-1 activity is essential for AIF to translocate to the nucleus in cells exposed to oxidative stress, as shown by the lack of AIF translocation in cells with genetic suppression or pharmacological inhibition of PARP-1. As such, AIF is currently believed to play an important role in PARP-1-dependent cell death (**696**, **1424**). Although preliminary, these results support the notion that a nuclear mitochondrial cross-talk dependent on poly(ADP)-ribosylation is critical in determining the fate of oxidatively injured cells (**696**). According to most recent findings, this cross-talk involves a PARP-1-dependent activation of the MAPK JNK1 via a pathway using members of the tumor necrosis factor (TNF) signaling cascade (RIP1 and TRAF2) (**1399**). Obviously, further studies are required to clarify this intriguing aspect of PARP1 biology.

The second additional role of PARP-1 is its involvement in the upregulation of inflammatory processes. The absence of functional PARP-1 (either genetic or pharmacological) alleviated the expression of a host of proinflammatory mediators, including cytokines, chemokines, adhesion molecules and enzymes (e.g., iNOS, COX-2), and it also reduced tissue infiltration with activated phagocytes in experimental models of inflammation, circulatory shock, and ischemia-reperfusion (see Refs. **361**, **765**, **1230** for review). The proinflammatory function of PARP was initially believed to reflect exclusively its role as an inducer of cell necrosis, which promotes inflammation via the spilling of noxious cellular debris into neighboring tissues. However, this concept was reviewed after the demonstration by Oliver et al. (**973**) of a functional association between PARP-1 and the proinflammatory transcription factor nuclear factor kappa B (NFκB). In vitro, these investigators found deficient NFκB transcriptional activation induced by TNF-α in cells genetically deficient in PARP-1 (**973**). They also reported that the administration of lipopolysaccharide (LPS) in vivo resulted in NFκB activation in macrophages harvested from PARP wild-type, but not PARP-1 knockout, mice (**973**). This effect was associated with a massive reduction in the expression of iNOS, TNF-α, and interferon (IFN)-γ, which provided a complete protection against endotoxin lethality in PARP-1$^{-/-}$ animals (**973**). These seminal observations have been extended to show that PARP-1 further participates to the activation of other essential proinflammatory signaling cascades, including JNK (**1458**, **1459**) and p38 MAPKs (**501**), as well as the transcription factors activator-protein-1 (AP-1), stimulating factor-1 (Sp-1), octamer-binding transcription factor-1 (Oct-1), Yin Yang-1 (YY-1), and signal transducer and activator of transcription-1 (STAT-1) (**502**).

In summary, a large body of experimental evidence accumulated over the past 15 years indicates that peroxynitrite generation from NO and $O_2^{\cdot-}$ represents a major threat in the cellular environment. The damaging potential of peroxynitrite is explained by its peculiar chemistry involving direct oxidation as well as radical-mediated nitration reactions. These properties allow peroxynitrite to significantly alter the function of a considerable number of proteins, to degrade membrane structure by peroxidizing lipids, to turn off crucial metabolic functions within mitochondria, and to inflict serious damage to nucleic acids, activating a major pathway of cell injury and inflammation orchestrated by the nuclear enzyme PARP. Once severe enough to overwhelm repair mechanism, these various cytotoxic effects commit cells to death, either through the necrotic or apoptotic pathway. In the living organism, the aggressive behavior of peroxynitrite is emerging as an essential triggering mechanism in the initiation and progression

of a large number of acute and chronic diseases. The current state of knowledge regarding these pathological aspects of peroxynitrite in vivo is explored in the next sections of this review.

V. PEROXYNITRITE AND CELL SIGNALING

The concept of cell signaling defines the ability of cells to detect changes in their environment to generate an appropriate physiological response (**1362**). In the past few years, significant experimental efforts have been put forward to explore the relationships between cellular oxidative processes and the modulation of cell signal transduction, collectively grouped under the concept of "redox signaling" (**848**). The early observation that NO could regulate many critical cell signaling processes through *S*-nitrosylation of critical cysteine residues in proteins was a milestone discovery in our understanding of redox regulation of signal transduction (**1200**). Soon thereafter, the identification of peroxynitrite's ability to nitrate tyrosine residues rapidly focused attention on phosphorylation cascades, as this protein modification was found to inhibit cell signaling processes relying on tyrosine phosphorylation. Although this view was initially strongly considered, it proved to be overly simplistic, as peroxynitrite often promoted phosphotyrosine signaling in many instances. Further evidence was gathered that, in many different cell systems in vitro, peroxynitrite behaved as a potent modulator of an array of cell signal transduction pathways, independently from its ability to nitrate tyrosine. After a brief summary of the main cell signal transduction pathways, these emerging aspects of peroxynitrite biology are discussed in detail.

A. An Overview of Cell Signal Transduction

Most extracellular signals are sensed by two major families of cell membrane receptors, G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (**1362**). GPCRs interact with G proteins (guanine nucleotide binding proteins), which act on several downstream effectors to generate second messengers such as inositol trisphosphate, cyclic nucleotides, or Ca^{2+}, which in turn modulate the degree of protein phosphorylation. GPCRs also activate small G proteins (Ras and Rho families) that lie upstream of the MAPK superfamily of proteins (see below) (for review, see Refs. **98**, **497**). Receptor tyrosine kinases (RTKs) are transmembrane glycoproteins consisting of at least 13 families, e.g., receptors for insulin and growth factors. Upon binding by specific ligands, RTKs create docking sites for specific phosphotyrosine binding domains to recruit and activate downstream effectors, including Ras-MAPKs, phosphatidylinositol 3-kinase (PI3K), and protein kinase C. RTKs control most fundamental cellular processes such as cell proliferation, differentiation, and cell survival, and abnormal RTK-dependent signaling has been linked to a number of disease processes, notably cancer and cardiovascular diseases (for review, see Refs.**577**, **1129**).

The cornerstone of signal transduction is represented by reversible protein phosphorylation, controlled both at the level of phosphorylation (kinases) and dephosphorylation (phosphatases). Protein kinases transfer a phosphate to specific amino acids (tyrosine, serine, and threonine) and are defined as tyrosine kinases or serine/threonine kinases. Tyrosine kinases comprise receptor and non-receptor tyrosine kinases (RTKs and NRTKs, respectively). NRTKs are activated by GPCRs and RTKs and represent integral components of the signaling cascades triggered by cell surface receptors (**1362**). The three main members of NRTKs are the Janus kinases (JAKs),

involved in cytokine signaling (**1067**), focal adhesion kinase (FAK), which transmits adhesion-dependent signals (**861**), and src kinases, which are essential integrators of signals triggered by growth factor receptors, GPCRs, and cytokine receptors (**796**, **1274**).
The major subtypes of serine-threonine kinases are protein kinase A (PKA), which modulates cell metabolism, synaptic transmission, and ion channel activity (reviewed in Ref. **382**), protein kinase B (PKB), an inhibitor of apoptosis that also plays roles in glucose metabolism and cell proliferation (for review, see Ref. **512**), protein kinase C (PKC), involved in the regulation of cell growth and differentiation, cell death, and stress responsiveness (**174**), and the MAPKs. MAPKs comprise extracellular signal-regulated protein kinase (ERK), which mainly transduces signals involved in cell proliferation, p38 MAPK, and c-Jun NH_2-terminal kinase (JNK) (**652**), which are both linked to stress and therefore collectively termed stress-activated protein kinases (SAPKs). The MAPKs have multiple downstream targets, activation of which regulate virtually every critical cellular functions (**1048**). An additional pathway involves NFκB, a crucial transcription factor involved in inflammatory and antiapoptotic signaling, which is activated in response to serine phosphorylation of an upstream kinase complex termed IKK (**116**). The rapid reversibility of phosphorylation is a key point of signaling, catalyzed by three types of protein phosphatases, including tyrosine, serine/threonine, and dual-specificity phosphatases, which have been the matter of several recent reviews (**1126**, **1206**, **1283**). Dephosphorylation is as tightly regulated as phosphorylation by modulatory proteins that associate with the phosphatases.

B. Modulation of Cell Signaling by Peroxynitrite

1. Inhibition of phosphotyrosine-dependent signaling

The ability of peroxynitrite to nitrate tyrosine residues can impair signaling processes depending on tyrosine phosphorylation. Early in vitro studies using peptide substrates showed that phosphorylation of critical tyrosine residues within these peptides was markedly inhibited by peroxynitrite-mediated tyrosine nitration (**463**, **702**), and further results indicated that tyrosine nitration blocked downstream signaling in intact cell systems in vitro. In the human neuroblastoma SH-SY5Y cells, the peroxynitrite generator SIN-1 triggered the nitration of the focal adhesion protein $p130^{cas}$, resulting in the blockade of its phosphorylation and interfered with the assembly of focal adhesion complexes (**1100**). Also, peroxynitrite-dependent nitration of a key tyrosine residue (Tyr686) within the cytoplasmic domain of the adhesion molecule platelet-endothelial cell adhesion molecule-1 (PECAM-1), interfered with its phosphorylation by src family protein kinases, and prevented its binding to the protein-tyrosine phosphatase SHP-2 (**941**).
The impairment of tyrosine phosphorylation by peroxynitrite may affect various fundamental cellular functions. For example, in T lymphocytes, peroxynitrite triggered widespread protein nitration and blocked tyrosine phosphorylation in response to cell activation through the T-cell receptor (TCR)/CD3 complex. This resulted in a depressed proliferative response of activated T cells, suggesting that peroxynitrite might negatively affect normal immune responses depending on T cells in vivo (**137**). Similarly, nitrotyrosine formation in human platelets inhibited tyrosine phosphorylation in response to thrombin, thereby preventing their activation (**795**, **896**). Under certain conditions, competition between nitration and phosphorylation on a single tyrosine residue may completely disrupt a complex chain of signal transduction, as recently shown in primary rat hepatocytes. These cells undergo apoptotic cell death upon stimulation with CD95

(Fas) ligand, through a pathway requiring epidermal growth factor receptor (EGFR) activation followed by EGFR-mediated CD95 tyrosine phosphorylation. Activated CD95 then promotes the formation of a death-inducing signal complex (DISC), committing the cell to apoptosis. In the presence of a short pretreatment with peroxynitrite, CD95 becomes tyrosine nitrated, completely blocking its phosphorylation by activated EGFR, preventing the formation of DISC and the induction of the apoptotic program (**1072**).

2. Activation of phosphotyrosine-dependent signaling

The initial hypothesis that tyrosine nitration would essentially inhibit phosphotyrosine-dependent cell signaling has been largely reviewed at the light of multiple observations indicating that peroxynitrite promoted, rather than inhibited, tyrosine phosphorylation in a variety of cell types, including red blood cells (**823**, **836**–**840**), bovine brain synaptosomes (**318**), SH-SY5Y cells (**760**), pancreatic adenocarcinoma cells (**829**), and endothelial cells (**1470**). Furthermore, the realization that peroxynitrite, in a myriad of distinct cell types, strongly activates all MAPK family members (see specific section below), which depend on the upstream activation of various protein tyrosine-kinases, further endorsed the ability of peroxynitrite to regulate positively tyrosine phosphorylation.

Two salient features of phosphotyrosine signaling upregulation by peroxynitrite were generally demonstrated: its transient and reversible nature (a typical aspect of cell signaling processes) and its dependence on relatively low bolus additions of 10–200 μM, consistent with a signaling role of peroxynitrite in vivo. Equivalent exposures to endogenous peroxynitrite, as measured by the area under the curve, can be achieved in tissues after a few minutes of sustained peroxynitrite formation. In general, higher concentrations enhanced nitrotyrosine formation (which was generally not reversible) and downregulated phosphotyrosine signaling, suggestive of a direct competition between nitration and phosphorylation of tyrosine at high peroxynitrite concentrations. This has been notably well demonstrated with the band 3 protein of human erythrocytes, a membrane anion-exchange protein whose activation results in a cascade of signaling events stimulating glycolytic activity. Peroxynitrite at 10–100 μM activated band 3 Tyr phosphorylation, resulting in the activation of glycolysis, whereas higher concentrations (200–1,000 μM) induced band 3 nitration, blocked its phosphorylation, and irreversibly inhibited glycolysis (**839**). What, then, explains the phosphorylation of tyrosine at (relatively) low peroxynitrite concentrations? As mentioned earlier, the upregulation of phosphotyrosine signaling reflects either the inhibition of phosphotyrosine phosphatases (PTPs) or the activation of phosphotyrosine kinases (PTKs). Recent evidence indicates that peroxynitrite can act on these two levels of regulation.

First, irreversible inhibition of PTPs by very low concentrations of peroxynitrite has been demonstrated both in cells (**791**, **839**) and purified enzymes (**175**, **1254**). All PTPs contain a conserved cysteine residue, which forms an intermediate phosphocysteine with the phosphatase substrate of the PTP, and oxidation of this critical cysteine has been shown to inactivate the PTPs (**1254**). Peroxynitrite anion is structurally similar to phosphate anion, so that the extreme vulnerability of PTPs to peroxynitrite-mediated inactivation is consistent with attraction of peroxynitrite to the active site of the enzyme and subsequent oxidation of this essential cysteine (**1254**).

The second mechanism of phosphotyrosine upregulation by peroxynitrite relies on the direct activation of protein tyrosine kinases. Receptor tyrosine kinases, notably the growth factor

receptors EGFR and PDGFR, undergo Tyr phosphorylation upon exposure to oxidants, through mechanisms that remain only partially defined. Tyr phosphorylation and activation of EGFR by peroxynitrite has been reported in human skin fibroblasts (**687**) and rat lung myofibroblasts (**1434**), while PDGFR activation occurred in fibroblasts, where it was followed by the downstream activation of the antiapoptotic PI3K/Akt signaling pathway (**687**). Similarly, peroxynitrite triggered phosphorylation of TrkB, the receptor for brain-derived neurotrophic factor and activated downstream phospholipase C signaling in 3T3 murine fibroblasts (**1427**). Such activation, however, appears highly cell specific, in view of the contrasted results obtained in other cell systems. Indeed, in A431 epidermoid carcinoma cells, EGFR was shown to dimerize covalently upon treatment with peroxynitrite, with no increased activity in terms of autophosphorylation; rather, the activation by EGF of a downstream molecule, phospholipase C-γ1, was attenuated (**1316**). Also, peroxynitrite-dependent nitration of EGFR prevented its phosphorylation in intestinal Caco-2 cells and blocked cell proliferation in response to EGF stimulation (**1301**).

Several independent groups have provided strong experimental support implicating the NRTK family member Src as a preferential target of peroxynitrite. Src family members participate in a variety of signaling processes, including mitogenesis, T- and B-cell activation, cell differentiation and proliferation, as well as cytoskeleton restructuring, through the activation of an array of downstream effectors such as PI3K, phospholipase C, and FAK (**1087**). Activation of src kinases by peroxynitrite has been demonstrated in red blood cells (**836**–**838**, **840**), brain synaptosomes (**837**), pancreatic adenocarcinoma cells (**829**), SH-SY5Y cells (**760**), bovine endothelial cells (**1470**), PC12 cells (**638**), and rat astrocytes (**519**).

The particular mechanism of regulation of src kinases helps explain why these kinases are so susceptible to the action of peroxynitrite. Src members possess a common structure, with a tyrosine kinase domain and two conserved protein-protein interaction domains, SH2 and SH3, which create docking sites for phosphotyrosine and proline-containing sequences, respectively (**1087**). The catalytic activity of src kinases is tightly regulated in two opposite ways by phosphorylation of two distinct tyrosine residues. Phosphorylation of Tyr-527 within the COOH-terminal domain induces its binding to SH2, which maintains the kinase in a closed conformation. Dephosphorylation of Tyr-527 by various phosphatases opens the structure and activates the kinase (**796**, **1087**, **1274**). Alternatively, the activation of src is promoted by autophosphorylation of Tyr-416 within the catalytic domain and may further be triggered by oxidation of specific cysteines within the COOH-terminal domain (**10**, **1045**).

Two distinct mechanisms of activation of src kinases by peroxynitrite have been identified. In human red blood cells, the src kinase *hck* was activated by peroxynitrite via cysteine oxidation, whereas another src kinase, *lyn*, was activated through a mechanism involving the inhibition of Tyr527 binding to the SH2 domain (**838**, **840**). In fact, several tyrosine-containing peptides were also able to activate *lyn* when the tyrosine was substituted with 3-nitrotyrosine, by displacing phosphotyrosine 527 from its binding site within the SH2 domain (**838**). This is not completely surprising, since nitration has the effect of decreasing the pK_a of phenoxyl groups in free tyrosine from 10 to ~7.2. This effectively produces a negative charge on the tyrosine and thus mimics the change imposed by phosphorylation (**887**). Mallozzi et al. (**838**) proposed the hypothesis that, in erythrocytes, peroxynitrite would preferentially induce nitration of the band 3 protein and that nitrotyrosine-containing band 3 would then divert SH2 binding to Tyr-527 of *lyn*, fostering its activation. These findings are of great biological significance, as they suggest that tyrosine nitration may represent a gain-of-function in the regulation of *src* kinases, with potential

consequences in several pathological conditions. Indeed, upregulation of *src* kinases may induce rapid and uncontrolled cell growth and transformation, which might link peroxynitrite to carcinogenesis.

3. Peroxynitrite and MAPK signaling

MAPKs (ERK, JNK, and p38) are all activated by a dual phosphorylation at a specific tripeptide motif, mediated by a conserved protein kinase cascade, involving MAP kinase kinase kinases (MKKK or MEKK) and MAP kinase kinases (MKK or MEK) (**328**). The upstream signaling pathways leading to MKKK activation largely depend on the activation of growth factor receptors and small G proteins, such as Ras, Rac, and Cdc42 (**328**, **848**). Downstream targets of MAPKs include an array of proteins as well as transcription factors, whose activation regulates virtually every critical cellular function, especially apoptosis, cell proliferation, and inflammatory genes expression. The particular mode of MAPK activation, as well as some evidence indicating their activation by peroxynitrite, is depicted in **Figure 8**.

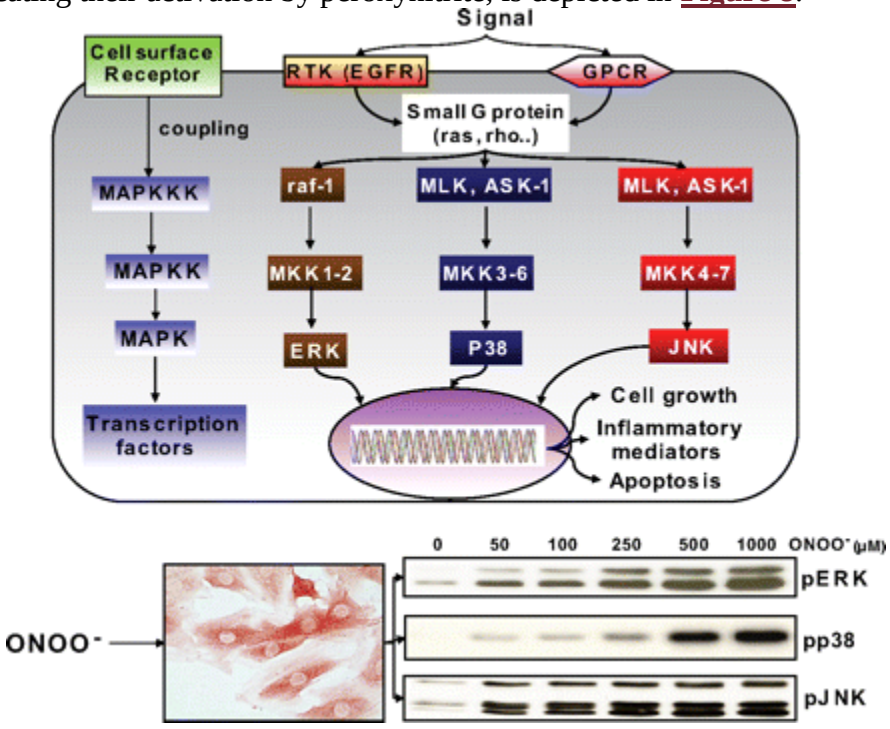

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FIG. 8.

Schematic diagram of mitogen-activated protein kinase (MAPK) signaling and stimulating effects of peroxynitrite. MAPKs are activated by a dual phosphorylation at a specific tripeptide motif, as indicated on the *left*, mediated by a conserved protein kinase cascade, involving MAPK kinases (MAPKK or MKK) and MAPK kinase kinases (MAPKKK or MKKK). The activation of the upstream MKKK is mediated by various cell surface receptors, including G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTK),

such as the receptor for epidermal growth factor (EGFR), which activate several small G proteins, such as Ras, Rho, Rac, and Cdc42. Three groups of MAPKs exist in mammalian cells, including extracellular signal-regulated protein kinase (ERK), p38 MAPK, and the c-Jun NH_2-terminal kinase (JNK), whose upstream signaling intermediates include raf-1 and MKK1–2 (ERK pathway), MLK/Ask-1 (mixed lineage kinase/apoptosis-signal regulating kinase-1) and MEK 3–6 (p38), and MLK-1/Ask-1 and MKK 4–7 (JNK). Downstream targets of MAPKs are transcription factors, enzymes, and various proteins, which regulate cell growth, apoptosis, as well as inflammation. The Western blots at the *bottom* show the activation pattern of the three MAPKs, evidenced by their phosphorylation, induced in the cardiomyoblast cell line H9C2 by treatment with increasing concentrations of peroxynitrite. [Adapted from Pesse et al. (**1024**).]

A) ERK PATHWAY.

ERK is involved in the signaling pathways triggered by growth factors and their receptors, via the successive activation of the small G protein ras, Raf-1 kinase and MEK 1 (**1434**). ERK can also be activated by various extracellular stresses, including oxidants and free radicals (**848**). In vitro, peroxynitrite potently activated ERK in fibroblasts (**57**, **1434**), neutrophils (**735**, **1477**), endothelial and vascular smooth muscle cells (**1307**), neural cells (**191**, **638**, **645**, **1099**), and cardiomyocytes (**1024**), through strikingly distinct and cell-specific mechanisms. In PC 12 cells, ERK activation occurred via activation of EGFR, in a src tyrosine kinase- and calcium/calmodulin-dependent manner (**638**), whereas in human neutrophils, ERK activation was associated with the concomitant activation of ras, Raf-1, and MEK (**1477**). We recently provided evidence that peroxynitrite activates ERK in H9C2 cardiomyocytes via the upstream activation of Raf-1 and MEK, independently from ras and EGFR activation (**1024**). We proposed that Raf-MEK-ERK activation by peroxynitrite was due to oxidative, but not nitrative, modifications since it was unaffected by epicatechin (**1024**), a potent inhibitor of nitration reactions (**1134**). Such findings contrasted with those of Zhang et al. (**1434**), who found that ERK activation depended entirely on tyrosine nitration of MEK in rat lung myofibroblast. An additional mechanism of ERK activation by peroxynitrite, relying on a direct interaction with a calcium-dependent PKC isoform, has also been reported in rat-1 fibroblasts (**57**).
Information regarding the consequences of ERK activation in response to peroxynitrite remains limited. In human neutrophils, ERK activation by peroxynitrite (up to 200 μM) has been associated with the upregulation of surface expression of the β_2-integrins CD11b/CD18 and increased neutrophil adhesion to endothelial cells (**1477**), as well as an enhanced oxidative burst upon stimulation (**735**). These data then support a potential role of peroxynitrite in mediating excessive neutrophil trafficking and superoxide generation under inflammatory conditions.
Another important aspect of ERK activation by peroxynitrite is related to apoptosis. Of note, the role of ERK in apoptosis is not uniform, acting either as an antiapoptotic, or proapoptotic signaling pathway, depending on the kinetics of its activation and on the kind of activating stimulus (**848**). With respect to peroxynitrite stimulation, it is noticeable that all studies performed so far have indicated a proapoptotic role of ERK. Indeed, peroxynitrite-induced apoptosis in primary rat astrocytes (**1420**), human SH-SY5Y neuroblastoma cells (**1099**), human bronchial epithelial BEAS-2B cells (**922**), and primary murine neurons (**645**) was associated with the activation of ERK and was significantly attenuated by MEK-ERK pathway inhibitors. The mechanisms linking ERK activation with apoptosis after peroxynitrite stimulation are poorly

understood, but may involve a ras/ERK-dependent activation of the proapoptotic protein p53 in response to peroxynitrite, as demonstrated in primary neural cells (**645**).

B) JNK PATHWAY.

JNK exists as three distinct isoforms, activated in response to many different environmental stresses via a signaling cascade involving the small G proteins ras and rac, several MAPKKKs, MAPKK, MKK1, and MKK4, linked together by various scaffold proteins in specific signaling modules (**198**, **291**). Activated JNK phosphorylates the protoconcogene product c-*jun*, allowing its homodimerization or heterodimerization with c-*fos* to form the active transcription factor AP-1. JNK is involved in the regulation of inflammation and cell death, with both pro- and antiapoptotic reported functions (**198**, **291**).
JNK activation in response to peroxynitrite has been reported in many different cell types (**23**,**450**, **922**, **1024**, **1128**, **1162**), but the mechanisms and outcome of JNK activation have only been addressed in two distinct studies. Go et al. (**450**) showed that endogenously produced peroxynitrite was responsible for the activation of JNK triggered by laminar shear stress in endothelial cells (**450**). Importantly, laminar shear stress is a key mechanism protecting blood vessels from the development of atherosclerosis, and JNK activation might be crucial for that function. The study by Go et al. (**450**) thus has important physiological implications, as it suggests that peroxynitrite could represent a fundamental signaling device connecting mechanical stress to such protective responses. A second study revealed that JNK activation by peroxynitrite was causally linked to apoptotic cell death in murine alveolar C10 cells, as cells expressing a dominant negative mutant of JNK1 were protected from peroxynitrite-mediated apoptosis (**1162**). The mechanism of JNK activation involved oxidation and aggregation of the death receptor Fas, followed by the recruitment of Fas-associated death domain (FADD) and subsequent activation of JNK (**1162**), a signaling cascade which might partly explain the apoptosis of lung epithelial cells occurring in chronic lung inflammatory diseases, where high levels of peroxynitrite have been reported (**628**).

C) P38 MAPK.

The p38 family consists of at least five different isoforms: α, β_1, β_2, γ, and δ, whose activation by environmental stress is controlled by several MAPKKKs as well as MKK3 and MKK6. The activation of p38 has been linked with apoptotic cell death and mitotic arrest in a great variety of cells exposed to different oxidants and free radicals (**848**). Peroxynitrite is extremely efficient in activating p38, as shown by the very early (within minutes) phosphorylation of p38 upon peroxynitrite stimulation, even at low concentrations (<10 μM) in cardiomyocytes (**1024**), endothelial (**350**, **450**) and vascular smooth muscle cells (**1307**), hepatocytes (**414**, **1128**), bronchial epithelial cells (**922**), and neural cells (**120**, **638**, **965**, **1120**, **1440**). In most of these cell systems, peroxynitrite-mediated p38 activation could be directly linked to apoptosis, the latter being efficiently prevented by pharmacological inhibitors of p38 (**120**, **922**, **965**, **1120**). As with other signaling cascades triggered by peroxynitrite, the mechanisms activating p38 appear as diverse as the cell type studied. Peroxynitrite activated p38 via MKK3 and MKK6 in response to ERK-dependent activation of cytosolic phosholipase A_2 in human bronchial epithelial cells (**1307**), via the upstream activation of calcium/calmodulin kinase II and src in PC12 cells (**638**), and via the release of Zn^{2+} in primary neurons (**120**, **1440**). The latter mechanism might be set in motion in various neurological disorders (notably stroke and neurodegenerative disorders),

where excessive neuronal NO synthesis and peroxynitrite generation have been associated with enhanced apoptotic cell death in the brain.

4. PI3K/protein kinase B (Akt) pathway

Protein kinase B (Akt) is a serine-threonine protein kinase that plays key roles in integrating cellular responses to growth factors and other extracellular signals. Akt activation also represents an important protective mechanism to limit apoptotic cell death in conditions of oxidative stress (**848**). The activation of Akt critically depends on PI3K signaling, via the generation of 3′-phosphorylated phosphoinositides (**848**).

Data regarding the influence of peroxynitrite on the PI3K-Akt pathway are highly controversial. In human skin fibroblasts, peroxynitrite induced Akt activation in a PDGFR- and PI3K-dependent manner (**687**). Similarly, peroxynitrite activated PI3K and Akt phosphorylation in a rat hepatoma cell line, resulting in the activation of the transcription factor Nrf2/ARE and the induction of the detoxifying enzyme glutathione-*S*-transferase (**652**). Schroeder et al. (**1133**) proposed that thiol oxidation, but not tyrosine nitration, underlies the activation of Akt by peroxynitrite, as the latter was not modified by the nitration inhibitor epicatechin in mouse endothelial cells. In striking contrast, several studies concluded that peroxynitrite inhibited PI3K signaling and the activation of Akt in several cells, including Raw 264.7 macrophages (**536**), 3T3-L1 adipocytes (**949**), PC12 cells (**367**, **1193**), retinal cells (**353**), and bovine endothelial cells (**1471**) via a postulated mechanism involving nitration of a critical tyrosine residue within the p85 regulatory subunit of PI3K (**353**, **536**). It is unclear at present why peroxynitrite exerts such a contrasted influence on a single signaling pathway, but the concentration of peroxynitrite, the type of cell under investigation, and most importantly the particular chemical microenvironment are important issues to consider. In particular, the local content of CO_2 might represent a crucial factor influencing the outcome of PI3K signaling in response to peroxynitrite, given that reaction between CO_2 and peroxynitrite will redirect its chemistry towards radical-mediated nitration reactions (see sect. IV) (**1061**).

5. PKC pathway

PKC represents a family of phospholipid-dependent serine/threonine kinases involved in signaling pathways regulating cell growth and differentiation, cell death, immune response, transcriptional regulation, and stress responsiveness (notably oxidative stress) (**458**, **848**). PKC-mediated cellular effects are both tissue and isoform specific. PKC exists as 11 different isoforms, subdivided in three distinct subgroups (classical PKC α, βI, βII, γ; novel PKC δ, ε, η, θ; and atypical PKC λ, ι, ζ), separated upon their particular mechanism of activation (**45**).

In the heart, an NO-dependent activation of PKC-ε has been implicated in the development of cardioprotection afforded by ischemic preconditioning. A recent study, using both in vitro and in vivo approaches, provided new insights into these mechanisms, by showing that peroxynitrite, rather than NO itself, may be the species responsible for the activation of PKC-ε during preconditioning (**52**). Peroxynitrite-dependent activation of PKC has been further reported in endothelial cells, where it has been linked with the activation of cytosolic phospholipase A_2(cPLA2) and an enhanced release of vasoactive mediators (**195**), a mechanism possibly involved in the phenomenon of nitrate tolerance (**5**). Alternatively, peroxynitrite has been associated with a significant reduction of the activity of PKC α, β, ε, and ζ in neuronal cells, and

the degree of this inhibition correlated completely with the degree of tyrosine nitration within the enzyme (689). Importantly, PKC is essential for a number of aspects of neuronal functions including synaptic plasticity, learning, and memory. Decreased PKC activity may contribute to several neurodegenerative disorders (66, 689), which are also associated with increased peroxynitrite generation (1284). PKC inhibition might thus represent one of the mechanisms linking peroxynitrite in the brain with neurodegeneration.

6. NFκB

NFκB is a crucial transcription factor activating inflammatory and antiapoptotic genes in response to immunostimulation. NFκB is a family of dimeric proteins (p50 and its precursor p105, p52 and its precursor p100, p65 or RelA, RelB, and c-Rel) normally held in the cytoplasm in an inactive form, bound to inhibitory proteins, the IκBs. The critical step in NFκB activation relies on its dissociation from the IκB protein, secondary to phosphorylation and proteasomal degradation of IκB. IκBs are phosphorylated by a protein kinase complex, IκB kinase (IKK), composed of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ (for review, see Refs. 116, 442). The classical ("canonical") pathway of NFκB activation mainly depends on IKKβ and triggers transcription of inflammatory and antiapoptotic genes (205, 340, 477). The alternative pathway ("noncanonical"), which is dependent on IKKα, has been shown to be important for B-cell maturation and lymphoid organ development (306, 330, 1145).

In addition to usual activators of NFκB (mainly cytokines and microbial products), there is ample evidence indicating that reactive oxygen species can also trigger this signaling cascade (449). Only a few studies have addressed the potential role of peroxynitrite. A series of elegant studies from Janos Filep's group in Montreal have shown that peroxynitrite, both exogenously added or endogenously produced in response to LPS, cytokines, or Toll-receptor 9 stimulation, potently activated NFκB and stimulated thereby interleukin (IL)-8 secretion by human polymorphonuclear cells (391, 640, 674, 1476). These studies thus identified an important signaling mechanism by which peroxynitrite amplifies neutrophil-dependent responses under inflammatory conditions. Matata et al. (851) also reported that mononuclear cells exposed to micromolar concentrations of peroxynitrite disclosed NFκB activation and a stimulated production of TNF-α and IL-6. These authors proposed that nitration of tyrosine-42 in IκB might increase its degradation, triggering NFκB activity (851).

The stimulating effect of peroxynitrite on NF-κB is however not so straightforward. Two recently published studies rather proposed that this species functions as a potent repressor of NFκB activation. Park et al. (1006) found that peroxynitrite eliminated both constitutive and stimulated NFκB activities in P19, SH-SY5Y, and HEK293 cells. Liquid chromatography-coupled nanoelectrospray mass spectrometry revealed specific nitration on Tyr-66 and Tyr-152 residues of p65, leading to p65 destabilization, nuclear export, and inactivation of NFκB activity (1006). We further confirmed such observations by demonstrating that a brief exposure to peroxynitrite suppressed NFκB activation triggered by LPS and inflammatory cytokines in cardiac H9C2 cells, as well as endothelial EAHY-926 and HMEC-1 cells. The mechanism underlying such inhibition was a complete inhibition of IKKβ activity in these cells. Intriguingly, whether IKKβ was suppressed, there was a simultaneous activation of IKKα phosphorylation, suggesting that peroxynitrite differentially regulates the classical and the alternative pathways of NFκB activation (749). The ramifications of these effects with respect to inflammation are still

unclear at present, but the results of the two later studies open the unexpected possibility that peroxynitrite might downregulate the expression of proinflammatory mediators and thereby provide a counterregulatory mechanism to prevent overt inflammation in various pathological conditions, an issue that should be more precisely characterized in years to come.

In summary, peroxynitrite exhibits typical properties of a signaling molecule in vitro, either activating or inhibiting several major signal transduction pathways, which are summarized in**Table 2**. Initial studies only considered that peroxynitrite would behave as an inhibitor of phosphotyrosine-dependent signaling, owing to its ability to nitrate tyrosine residues within proteins. However, it rapidly turned out that, in many instances, peroxynitrite rather acted to upregulate an array of signaling cascades, by mechanisms involving the inhibition of phosphatases and the direct activation of many different protein kinases. In spite of this experimental evidence, two major difficulties presently limit the interpretation of these findings: their considerable cell specificity and the lack of confirmation in vivo. Further studies must parse the multiple effects triggered by peroxynitrite in culture on the NFκB in the intact organism to understand the potential pathological relevance of peroxynitrite on this crucial proinflammatory pathway.

VI. NITRIC OXIDE AND PEROXYNITRITE IN DISEASE

A. Nitric Oxide and Peroxynitrite in Cardiac Diseases

Calcium-dependent NOSs are responsible for the generation of NO in cardiomyocytes, endocardial endothelium, coronary endothelium, and cardiac nerves. NO serves many important physiological roles in the regulation of cardiac function including coronary vasodilation, inhibiting platelet and neutrophil adhesion and activation, modulation of cardiac contractile function, and inhibiting cardiac oxygen consumption (**849**, **1014**) (**Fig. 9**). NO is necessary for normal cardiac physiology and plays a protective role in the ischemic heart by numerous mechanisms including stimulation of soluble guanylyl cyclase to decrease of intracellular Ca^{2+} through activation of cGMP-dependent protein kinase, as well as termination of chain-propagating lipid radical reactions caused by oxidative stress (**636**, **1149**) (**Fig. 9**). NO, through its interactions with components of the mitochondrial respiratory chain, may function as a physiological regulator of cell respiration and a modulator of the generation of reactive oxygen species by mitochondria, thereby affecting mechanisms of cell survival or death (**891**). In higher levels, or in the presence of reactive oxygen species, NO can alsoexert cytotoxic effects, potentially through the formation of peroxynitrite (**1149**). The hypothesis that peroxynitrite generation contributes to myocardial and vascular dysfunction during ischemia and reperfusion (I/R), myocarditis, chronic heart failure, and various other cardiovascular pathologies has been the focus of intensive investigations during the last decade.

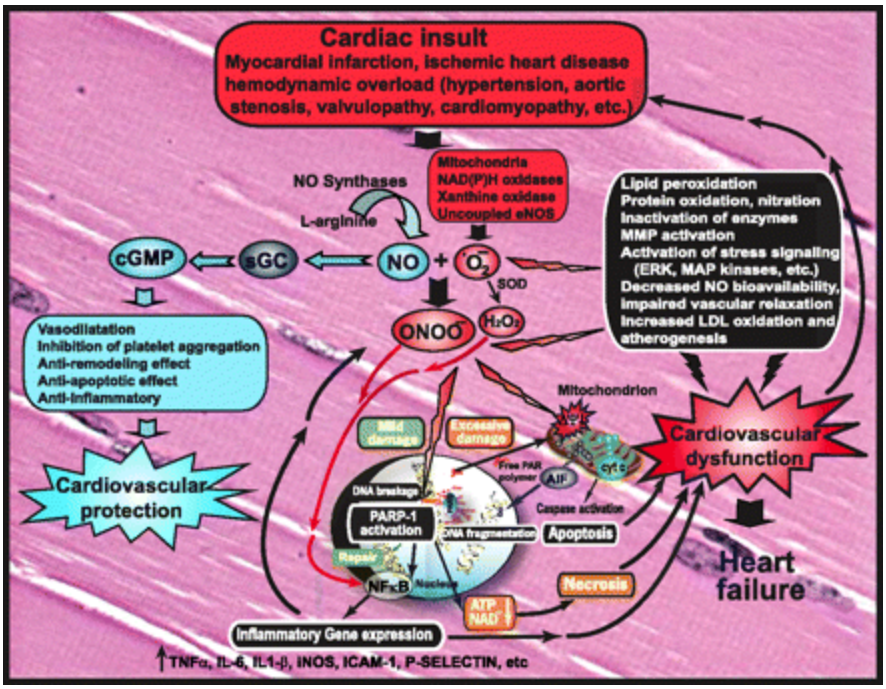

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FIG. 9.

Role of nitric oxide (NO) and peroxynitrite in cardiovascular pathophysiology. On the one hand, NO by activating soluble guanylate cyclase (sGC)-cGMP signal transduction pathway mediates various physiological/beneficial effects in the cardiovascular system including vasodilation, inhibition of platelet aggregation, anti-inflammatory, antiremodelling, and antiapoptotic effects. On the other hand, under pathological conditions associated with increased oxidative stress and inflammation (myocardial infarction, ischemic heart disease, myocarditis, cardiomyopathy, hypertension, etc.), NO and superoxide ($O_2^{\bullet-}$) react to form peroxynitrite ($ONOO^-$) which induces cell damage via lipid peroxidation, inactivation of enzymes and other proteins by oxidation and nitration, and also activation of stress signaling, matrix metalloproteinases (MMPs) among others (see also **Table 2**). Peroxynitrite also triggers the release of proapoptotic factors such as cytochrome *c* and apoptosis-inducing factor (AIF) from the mitochondria, which mediate caspase-dependent and -independent apoptotic death pathways. Moreover, peroxynitrite, in concert with other oxidants, causes stand breaks in DNA, activating the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1). Mild damage of DNA activates the DNA repair machinery. In contrast, once excessive oxidative and nitrosative stress-induced DNA damage occurs, like in various forms of myocardial reperfusion injury and heart failure, overactivated PARP initiates an energy-consuming cycle by transferring ADP-ribose units from nicotinamide adenine dinucleotide (NAD^+) to nuclear proteins, resulting in rapid depletion of the intracellular NAD^+ and ATP pools, slowing the rate of glycolysis and mitochondrial respiration, eventually leading to cellular dysfunction and death. Poly(ADP-ribose) glycohydrolase (PARG) degrades poly(ADP-ribose) (PAR)

polymers, generating free PAR polymer and ADP-ribose. Overactivated PARP also facilitates the expression of a variety of inflammatory genes leading to increased inflammation and associated oxidative stress, thus facilitating the progression of cardiovascular dysfunction and heart failure.

1. Cardiovascular effects of peroxynitrite in vitro and in vivo, potential targets of peroxynitrite-induced toxicity in the cardiovascular system

Experimental studies utilizing isolated cardiomyocytes, endothelial and smooth muscle cells, papillary muscle, and perfused hearts have generally taken two approaches: exogenous application of peroxynitrite or addition of precursors that enter the cells and generate peroxynitrite endogenously (**320**, **790**, **816**, **1135**).

Peroxynitrite has been shown to trigger apoptosis in cardiomyocytes (**30**, **480**, **750**) as well as endothelial (**319**, **879**) and vascular smooth muscle (**755**, **756**) cells, induce decrease in spontaneous contractions of cardiomyocytes (**614**), and cause irreversible inhibition of the mitochondrial respiratory chain (**148**, **1383**). Peroxynitrite also activates ERK, a MAPK which has been linked with hypertrophic and antiapoptotic responses in the heart, and inhibits NFκB activation triggered by inflammatory stimuli in cardiac and endothelial cell lines (**749**, **1024**). Furthermore, it induces the upregulation of adhesion molecules in endothelial cells, the disruption of endothelial glycocalyx, and may enhance the adhesion of neutrophils to the endothelium, through complex interactions with various cell signaling pathways (see sects. IV and V) (**424**, **723**,**1178**, **1447**, **1477**), and depending on the environment can stimulate or inhibit platelet aggregation (**908**, **953**). Peroxynitrite also activates MMPs and nuclear enzyme PARP, which contribute to impaired cardiovascular function in most cardiovascular pathologies and inflammatory disorders discussed below (reviewed in Refs. **624**, **995**, **1333**).

In isolated rat left ventricular papillary muscle preparations, exogenously applied peroxynitrite, or peroxynitrite generated with NO donor *S*-nitroso-*N*-acetyl-D,L-penicillamine (SNAP) plus superoxide-releasing agent pyrogallol, caused an irreversible inhibition of cardiac contractile and respiratory function (**320**, **1396**). Using rat cardiac myofibrils and trabeculae, Mihm and Bauer (**877**) have demonstrated that the myofibrillar isoform of creatine kinase (a critical energetic controller of cardiomyocyte contractility) is a vulnerable target of peroxynitrite-induced nitration and inactivation in vitro (**877**). The extent of nitration was linearly related to peroxynitrite concentration and highly correlated to the extent of myofibrillar creatine kinase inhibition (**877**). Importantly, the creatine kinase-dependent force generation was impaired at peroxynitrite concentrations as low as 50 nM, suggesting potent inactivation of the enzyme. Furthermore, the extent of peroxynitrite-induced tyrosine nitration of myofibrillar creatine kinase negatively correlated to myofibrillar creatine kinase-dependent force generation, suggesting that the cardiac contractile apparatus is a highly sensitive target to peroxynitrite-induced injury, and that myofibrillar creatine kinase may be a uniquely vulnerable target (**882**). Peroxynitrite may also inactivate myocardial aconitase, a critical citric acid cycle enzyme present both in mitochondria and cytosol that converts citrate to isocitrate (**211**). Furthermore, myocardial α-actinin (a cytoskeletal, tyrosine-rich protein crucial for the maintenance of the Z line and for the integrity of the sarcomeres) and sarcoplasmic reticulum Ca^{2+}-ATPase are also potential targets for peroxynitrite-induced protein nitration in human heart (**117**, **789**).

Physiological relevant concentrations of peroxynitrite achieved either by the combination of the NO donor SNAP and pyrogallol (**790**) or by using the peroxynitrite generator 3-

morpholinosidnonimine (SIN-1) (816) also induced ventricular dysfunction and myocardial injury of crystalloid perfused (Langendorff) rat hearts which were attenuated with the addition of the antioxidant agent glutathione, SOD, or MMP inhibitor (816, 1345). However, infusion of peroxynitrite into the working Langendorff rat heart revealed two contrasting effects dependent on concentration (1136). After exposures to a nominal concentration of 3 μM, which, due to the short half-life of peroxynitrite, translates into a more actual exposure in the nanomolar concentration range, vascular responses were severely impaired. Specifically, the vasodilatation elicited by acetylcholine, isoproterenol, or an NO donor were inhibited. Consistently, Mihm et al. (879) have demonstrated that the preincubation of rat thoracic aorta segments with clinically relevant concentrations of 3-nitrotyrosine observed in various pathophysiological states resulted in concentration-dependent impairment of endothelium-dependent vascular relaxation, and induced DNA damage in vascular endothelial cells. They also found a highly statistically significant association between 3-nitrotyrosine-induced endothelial dysfunction and frequency of TUNEL-positive cells, suggesting that DNA fragmentation and/or apoptosis may be an important mechanism of endothelial dysfunction in vivo, and that 3-nitrotyrosine may participate in the initiation of these events (879, 1473). Peroxynitrite was also reported to inhibit voltage-gated K^+K(v) and Ca^{2+}-activated K^+ channels in coronary arterioles (754, 786) and vascular prostacycline synthase (1466, 1467, 1472, 1475). Repetitive exposure to a nominal concentration of 100 μM peroxynitrite, or greater, resulted first in a marked vasodilatation in Langendorff heart preparations, isolated coronary, pulmonary, and cerebral arteries presumably by mechanisms including the secondary formation of molecules with the properties of NO donors (e.g., nitrosothiols), and by activation of ATP-dependent K^+ channels (744, 783, 909, 1328, 1365,1389). However, these experiments showed tachyphylaxis, since vasodilation could no longer be elicited after repetitive exposures to these large amounts of peroxynitrite (1136) and loss of ATP-dependent K^+ channel function (471).

The systemic application of peroxynitrite in anesthetized rats also elicited an initial pronounced fall in mean arterial blood pressure followed by a rapidly developing tachyphylaxis and increase in blood pressure (83, 84, 471–473, 704). It is likely that these responses are due to the effects of peroxynitrite, or to the resulting vasoactive reaction products on the vasculature (470, 1328). Intravenous administration of 3-nitrotyrosine, to anesthetized rats markedly inhibited the hemodynamic responses produced by catecholamines (norepinephrine and epinephrine), α1-adrenoceptor agonist phenylephrine, β-adrenoceptor agonist isoproterenol, as well as angiotensin II, raising the possibility that 3-nitrotyrosine may be involved in the pathogenesis of hemodynamic alterations associated with inflammatory conditions, such as I/R, myocarditis, chronic heart failure, atherosclerosis, and sepsis, where formation of peroxynitrite is favored (705, 706). Tables 1–3summarize the known targets of peroxynitrite-induced protein nitration that might be relevant to the majority of cardiovascular pathophysiologies discussed in the following parts.

2. Myocardial I/R injury

Reperfusion injury is the leading cause of tissue damage occurring in conditions such as myocardial infarction, stroke, organ transplantation, and cardiopulmonary bypass, as well as a major mechanism of end-organ damage complicating the course of circulatory shock of various etiologies. In all these conditions, the initial trigger of the damage is the transient disruption of the normal blood supply to target organs followed by reperfusion. From a clinical viewpoint, no

therapy is currently available to limit reperfusion injury, which emphasizes the importance of a better understanding of its underlying pathological mechanisms, to devise potential future therapeutic strategies.

Reperfusion of ischemic myocardium is the ultimate treatment to reduce myocardial damage. Unfortunately, reperfusion itself leads to additional tissue injury mediated by numerous factors including reactive oxygen (superoxide anion, hydrogen peroxide, and hydroxyl radical) and reactive nitrogen species (e.g., peroxynitrite and nitrogen dioxide) upon reperfusion (reviewed in Refs. **386**, **995**, **1083**), as well as to the rapid transcriptional activation of an array of proinflammatory genes (**128**, **197**, **541**, **642**, **1032**). Immediate consequences are the local sequestration and activation of polymorphonuclear leukocytes, resulting in a rapid amplification of the initial inflammatory response and ROS generation, the so-called "respiratory burst" (**799**, **800**). Reactive oxygen species in I/R can also be produced by additional sources such as mitochondria, NAD(P)H oxidases, cyclooxygenase, NOS, and xanthine oxidase (reviewed in Refs. **478**, **993**,**995**, **1306**). Indeed, since the introduction of the concept of I/R injury in the early 1980s (**467**,**858**), several lines of evidence support the pathophysiological role of xanthine oxidase-derived ROS generation, and the beneficial effects of xanthine oxidase inhibitors such as allopurinol and oxypurinol against myocardial I/R injury (**993**). The burst of ROS immediately upon reperfusion initiates a chain of deleterious cellular responses eventually leading to coronary endothelial dysfunction (**1292**); adherence of neutrophils to endothelium, transendothelial migration, and the release of mediators (**600**, **743**); transient impairment of left ventricular systolic contractile function or "myocardial stunning" (**113**, **131**); acute diastolic dysfunction; cellular calcium overload (**112**,**113**); reenergization-induced myocyte hypercontracture (**1030**); arrhythmia; and cell death.

The first evidence implicating that increased peroxynitrite formation during myocardial I/R might contribute to the tissue damage came from the study by Wang and Zweier (**1344**). They used isolated rat hearts subjected to global ischemia to measure the release of NO, superoxide, and peroxynitrite from the coronary effluent utilizing EPR spectroscopy and luminol chemiluminescence. The release of NO, superoxide, and peroxynitrite was increased within the first 2 min of reperfusion, and postischemic contractile function was improved by NOS inhibitors [N^G-nitro-L-arginine methyl ester (L-NAME), N^G-monomethyl-L-arginine (L-NMMA)], SOD, urate, or glutathione (**212**, **429**, **1344**, **1478**). The likelihood of peroxynitrite-mediated injury was further supported by the demonstration of increased nitrotyrosine immunostaining both in hearts perfused with peroxynitrite or subjected to I/R, but not in controls (**1344**). A similar observation was reported by Yasmin et al. (**1413**) using dityrosine fluorescence as an index of peroxynitrite generation upon reperfusion of buffer-perfused rat hearts subjected to ischemia. Consistently, peroxynitrite aggravates myocardial reperfusion injury in isolated perfused rat heart (**816**) and contributes to the development of reperfusion arrhythmias (**1268**). The marked inhibition of both contractility and respiration during reoxygenation of isolated rat left ventricular papillary muscles or hearts prior subjected to hypoxia could be attenuated by SOD or urate, suggesting that the formation of peroxynitrite contributes to the suppression of cardiac contractile performance and mitochondrial respiration caused by hypoxia and reoxygenation (**740**, **1380**, **1396**). The peroxynitrite-induced tyrosine nitration of prostacyclin synthase was implied to be responsible for the hypoxia/reoxygenation-induced coronary vasospasm in isolated bovine coronary arteries (**1466**, **1467**, **1472**, **1475**). Chronic treatment of rats with SOD mimetic EUK-8 or estrogen markedly improved functional recovery of isolated perfused hearts subjected to I/R, which was associated with decreased NADPH oxidase expression and myocardial

nitrotyrosine staining (1398). Interestingly, the most commonly used pain medication, acetaminophen, either administered to the perfusion buffer or used as a chronic treatment was found to attenuate the myocardial damage and peroxynitrite formation induced by myocardial I/R in isolated perfused rat hearts (453, 869–871, 1398).

Liu et al. (781) using an in vivo rat model of regional myocardial I/R provided immunohistochemical evidence of increased myocardial iNOS expression and protein nitration. These results are also supported by an in vivo dog study demonstrating that intracoronary administration of L-arginine (the precursor of NO) aggravates myocardial stunning (prolonged contractile dysfunction during reperfusion following a brief episode of myocardial ischemia) and increases nitrotyrosine immunoreactivity in the myocardium (902). Consistent with this observation, NOS inhibition decreases coronary sinus free radical concentration, myocardial nitrotyrosine formation, and ameliorates myocardial stunning following I/R in a similar in vivo canine model, while NO donor SNAP exerts opposite effects (1437, 1438). Another recent study has suggested that peroxynitrite-induced myocardial protein nitration contributes to the enhanced stunning and development of infarct in pigs with regional cardiac denervation (573). Recent in vivo studies have also provided convincing evidence that various potent cell-permeable metalloporphyrin-based peroxynitrite decomposition catalysts reduce myocardial infarct size, myocardial protein nitration, and improve cardiac function in rat and pig models of myocardial I/R (100, 750, 985, 1027) (Fig. 10).

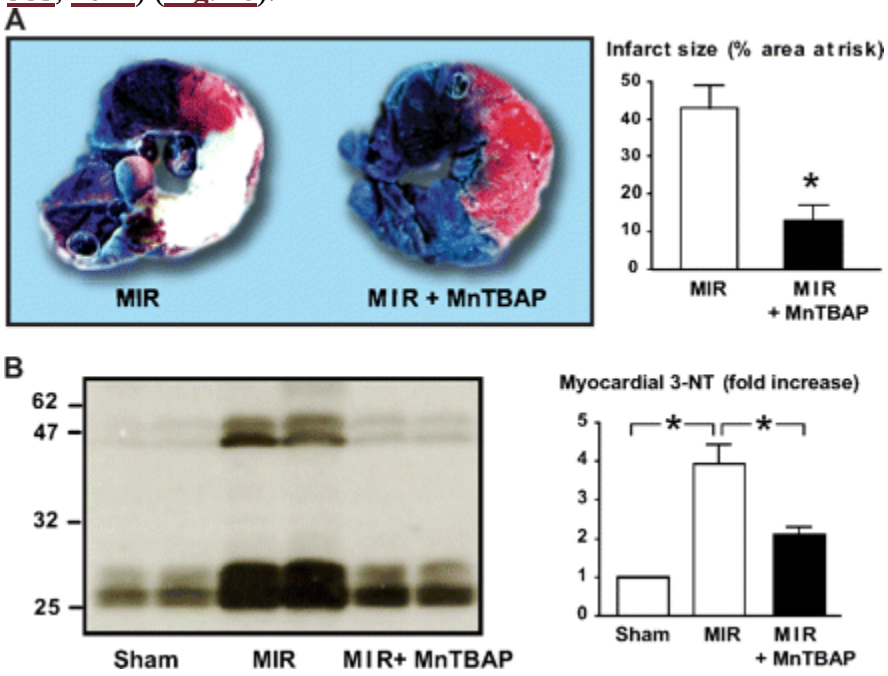

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FIG. 10.

Role of peroxynitrite in myocardial infarction. Peroxynitrite scavenger MnTBAP reduces infart size (*A*) and suppresses myocardial 3-nitrotyrosine formation (*B*) in rat. [From Levrand et al. (750) with permission from Elsevier.]

Intriguingly, several recent studies have investigated the role of peroxynitrite in myocardial I/R in human patients undergoing open heart surgery (**525**, **526**, **864**). In these studies, plasma nitrotyrosine levels from coronary sinus effluent and/or arterial blood (**525**, **526**) or myocardial nitrotyrosine immunoreactivity (**864**) from left ventricular biopsy specimens were evaluated before and at the end of cardiopulmonary bypass. The difference between plasma nitrotyrosine levels from coronary sinus effluent and arterial blood (index of myocardium-derived peroxynitrite generation) peaked at 5 min following reperfusion, and was significantly correlated with the peak coronary sinus effluent and arterial blood difference in plasma malondialdehyde concentrations (index of myocardial oxidative stress and lipid peroxidation), and with postoperative maximum creatinine kinase level (index of myocardial damage) (**526**).
Furthermore, the cardioplegia-induced myocardial I/R was also associated with increased iNOS expression, nitrotyrosine, and 9-isoprostane formation in human myocardium (**864**), indicating that the injury was likely to be mediated by both peroxynitrite and ROS. Increased immunostaining for iNOS and nitrotyrosine was detected in left ventricular biopsy specimens of patients with hibernating myocardium, a state of chronic contractile dysfunction present at rest in a territory subtended by a stenosed coronary artery that recovers following revascularization, most likely originated from repetitive episodes of transient ischemia (**47**). Increased iNOS expression and nitrotyrosine formation were also demonstrated in human coronary arteries of patients with human transplant coronary artery disease, a major cause of late mortality after cardiac transplantation (**1069**), and during cardiac allograft rejection (**1249**).
Interestingly, serum urate levels are elevated following myocardial I/R in experimental animals (**1271**) and also in patients undergoing thrombolysis and percutaneous transluminal coronary angioplasty (**1412**). Because urate is a well-known natural inhibitor of peroxynitrite-dependent nitration, these findings raise the intriguing possibility that increased urate production during hypoxia may represent an endogenous protective mechanism against peroxynitrite-mediated damage (**1271**).
In contrast to the large number of studies discussed above demonstrating detrimental effects of exogenous and/or endogenous peroxynitrite or nitrotyrosine during myocardial I/R, there are only a few reports describing beneficial (e.g., reduced infarct size, improved contractile and vascular function) or biphasic effects when peroxynitrite is injected into the blood, but not into the crystalloid environment at the time of reperfusion (**744**, **950**, **951**, **1084**). However, the actual concentration of peroxynitrite delivered to its cellular targets in these experiments is questionable since at physiological pH the molecule undergoes rapid reactions and transformations with certain blood and nearby tissue components such as carbon dioxide, NO, thiol-containing albumin, glutathione, and cysteine, among many others (**613**). The oxidization of thiols by peroxynitrite leads to formation of NO donor nitrosothiols, which have been reported to protect the heart during I/R, in addition to the neutralization of peroxynitrite itself (**211**, **854**, **1328**). It should also be noted that to our knowledge, there are no published studies demonstrating a tissue-protective effect of endogenously formed peroxynitrite. On the contrary, multiple lines of evidence discussed above and below support the toxicity of endogenously formed peroxynitrite in myocardial I/R and various other cardiovascular pathologies (reviewed in Refs. **995**, **1300**; **Table 4**).

3. Preconditioning, postconditioning, and development of nitrate tolerance

Ischemic preconditioning (IPC), a potent endogenous form of cardioprotection against I/R injury, was first introduced by Murry et al. in 1986 (**920**). In hearts subjected to I/R IPC, brief episode(s) of ischemia applied before I/R reduces infarct size as well as the incidence and severity of postischemic arrhythmias and enhances the recovery of cardiac and vascular function (reviewed in Ref. **1415**). Postconditioning is a recently described form of cardioprotection (similar to preconditioning in degree of protection) when a short series of repetitive cycles of brief reperfusion and reocclusion of the coronary artery are applied immediately at the onset of reperfusion (**1415**, **1449**). Numerous studies have suggested that NO, superoxide, and peroxynitrite, among many other mediators, may also be involved in the mechanisms of this endogenous protection (reviewed in Refs. **87**, **386**, **636**, **1149**). Most notably, while endogenous peroxynitrite formation may contribute to the endogenous IPC-triggered protection, the preconditioning and the postconditioning by itself reduces both peroxynitrite/nitrotyrosine formation and the activation of the necrosis-inducing enzyme PARP upon subsequent I/R, leading to attenuated myocardial damage (**14**, **252**, **770**, **1341**). Similarly, as already mentioned above, chemical preconditioning with various drugs (**100**, **453**, **750**, **869**–**871**, **985**, **1027**, **1297**, **1398**) also leads to reduced formation of nitrotyrosine in the myocardium. Most studies above also support an important role of peroxynitrite-induced protein tyrosine nitration in the development of postischemic myocardial injury.

For more than a century, nitroglycerin and other organic nitrates have been effectively used to treat acute myocardial infarction, various anginas, and congestive heart failure (**1272**). However, during chronic treatment, the efficacy of nitrates is often lost secondary to the development of nitrate tolerance. Numerous recent studies have suggested that the redox modification of key enzymes of the NO-soluble guanylate cyclase (sGC)-cGMP-cGMP-dependent protein kinase (cGK) pathway and PDE (the enzyme responsible for the cGMP catabolism) might explain the partial decrease in the response to endothelium-dependent and other NO-dependent vasodilators, giving rise to the oxidative stress concept of nitrate tolerance (**283**, **461**). Indeed, several studies have demonstrated that superoxide or peroxynitrite may inhibit sGC, presumably through oxidation of thiol groups in its catalytic site that appear to be critical for the direct activation of the enzyme by nitroglycerin (**32**, **650**, **1351**). Furthermore, peroxynitrite and superoxide are known to impair the activity of ion channels responsible for the generation of $K^+$and Ca^{2+} currents, the final mediators of nitroglycerin-induced vasodilatation (**482**, **785**). Also, as mentioned in section V*B5*, activation of PKC in endothelial cells by peroxynitrite has been proposed as an additional mechanism of nitrate tolerance.

4. Myocarditis, transplant coronary artery disease, and cardiac allograft rejection

Acute viral myocarditis accounts for the majority of “idiopathic” dilated cardiomyopathies and is the leading cause of cardiac failure in young patients. The clinical course is often unpredictable with limited cardiac dysfunction and inflammation. On the other hand, in a subset of patients, it may be associated with overwhelming inflammation leading to fulminant acute cardiac injury or chronic heart failure due to autoimmune myocarditis with very limited treatment options.

The role of NO in myocardial inflammatory disease is controversial. Some investigators have suggested that iNOS overexpression in the hearts (found predominantly in the infiltrating inflammatory cells) in experimental mouse models of viral Coxsackie B3 myocarditis is beneficial (presumably by the antiviral effect of NO) (**797**, **884**), which is consistent with the more severe myocarditis in response to viral infection in iNOS knockout mice (**825**, **1352**).

In contrast, in a more recent study increased levels of NO as a result of iNOS overexpression correlated with increased numbers of heart lesions and increased myocardial nitrotyrosine accumulation in infected mice (96). Similarly, progressive cardiac dysfunction correlated with increased myocardial inflammation and protein nitration in a murine model of AIDS-induced myocarditis (201). Most importantly, increased nitrotyrosine immunoreactivity was found in human biopsy specimens with viral myocarditis and sepsis, suggesting a pathogenetic role of peroxynitrite formation and/or protein nitration in these diseases (201, 707; Fig. 11). Consistent with these later observations, mixture of inflammatory cytokines or endotoxin induces cardiac dysfunction, increased iNOS expression, superoxide and peroxynitrite generation, and MMP-2 activation in myocytes or isolated-perfused mouse or rat hearts, and these changes were attenuated by iNOS inhibitor or peroxynitrite scavenger (384, 428, 604, 663, 670, 729). Increased production of NO and superoxide and nitrotyrosine staining were also observed in a rat model of autoimmune myocarditis induced by porcine myosin (616, 1160) and in dog hearts injected with intracoronary inflammatory cytokines (210, 978).

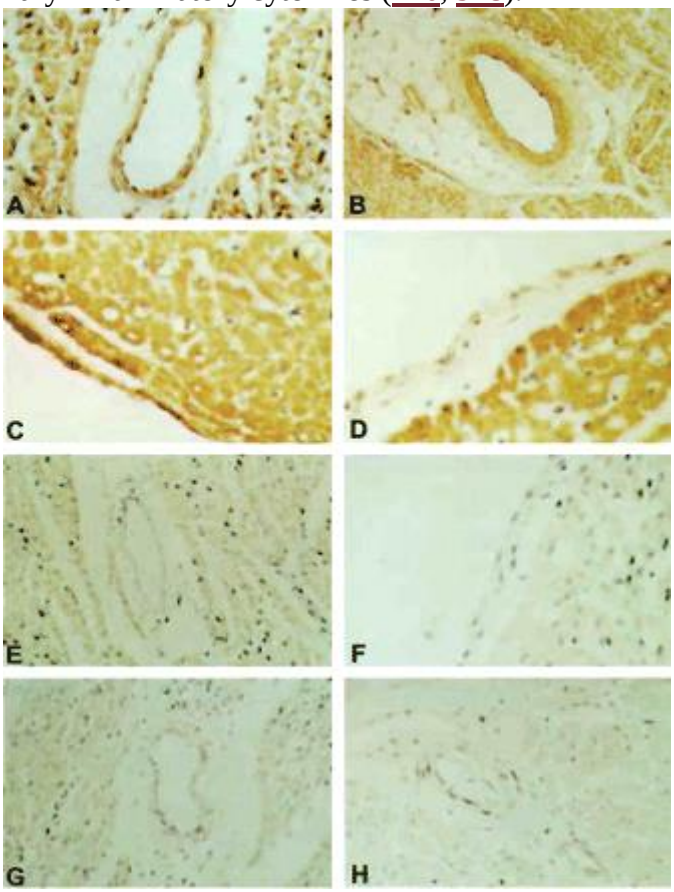

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FIG. 11.

Evidence for nitrotyrosine formation in human myocardial inflammation. Representative examples are shown of nitrotyrosine immunoreactivity in cardiac tissue samples from patients with myocarditis, sepsis, or no

cardiac disease (control patients). *A*: low-power (×20) photomicrograph of nitrotyrosine immunoreactivity (brown staining) in the myocardium, vascular endothelium, and vascular smooth muscle of myocarditis patient. *B*: low-power (×20) photomicrograph of nitrotyrosine immunoreactivity in the myocardium, vascular endothelium, and vascular smooth muscle of sepsis patient. Note the relative absence of staining of the connective tissue elements. *C*: higher-power (×40) photomicrograph of intense nitrotyrosine immunoreactivity in the endocardium of myocarditis patient. *D*: higher-power (×40) photomicrograph of nitrotyrosine immunoreactivity in the endocardium of sepsis patient. *E*: low-power (×20) photomicrograph of minimal nitrotyrosine immunoreactivity in the myocardium and the virtual absence of nitrotyrosine immunoreactivity in the vascular endothelium and vascular smooth muscle of control patient 1C. *F*: higher-power (×40) photomicrograph of nitrotyrosine immunoreactivity in the endocardium of control patient. *G*: low-power (×20) photomicrograph demonstrating the inhibition of nitrotyrosine immunoreactivity by the preincubation of the primary antibody with 10 mM nitrotyrosine before tissue staining in myocarditis patient. *H*: low-power (×20) photomicrograph demonstrating the inhibition of nitrotyrosine immunoreactivity by the preincubation of the primary antibody with 10 mM nitrotyrosine before tissue staining in sepsis patient. [From Kooy et al. (**707**) with permission from Lippincott Williams & Wilkins.]

Increased iNOS expression and nitrotyrosine formation were also found in human coronary arteries of patients with human transplant coronary artery disease (**1069**) and during cardiac allograft rejection both in experimental models (**11**, **1104**, **1247**) and in human hearts (**1069**,**1249**, **1371**). Furthermore, iNOS gene deletion or treatment with an iNOS inhibitor or metalloporphyrin-based peroxynitrite decomposition catalysts improved graft function, decreased histological rejection, and attenuated myocardial lipid peroxidation, nitrotyrosine formation, and PARP activation in mouse and rat cardiac transplant models (**342**, **1027**). Collectively, the above-mentioned results strongly suggest that NO, superoxide, and peroxynitrite contribute to tissue injury in cardiac allografts during acute rejection (see also **Table 4**).

5. Chronic heart failure

Chronic heart failure (CHF) represents a major and growing public health concern that affects all Western countries and is the leading cause of hospitalization, morbidity, and mortality worldwide. CHF is considered a multiorgan and multicell syndrome characterized by myocardial functional and structural abnormalities, sodium retention, neurohumoral maladaptations, and vascular dysfunction. Different pathophysiological conditions, such as acute and chronic ischemic heart disease resulting from impaired coronary artery circulation or infarction, pressure overload, myocarditis, cardiomyopathies, and defects in genes encoding contractile apparatus, cytoskeleton, mitochondrial proteins, or intercellular matrix ultimately bring about impaired myocardial function (reviewed in Refs. **516**, **905**, **995**, **1306**; **Fig. 12**). The complex interplay of diverse secondary pathways (neuropeptides, neurohormones, cytokines, iNOS, oxidative stress and peroxynitrite, MMPs, and the nuclear enzyme PARP) is involved in the deleterious way of the progression of cardiovascular dysfunction to heart failure, resulting in abnormalities in various cardiac receptors and signaling processes, calcium homeostasis, contractile proteins, besides structural alterations such as cardiovascular remodeling with hypertrophy, fibrosis, necrosis, and cardiac dilation (reviewed in Refs. **516**, **905**, **995**, **1306**; **Figs. 9** and **12**). The

increased peripheral resistance (a result of vasoconstriction and vascular remodeling) coupled with adverse cardiac remodeling further exacerbate heart failure initiating a vicious self-destructive cycle (**Fig. 12**).

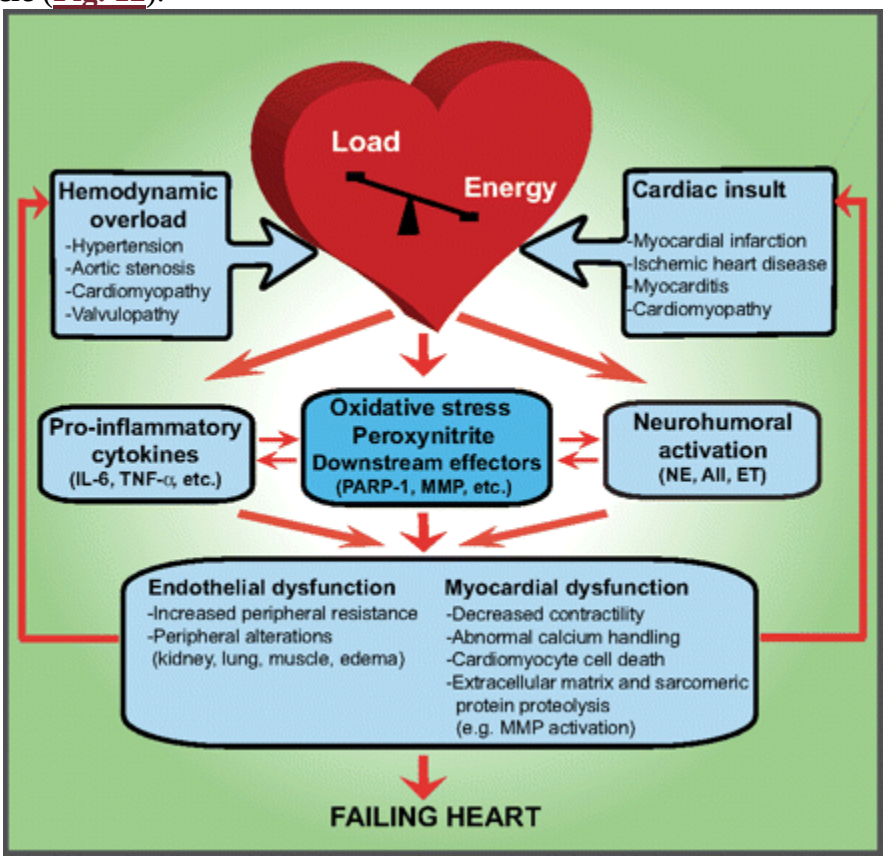

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FIG. 12.

Progression of heart failure and the role of oxidative stress and peroxynitrite. The mechanisms leading to heart failure are of multiple origins and include acute and chronic ischemic heart disease, cardiomyopathies, myocarditis, and pressure overload just to mention a few. These diseases result in mismatch between the load applied to the heart and the energy needed for contraction, leading to mechanoenergic uncoupling. After initial insult, secondary mediators such as angiotensin II (AII), norepinephrine (NE), endothelin (ET), proinflammatory cytokines [e.g., tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), in concert with oxidative stress and peroxynitrite, activate downstream effectors (e.g., PARP-1 or MMPs)], act directly on the myocardium or indirectly via changes in hemodynamic loading conditions to cause endothelial and myocardial dysfunction, cardiac and vascular remodeling with hypertrophy, fibrosis, cardiac dilation, and myocardial necrosis, leading eventually to heart failure. The adverse remodeling and increased peripheral resistance further aggravate heart failure. MMPs, matrix metalloproteinases; PARP-1, poly(ADP-ribose) polymerase. [Derived from Pacher et al. (**995**) with permission from Elsevier.]

Numerous experimental and clinical studies have demonstrated increased production of reactive oxygen species (ROS: superoxide, hydrogen peroxide, hydroxyl radical) both in animals and patients with CHF (reviewed in Ref. **1306**). Myocardial ROS generation has been shown to be triggered by repetitive episodes of I/R, increased levels of inflammatory cytokines (e.g., TNF-α, IL-6), impaired antioxidant defense mechanisms, and catecholamine auto-oxidation and/or during prostaglandin biosynthesis. The possible sources of increased production of superoxide, hydrogen peroxide, and hydroxyl radical in failing myocardium are multiple, including xanthine oxidase, NAD(P)H oxidases, cyclooxygenases, the mitochondrial electron transport chain activity, activated neutrophils, NO synthases, and auto-oxidation of certain tissue metabolites (reviewed in Refs. **993**, **1182**, **1306**; **Fig. 9**). It is particularly exciting that xanthine oxidase inhibitors allopurinol and its active metabolite oxypurinol, the most widely used drugs for the clinical management of gout and conditions associated with hyperuricemia, show considerable promise in the treatment of CHF not only in experimental animals but also in small-scale human clinical trials (**993**).

Although numerous experimental and human studies have demonstrated overexpression and increased activity of iNOS in the myocardium of animals and patients with various forms of heart failure and benefits of iNOS inhibition on cardiac function (**208**, **383**, **389**, **421**, **529**, **693**, **878**,**1317**, **1409**, **1465**; **Table 4**), the role of iNOS and NO in the development and progression of the heart failure is a subject of recent debate (**914**). For example, one mouse study found positive correlation between the chronic overexpression of iNOS and peroxynitrite generation with cardiac enlargement, conduction defects, sudden cardiac death, and less commonly heart failure in mice (**913**), but this was not confirmed by another study (**534**). Increased myocardial iNOS activity was found to be responsible for depressed myocardial contractility and beta-adrenergic hyporesponsiveness in rats with volume-overload heart failure (**439**), but iNOS deficiency did not attenuate CHF in mice (**637**). Additional sources of increased NO production in the failing heart could be nNOS (**286**) and eNOS (**281**). In heart failure, the cGMP pathway is also disrupted, either with impaired production of NO or its excessive degradation or neutralization with oxidants such as superoxide, thus impairing the soluble guanylate cyclase signaling pathway (**372**, **995**).

The increased superoxide production and increased NO from iNOS overexpression favor the generation of peroxynitrite. As already mentioned, peroxynitrite generation has been demonstrated in various forms of myocardial I/R and myocarditis both in experimental animals and biopsies obtained from human subjects (**995**, **1300**; **Fig. 10**, **Table 4**). Increased myocardial iNOS expression, nitrotyrosine formation, and/or MMP-2 activation have also been reported in acute and chronic mouse models of doxorubicin-induced heart failure (**44**, **883**, **985**, **1355**; **Fig. 13**), in heart failure induced by permanent left anterior coronary artery ligation in mice (**383**) and rats (**878**, **987**), or by pacing in dogs (**192**). Importantly, increased myocardial iNOS expression and nitrotyrosine formation correlated with deterioration of cardiac function (**883**, **1355**) in mice. A correlation between increased nitrotyrosine formation with myofibrillar creatine kinase inhibition was also observed in human atrial appendages from patients with fibrillation (**881**). Increased iNOS protein expression also correlated with increased nitrotyrosine formation in myocardial specimens of patients with heart failure. Although iNOS-positive patients were generally characterized by larger left ventricular volume and depressed function, the preserved generation of NO appeared to be associated with higher cardiac work due to the preserved Frank-Starling relationship in end-stage heart failure (**1317**). Increased nitration of SERCA2a in idiopathic dilated cardiomyopathic human hearts was also reported, and a positive correlation

between the time to half relaxation and the nitrotyrosine/SERCA2a content in myocytes was observed (789). Furthermore, a novel peroxynitrite decomposition catalyst attenuated the development of cardiac dysfunction and myocardial nitrotyrosine formation, and increased the survival in doxorubicin-induced cardiomyopathy model (985).

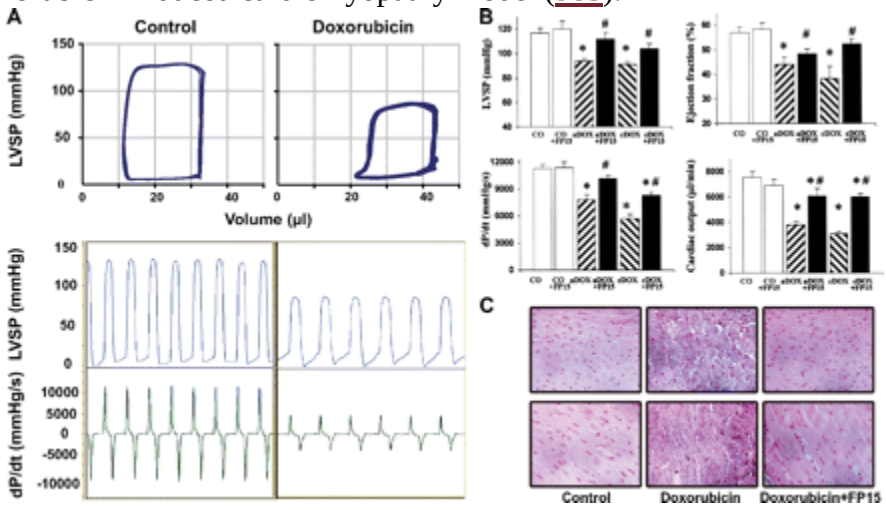

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FIG. 13.

Role of peroxynitrite in doxorubicin (DOX)-induced heart failure. *A*: evidence of severe cardiac dysfunction 5 days after DOX injection in mice. Representative PV loops (*top*) and left ventricular pressure signal (*bottom*) from control and DOX and DOX + INO-1001-treated mice. Please note that the rightward shift of PV loops in DOX-treated animals, the decrease of maximal left ventricular pressure, and +dP/d*t* indicate depressed cardiac contractility. *B*: peroxynitrite scavenger FP15 (black bars) attenuates DOX-induced (hatched bars) acute (aDOX; single dose of 25 mg/kg ip) and chronic (cDOX; 3 doses of 9 mg/kg ip every 10th day for 25 days) cardiac dysfunction. Hemodynamic parameters were measured 5 (aDOX) or 25 (cDOX) days after DOX administration. Results are means ± SE of 10–14 experiments in each group. *$P < 0.05$ vs. CO. #$P < 0.05$ vs. aDOX or cDOX. *C*: evidence of increased myocardial nitrotyrosine formation (widespread dark brown staining) 5 days after DOX injection in mice and reduction by FP15. [From Pacher and co-workers (985, 988) with permission from Lippincott Williams & Wilkins and Prof. Demetrios A. Spandidos.]

It appears that peroxynitrite decomposition catalysts exert beneficial effects on cardiac and endothelial function in various models of myocardial injury (e.g., heart failure, myocardial I/R, myocarditis, cardiac allograft rejection, and diabetic cardiomyopathy; see also below). The mechanism by which peroxynitrite neutralization protects hearts from dysfunction may involve protection against vascular and myocardial tyrosine nitration, lipid peroxidation, and inactivation of contractile proteins, MMP and PARP activation, and multiple other mechanisms shown in **Figure 9**and listed in **Table 3**. These observations support the concept that peroxynitrite is a major mediator of myocardial injury in various pathological conditions, and its effective neutralization or inhibition of downstream effector pathways (e.g., PARP and MMP activation) can be of significant therapeutic benefit (624, 986, 987, 989, 995, 1234, 1246).

B. Nitric Oxide and Peroxynitrite in Vascular Diseases

Endothelial cells in response to various physical and chemical stimuli (e.g., shear stress, change in pressure and pH), circulating hormones, cytokines, drugs, and substances released by sensory and autonomic nerves or platelets produce vasoactive relaxing substances (e.g., NO, endothelium-derived hyperpolarizing factor, prostacyclin, adenosine, C-natriuretic peptide) and contracting substances (e.g., angiotensin II, endothelin-1, thromboxane A_2, isoprostanes) that regulate vascular tone and permeability, hemostasis, angiogenesis, and inflammation (**381**). The vascular endothelium sustains the balance between prevention and stimulation of platelet aggregation, thrombogenesis and fibrinolysis, promotion and inhibition of the smooth muscle cell proliferation and migration, and also between vasoconstriction and vasodilation (**289**). The disruption of this tightly controlled balance leads to the development of endothelial dysfunction, a multifaceted disorder, which represents a predominant early feature of diabetes, hypertension, heart failure, and atherosclerosis and makes this population prone to cardiovascular complications and microthrombus formation (**166**, **381**, **731**). Although the hallmark of endothelial dysfunction is impairment of the endothelium-dependent vasodilation, other alterations (e.g., inflammation, increased lipoprotein oxidation, vascular smooth muscle proliferation and migration from the media to the intima, extracellular matrix deposition or lysis, platelet activation, and thrombus formation) associated with this disorder have also been described (**365**). Accumulating evidence supports the view that the endothelial dysfunction associated with diabetes, hypertension, heart failure, and atherosclerosis is related to the local formation of reactive oxygen and nitrogen species in the vicinity of the vascular endothelium (reviewed in Refs. **365**, **478**, **630**,**757**, **775**, **996**, **1004**, **1306**, **1378**, **1380**, **1381**).

As already mentioned previously and summarized in **Table 3**, peroxynitrite may contribute to vascular pathophysiology by various mechanisms including triggering apoptosis and/or PARP-dependent cell death in endothelial (**319**, **879**) and vascular smooth muscle (**755**, **756**) cells, inducing upregulation of adhesion molecules in endothelial cells, endothelial glycocalyx disruption, enhancing neutrophils adhesion (**424**, **723**, **1178**, **1447**, **1477**), inhibiting voltage-gated K^+ K(v) and Ca^{2+}-activated K^+ channels in coronary arterioles (**754**, **786**) and vascular prostacyclin synthase (**228**, **290**, **1466**, **1467**, **1472**, **1475**), and dependent on the environment stimulating or inhibiting platelet aggregation (**908**, **953**). Additionally, peroxynitrite-mediated oxidation of tetrahydrobiopterin, a critical cofactor for NO synthase, may represent a pathogenic cause of uncoupling of NO synthase, leading to production of superoxide rather than NO (**405**–**407**, **734**). Furthermore, clinically relevant concentrations of 3-nitrotyrosine (present in various pathophysiological diseases, **Table 4**) result in concentration-dependent impairment of acetylcholine-induced, endothelium-dependent vascular relaxation and induce DNA damage in vascular endothelial cells (**879**, **1473**).

Below, we are focusing on the evidence implicating peroxynitrite in the pathophysiology of vascular dysfunction associated with atherosclerosis, restenosis, hypertension, aging, and hyperhomocysteinemia. The cardiovascular dysfunction associated with heart failure, shock, and diabetes is reviewed in later or earlier parts (see also **Tables 4** and **5**).

1. Atherosclerosis and restenosis

Atherosclerosis is the principal cause of common cardiovascular disorders such as coronary artery disease, various forms of heart failure and stroke, abdominal aortic aneurysms, and

ischemic gangrene, which are the leading causes of death in the Western society. The prevalence of atherosclerosis is increasing worldwide in all age groups including the adolescent population (**1207**). The pathophysiology of atherosclerosis is multifaceted. It comprises endothelial injury leading to accumulation of lipids and their uptake by monocytes that is followed by platelet and monocyte adhesion and aggregation at the site of injury, and the release of a variety of factors that promote smooth muscle migration and proliferation (from the media into the intima), which then synthesize and deposit extracellular matrix (**514**, **603**).
Percutaneous transluminal angioplasty (surgical procedures aimed to repair the stenotic blood vessel by inflating a balloon-tipped catheter at the site of the vascular narrowing) is performed in ~2 million people worldwide annually and has become a widely available and efficient treatment option for patients with peripheral and coronary artery disorders. In many of these cases, a stent (an expandable wire mesh or hollow perforated tube) is inserted into the reconstructed blood vessel, to provide support after angioplasty and protection against restenosis. Despite the significant advances made in these surgical procedures during the past decade, the restenosis remains a significant clinical issue with a limited number of therapeutic options, affecting 20–30% of patients undergoing vascular interventions.

Recent experimental, clinical, and epidemiological studies have revealed the importance of the cross-talk between inflammation, generation of reactive oxygen and nitrogen species, and lipid metabolism in the pathogenesis of atherosclerosis and vascular remodeling following injury (**37**,**514**, **518**, **931**, **1012**, **1090**, **1093**). There is also evidence suggesting that atherosclerosis is not only associated with decreased NO bioavailability, but also with alterations in signal-transduction components downstream of NO, including among others, the NO receptor sGC, particularly in neointima (**372**, **865**).
Numerous studies support both anti- and proatherogenic roles of NO (**80**, **164**, **183**, **203**, **229**,**524**, **561**, **734**, **742**, **932**, **963a**, **1364**) and are covered by numerous excellent overviews (**514**,**931**, **1012**, **1090**, **1093**). One explanation for this paradox is that NO alone is an important antiatherosclerotic autacoid with antiaggregatory effects on platelets, antioxidant, anti-inflammatory, antiproliferative, and vasodilatory effects on vasculature, while in combination with proinflammatory oxidants (e.g., superoxide, hydrogen peroxide, hypochlorite) it forms proatherogenic mediators (e.g., peroxynitite) that modify lipids and proteins (**78**, **899**, **1009**, **1010**,**1091**, **1093**, **1300**, **1314**). According to the classic view, reactive oxygen and nitrogen species oxidatively damage LDL trapped in the arterial intima forming oxidized LDL, which in turn initiates numerous events (e.g., foam cell formation, monocyte recruitment and adhesion to the endothelium, inhibition of macrophage motility, smooth muscle cell proliferation, promotion of cytotoxicity, and attenuation of vascular reactivity) facilitating the development of atherosclerotic lesions (**1012**). Supporting the pathogenetic role of peroxynitrite in atherosclerosis, numerous studies have demonstrated increased 3-nitrotyrosine and iNOS expression in human atherosclerotic tissue (**49**, **80**, **164**, **240**, **313**, **363**, **584**, **742**, **802**, **1019**, **1211**), which correlated with plaque instability in patients (**313**, **584**). Peroxynitrite most likely contributes to the development of early vascular lesions and as the lesion develops, other reactive nitrogen species derived from the reaction of nitrite with proteins, such as myeloperoxidase, in inflammatory cells, are also thought to contribute to nitrosative stress (**530**, **835**, **1012**, **1033**). Numerous studies have also demonstrated that peroxynitrite is able to modify proteins and lipids in LDL and high-density lipoprotein (HDL) even in the presence of endogenous lipophilic antioxidants (**287**, **465**,**558**, **899**, **1002**, **1009**, **1010**, **1019**, **1094**) and regulates signaling pathways in the

endothelial and vascular smooth muscle, thereby modulating the vascular response to atherogenetic stimuli (**450**,**1093**, **1221**). Importantly, various drugs (e.g., cicletanine and estradiol) and fasting, which improve endothelial dysfunction or decrease the atherosclerosis progression in animal models of disease, also reduce serum or vascular nitrotyrosine level/staining (**653**, **1250**, **1411**), further supporting the pathogenetic role of peroxynitrite in atherosclerosis.

Recent studies also demonstrate enhanced production of superoxide and peroxynitrite in hypercholesterolemia, hyperlipidemia, and hyperhomocysteinemia, which are considered to be major risk factors for the development of atherosclerosis (**42**, **70**, **339**, **343**, **579**, **635**, **912**, **1181**,**1202**, **1264**, **1303**, **1431**, **1435**).

There is also accumulating evidence demonstrating that reactive oxygen and nitrogen species and downstream effector pathways (e.g., PARP) play an important role in the pathogenesis of restenosis following vascular injury (**37**, **82**, **618**, **667**, **747**, **921**). Numerous studies found increased 3-nitrotyrosine immunoreactivity and/or iNOS overexpression in media and neointima following balloon injury (a model of restenosis) and increased 3-nitrotyrosine-to-tyrosine ratio in the serum of patients following stent implantation (**37**, **82**, **602**, **618**, **667**, **747**, **921**). The serum 3-nitrotyrosine-to-tyrosine ratio appears to be an independent predictor of angiographic late lumen loss in patients (**602**). Supporting the pathogenetic role of superoxide and peroxynitrite and downstream effector pathways in restenosis, administration of SOD, SOD mimetic, NAD(P)H oxidase, or PARP inhibitors decreased not only vascular remodeling following injury but also 3-nitrotyrosine formation (**82**, **618**, **747**, **921**). In contrast, in experimental models of restenosis, systemic administration of NO donors (**846**, **1144**) or local transfer of genes encoding NOS (**1152**,**1336**) or sGC α_1- and β_1-subunits (**1172**) attenuate neointima formation.

2. Aging

Epidemiological studies revealed that even in the absence of established risk factors such as hypertension, diabetes, and hyperhomocysteinemia, advanced age itself significantly increases cardiovascular morbidity (**726**, **727**, **927**). Although there is substantial evidence demonstrating an aging-associated development of cardiac and vascular dysfunction (**25**, **26**, **114**, **171**, **510**, **521**,**545**, **990**, **1253**, **1311**; reviewed in Refs. **24**, **726**, **727**), the mechanisms responsible for this phenomenon have not yet been clearly established. This impairment is, at least in part, related to the increased local formation of reactive oxygen and nitrogen species coupled with impaired NO bioavailability, and associated chronic inflammation in the myocardium and vasculature (**81**, **249**,**517**, **601**, **938**, **1081**, **1212**, **1311**; reviewed in Refs. **51**, **248**, **394**).

Increased ROS production was reported in aorta (**509**, **1311**), carotid (**509**, **1311**), mesenteric (**409**), and small coronary arteries (**249**) of aged rats and mice (**409**). Aging-induced vascular oxidative stress is associated with increased activity of NAD(P)H oxidases (**7**, **249**, **1311**) and/or other oxidase mechanisms (**40**), a downregulation of antioxidants, such as ecSOD (**1213**), and an increased expression of iNOS (**409**, **1409**). Increased oxidative stress in aging also leads to functional inactivation of NO by elevated concentrations of superoxide favoring an enhanced peroxynitrite formation (**7**, **249**, **409**, **1213**, **1311**). Notably, age-related decline in eNOS expression (**249**, **556**, **853**, **1262**, **1386**) and/or a decreased intracellular L-arginine availability (**88**) further aggravate impaired NO bioavailability, limiting cardiac blood supply, altering

myocardial O_2 consumption and cardiac contractility (7), and enhancing apoptosis of endothelial cells (251, 556).

Several studies found increased cardiovascular peroxynitrite formation and/or protein nitration in aging (7, 249, 409, 1213, 1311). For example, Van der Loo et al. (1311) found increased accumulation of 3-nitrotyrosine (3-NT) in the aortas of aging rats compared with young controls; one of the nitrated proteins identified was mitochondrial Mn-SOD, a major antioxidant enzyme, which loses its activity upon nitration by peroxynitrite (830, 1405). Using proteomics techniques, Kanski et al. (655) identified, among others, numerous enzymes of the glycolytic machinery [α-enolase-1, α-aldolase, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH)] as targets for protein nitration (654). Several nitrated mitochondrial proteins (e.g., aconitase, creatine kinase, VDAC, ATP synthase, and other proteins involved in electron transfer) (654) were also discovered from the aging myocardium, suggesting that these proteins are particularly vulnerable to aging-related nitration. A more recent study investigated peroxynitrite- and 4-hydroxy-2-nonenal (HNE)-modified serum proteins from young and aging Fisher rats (676). This study identified 16 proteins (e.g., involved in blood coagulation, lipid transport, blood pressure regulation, and protease inhibition) modified by nitration and/or HNE adduction during aging (676). Another example of specific protein nitration associated with aging is the nitration of skeletal muscle and myocardial sarcoplasmic reticular Ca^{2+}-ATPases (692, 1131, 1329, 1330, 1397). Recent studies have also demonstrated that increased levels of ROS and reactive nitrogen species (RNS) may activate NFκB, a redox-sensitive transcription factor involved in the induction of the transcription of a large range of genes implicated in inflammation, including cytokines (e.g., TNF-α, IL-6, and IL-1β), chemokines, and adhesion molecules (771, 1270, 1441) expressed by both endothelial and smooth muscle cells. In agreement with this, there is recent evidence for a proinflammatory shift in cardiac (737) and vascular (249–251) cytokine expression profile (including an upregulation of TNF-α and IL-6) associated with aging. As discussed in previous sections in detail (see also **Tables 1**–3), there are numerous possible additional downstream targets of peroxynitrite-induced protein nitration and cytotoxicity (e.g., antioxidant enzymes, contractile proteins, stress kinases, MMPs, PARP, etc.) that may likely play an important role in the development of aging-associated cardiovascular pathophysiology (991, 992, 998; reviewed in Refs. 248, 1227).

3. Hypertension

Arterial hypertension, the chronic elevation of blood pressure, is a major public health concern even though it is not a disease per se. Untreated hypertension leads to premature morbidity and mortality due to stroke, accelerated coronary arterial disease, myocardial infarction, and cardiac and renal failure. In the majority of cases, the principal cause of the disease remains elusive (primary, essential, or idiopathic hypertension), and therapy, therefore, is symptomatic rather than preventive (506). The vascular effects of the chronic elevation of blood pressure are complex and comprise both local effects on the vascular endothelium and smooth muscle and effects mediated by the CNS and increased production of various neurohumoral factors (e.g., angiotensin II, catecholamines, endothelin, etc.) (499, 698, 1035).

Accumulating evidence suggests that alterations in NO synthesis and NO-sGC-cGMP signaling or a reduction in the bioavailability of endothelium-derived NO by increased oxidative stress are key contributors to the pathogenesis of hypertension (reviewed in Refs. 365, 372, 698, 964, 1004,1379). Numerous experimental studies using animal models of

disease [e.g., angiotensin II infusion, deoxycorticosterone with a high salt diet (DOCA salt), Dahl hypertensive rats, spontaneously hypertensive rats (SHR), chronic inhibition of eNOS, and aortic banding] and clinical reports have established that hypertension is associated with increased superoxide production, dysregulation of NOS, and endothelial dysfunction. However, the exact molecular mechanisms of these processes are not fully understood (**95**, **166**, **167**, **172**, **269**, **416**, **535**, **699**,**733**, **889**, **1065**, **1180**, **1305**, **1335**, **1343**).

There is controversy as to whether the endothelial dysfunction in hypertension is the cause or a consequence of increased blood pressure (**1318**). Likewise, the source of superoxide in hypertension is also a matter of recent debate; it may include NAD(P)H oxidases, xanthine oxidase, mitochondrial enzymes, and uncoupled NOS (reviewed in Refs. **365**, **993**, **1004**, **1381**,**1382**, **1408**). Nevertheless, increase in intraluminal pressure and oscillatory shear stress (both are associated with hypertension) have been shown to activate redox-sensitive signaling pathways, enhance oxidative stress in the vasculature, and impair endothelial function both in vivo and in vitro (**166**, **167**, **1004**, **1304**, **1305**, **1381**, **1408**).

Increased levels of superoxide have been shown to decrease the bioavailability of NO, thereby contributing to the maintenance of elevated peripheral resistance (**166**, **167**, **698**, **699**, **1305**). Production of various vasoconstrictor substances (e.g., angiotensin II, endothelin-1, thromboxane A_2, isoprostanes, etc.) may also contribute to increased ROS production and reduced endothelium-dependent relaxation in hypertension (**365**, **1004**). The hypertrophy of the vascular wall as a consequence of reduced NO bioavailability can further aggravate an increase in the vascular resistance (**365**, **1004**).

Compelling evidence has emerged supporting the importance of endogenous peroxynitrite formation and protein nitration in the pathogenesis of arterial hypertension (reviewed in Refs. **365**,**1300**). Increased superoxide formation, gene expression of several subunits of NAD(P)H oxidases, eNOS, and nitrotyrosine were markedly increased in the aorta segment above aortic coarctation (hypertensive zone) and in hearts of aortic-banded rats and mice compared with normotensive controls (**65**, **125**, **724**, **1324**). Interestingly, substantial changes in endothelial dysfunction were only observed when NOS expression and superoxide production were simultaneously increased and were associated with enhanced nitrotyrosine formation (**125**, **1300**), suggesting that enhanced superoxide production alone is not sufficient to produce endothelial dysfunction. Increased peroxynitrite formation or protein nitration was also reported in the serum (**643**, **1402**), vasculature (**269**, **565**, **643**, **776**, **815**, **1217**, **1252**), and kidneys (**1080**) of SHR rats, malignant stroke-prone spontaneously hypertensive rats (M-SHRSP), and SHR/NDmcr-cp (SHR/cp) rats (genetic model of the metabolic syndrome). Antioxidant-rich diet (**1080**), the SOD mimetic M40403 (**269**), the polyphenol chlorogenic acid (**1217**), the angiotensin-converting enzyme inhibitor ramipril (**776**), the adrenoceptor blocker with antioxidant properties carvedilol (**815**), and the cofactor of eNOS tetrahydrobiopterin (**565**) attenuated hypertension and nitrotyrosine formation in vasculature and kidneys and improved compromised vascular function and end-organ damage.

Angiotensin II, a well-known factor in the pathogenesis of most cardiovascular disorders and a natural regulator of blood pressure, can induce superoxide formation mediated at least in part by vascular NAD(P)H oxidases (**416**, **478**, **733**, **889**, **1065**). Reactive oxidant species in turn can exert direct oxidative effects, but can also signal through pathways such as mitogen-activated protein kinases, tyrosine kinases, and transcription factors and lead to events such as inflammation, hypertrophy, remodeling, and angiogenesis (**478**, **969**, **1004**). Recent studies have demonstrated that angiotensin II can also induce peroxynitrite formation and PARP activation in

endothelial cells in vitro (880, 1236) and in aorta, heart, and kidneys of rats (492, 656, 1236,1349) and mice (1159, 1342) following chronic infusion in vivo. Protein nitration correlated with the extent of endothelial dysfunction (1349), and both were attenuated by supplementation with tetrahydrobiopterin (656).

Other forms of experimental hypertension induced by lead (325, 1323), mineralocorticoids (1214), cyclosporin (170), diet-mediated obesity (327, 1077), and renovascular/renal dysfunction (119,327, 1325) are associated with increased ROS-mediated inactivation of NO with sequential increases of 3-NT in plasma (170, 1323, 1325), vasculature (119, 327, 1077, 1325), heart (1077,1214, 1323, 1325), kidney (119, 327, 1077, 1323), liver (1077, 1325), and brain (1323). Remarkably, in most of these conditions, the decrease in blood pressure and improvement in hypertension-associated endothelial dysfunction and end-organ damage to various drugs or interventions aiming to reduce blood pressure and decrease oxidative stress (e.g., vitamin E, losartan, tempol, carvediol, diet, etc.) was always associated with reduction of 3-NT in vasculature, heart, and various other organs (170, 327, 1323, 1325). Thus it appears that peroxynitrite plays an important role in the pathophysiology of hypertension.

In conclusion, multiple lines of evidence discussed above and listed in **Table 4** suggest that peroxynitrite plays an important role in various forms of cardiovascular dysfunction and injury; pharmacological neutralization of this reactive oxidant or targeting the downstream effector pathways may represent a promising strategy to treat various cardiovascular disorders.

C. Nitric Oxide and Peroxynitrite in Circulatory Shock

Circulatory shock defines a syndrome precipitated by a systemic derangement in perfusion leading to widespread cellular hypoxia and vital organ dysfunction. Depending on its initial pathophysiological mechanisms, shock is subdivided in three main categories, namely, cardiogenic, hemorrhagic, and septic shock. In the advanced stages, all shock states evolve to a common clinical picture characterized by profound cardiovascular failure, the activation of cellular cytotoxic effectors (polymophonuclear leukocytes), and the upregulation of an array of proinflammatory genes, leading to systemic inflammation, organ dysfunction, and death (569). An extensive body of experimental evidence supports the view that ROS and RNS, in particular peroxynitrite, are crucial components of this chain of pathophysiological events.

Circulatory shock is a perfect condition to enhance the production of peroxynitrite, as both parent radicals NO and $O_2^{\cdot-}$ are formed in large amounts and in close proximity in this setting (380, 766). The upregulated production of $O_2^{\cdot-}$ principally arises from the reactions catalyzed by NADPH oxidase (629, 757), present in leukocytes and endothelial cells, and by the conversion of xanthine dehydrogenase into xanthine oxidase, which occurs during inflammation or episodes of tissue ischemia (425, 1261). $O_2^{\cdot-}$ is also formed by the partial reduction of molecular oxygen within mitochondria, due to electron leak from the respiratory chain, a natural phenomenon that is enhanced in conditions of cellular hypoxia and oxidant-mediated mitochondrial damage (947). Finally, $O_2^{\cdot-}$ may be generated by the uncoupling of NOS in conditions of substrate (L-arginine) or cofactor (tetrahydrobiopterin, BH4) deficiency, as prevails in underperfused tissues during shock or ischemia (1011, 1392, 1393). With respect to NO, its major sources are the enzymatic activities of the various NOS. In the early stages of shock, production of NO is essentially driven by the stimulated activity of eNOS, triggered in part by the action of platelet activating factor (PAF) on the endothelium (1226). At later stages, production of NO is markedly enhanced following the diffuse expression of iNOS, upon cellular activation by microbial products and

proinflammatory cytokines (for review, see Refs. **380**, **766**). According to some recent studies, a mitochondrial isoform of NOS (mtNOS) might also represent a significant source of NO during circulatory shock (**17**, **107**). A nonenzymatic source of NO has also been described related to the reduction of nitrites in acid and reducing conditions, as can occur in ischemic tissues (**833**). Formation of peroxynitrite from $O_2^{\cdot-}$ and NO in circulatory shock has been evaluated by the detection of nitrotyrosine, and by the peroxynitrite-dependent oxidation of the fluorescent probe dihydrorhodamine 123 (DHR) to rhodamine (**605**, **610**). Plasma DHR oxidation and formation of nitrotyrosine in tissues (aorta, liver, lung, and small intestine) has been detected in rodents during systemic inflammation and shock induced by zymosan, a yeast cell wall component (**257**, **258**,**261**, **262**, **355**). These modifications were abrogated by genetic suppression of iNOS (**266**), and by various treatment strategies removing peroxynitrite, including MnTBAP (**261**), melatonin (**255**,**355**), and *N*-acetylcysteine (NAC) (**257**), proving the involvement of NO-derived peroxynitrite in DHR oxidation and nitrotyrosine formation. Comparable results were obtained in experiments using LPS as the inducer of shock. For example, nitrotyrosine formation occurred in skeletal muscle of rats challenged with LPS (**347**, **980**), with a time course similar to that of iNOS expression in this tissue (**347**), as well as in the aorta (**298a**, **1237**) and in the heart, where it was suppressed by melatonin (**298a**), the NOS inhibitor L-NAME (**1237**), and the peroxynitrite decomposition catalyst FeTPPS (**729**). Nitrotyrosine has further been detected in the lung (**12**), liver (**798**), kidney (**1430**), and gut (**243**, **1183**) in various animal models of septic shock. In humans, one study indicated increased plasma nitrotyrosine levels during septic shock, from undetectable levels in normal subjects to values as high as 118.0 ± 22 μM in septic patients (**420**). Increased myocardial nitrotyrosine immunostaining was also demonstrated from myocardial biopsy speciments of patients with sepsis (**Fig. 11**; Ref. **707**).

Evidence also exists that peroxynitrite formation is triggered during experimental hemorrhagic shock. Szabo et al. (**1238**) first reported an increased plasma oxidation of DHR in rat hemorrhagic shock that could be suppressed by the NOS inhibitor L-NAME. Later studies confirmed these observations by showing the formation of nitrotyrosine in organs (lung, gut, liver, and aorta) from rats after hemorrhage and resuscitation (**767**, **911**, **1296**, **1460**). Nitrotyrosine immunostaining in hemorrhagic shock was suppressed by NOS inhibitors, by uric acid, an endogenous peroxynitrite scavenger (**1296**, **1460**), and by genetic suppression of NADPH (**745**).

1. Mechanisms of tissue injury by peroxynitrite during circulatory shock

There are basically four major mechanisms underlying the toxicity of peroxynitrite formed from NO and $O_2^{\cdot-}$ in shock. These include lipid peroxidation; the depletion of antioxidant reserves, especially reduced GSH; the oxidation/nitration of proteins with special emphasis on mitochondrial proteins; and finally, the induction of DNA damage leading to the activation of the nuclear enzyme PARP.

Peroxynitrite is a major initiator of lipid peroxidation, generating lipid radicals that propagate free radical reactions, thereby degrading membrane lipids (**311**, **560**, **1055**). In vivo, the measurement of thiobarbituric acid reactive substances, such as malondialdehyde (MDA), has been used as an index of lipid peroxidation in pathological conditions. Elevated MDA levels have been measured in virtually every organ in experimental models of septic (**258**, **355**, **763**, **764**, **1109**, **1183**) and hemorrhagic shock (**767**, **1224**), where the contributing role of peroxynitrite has been attested by the reduction of MDA levels afforded by various

antiperoxynitrite strategies including NAC (258), melatonin (355), MnTBAP, or the peroxynitrite decomposition catalysts FeTMPS and FeTMPyP (1109), as well as the NOS inhibitor and peroxynitrite scavenger mercaptoethylguanidine (MEG) (1224).

A second major mechanism of peroxynitrite-dependent toxicity in shock is its ability to rapidly oxidize GSH, the major endogenous scavenger of oxidants and free radicals (273, 709, 1289). The importance of intact cellular GSH pools to limit peroxynitrite-induced cellular injury is illustrated by findings of Salvemini et al. (1107), who showed that endogenous GSH was essential to limit the development of vascular hyporeactivity and endothelial dysfunction in response to exogenous peroxynitrite and peroxynitrite endogenously produced during endotoxic shock. It is also noteworthy that the depletion of endogenous GSH with L-buthionine-sulfoximine (BSO) markedly enhanced peroxynitrite-mediated tissue injury in animal models of septic shock (273,278), whereas increasing cellular GSH by treatment with NAC reduced such detrimental consequences (257, 258).

Abnormal oxidative metabolism at the cellular level is a critical event triggering organ damage and dysfunction in shock (393, 762). Peroxynitrite readily inactivates mitochondrial enzymes involved in oxidative metabolism and can thereby shut down cellular energetics. This effect is particularly likely in shock, where mitochondria can produce copious amounts of peroxynitrite, due to stimulated activity of mitochondrial NOS and enhanced electron leak from the respiratory chain leading to $O_2^{\cdot-}$ formation (17, 127, 947, 1308), a phenomenon further amplified by the inactivation of mitochondrial MnSOD by peroxynitrite (826). In a recent experimental study, Alvarez et al. (17) showed that, following administration of endotoxin to the rat, steady-state concentrations of peroxynitrite rose from 8 to 12 nM in heart mitochondria and from 21 to 49 nM in diaphragm mitochondria. The relevance of these metabolic alterations with respect to human septic shock has been highlighted in a study by Brealey et al. (132). In septic patients, a decrease in tissue ATP levels and mitochondrial complex I activity was measured in skeletal muscle biopsies, which correlated with increased clinical severity and NO production within muscles, supporting a critical role of NO-peroxynitrite in the suppression of mitochondrial respiration in sepsis (132).

Peroxynitrite may further break down cellular energy metabolism by triggering DNA strand breaks, resulting in PARP activation and consumption of cellular NADH, the main reducing equivalent used to support oxidative phosphorylation (392, 624). The role of PARP activation in mediating cellular energetic failure has been widely established in septic (259, 276, 1046, 1457, 1462) and hemorrhagic (1224, 1350, 1460) models of shock. In humans, evidence for a similar role of PARP has been obtained in septic patients. Investigators measured mitochondrial respiration in cultured human umbilical vein endothelial cells (HUVEC) exposed to serum obtained from healthy patients or patients in septic shock. Compared with healthy serum, septic serum induced a marked reduction of mitochondrial respiration in HUVEC cells, which could be reversed by the NOS inhibitor N^G-methyl-L-arginine (L-NMA) or the PARP inhibitor 3-aminobenzamide, implying that a NO/peroxynitrite-dependent activation of PARP is involved in the inhibition of mitochondrial respiration in septic shock (124). In addition to impairing cell energetics, it must also be underscored that PARP may foster the development of inflammation during circulatory shock, by acting as a coactivator of an array of cell signal transduction pathways, and most sigificantly the transcription factor NFκB, as exposed previously (see sect. V).

2. Role of peroxynitrite in the pathophysiological alterations of circulatory shock

A) PERIPHERAL VASCULAR FAILURE.

Circulatory shock is characterized by profound disturbances in cardiovascular homeostasis, affecting all components of the circulation, i.e., the myocardium, the vascular smooth muscle, and the endothelium. In vivo, intense nitrotyrosine immunostaining occurs in the aorta in several models of shock, pointing to significant vascular peroxynitrite formation. Using several pharmacological approaches, peroxynitrite was proven to be an important culprit of peripheral vascular failure in shock, a condition characterized by arterial hypotension and vascular hyporeactivity to vasoconstricting agents. In rat endotoxic shock, both MnTBAP (**1457**), FeTTPs (**265**), and melatonin (**298a**) alleviated vascular hyporeactivity to norepinephrine, while inhibiting aortic peroxynitrite generation (**298a**, **1457**). Conversely, enhancing the formation of peroxynitrite by depleting endogenous glutathione with BSO markedly increased vascular hyporeactivity during endotoxic shock (**278**). Similar observations have been made in hemorrhagic shock: inhibition of peroxynitrite generation using MnTBAP (**1231**) or MEG (**1460**) improved aortic contractility and reduced arterial hypotension. Further evidence supports the concept that the final effector mechanism of vascular failure in shock may be due to the peroxynitrite-mediated activation of PARP. Vascular hyporeactivity occurring in experimental models of both septic and hemorrhagic shock was ameliorated by inhibitors of PARP or its genetic deletion (**275**, **451**, **623**, **768**, **1183**,**1223**, **1463**). Several recent investigations have also shown that peroxynitrite might also affect vascular contractility in shock by altering catecholamine signaling. The systemic administration of peroxynitrite markedly inhibited pressor and vasoconstrictor responses induced by α-adrenergic catecholamines in rats (**84**). In addition, peroxynitrite has been reported to oxidize and inactivate norepinephrine and dopamine, and to block the binding of these catecholamines to their α-adrenoreceptors (**1255**, **1256**).

B) VASCULAR ENDOTHELIAL DYSFUNCTION.

The vascular endothelium plays a number of critical functions in normal vascular physiology, maintaining vascular tone, tuning the balance between procoagulant and anticoagulant factors, and regulating leukocyte adhesion and emigration into the extracellular matrix. Most of these functions are accomplished through the finely regulated release of NO and prostacyclin (PGI_2) by endothelial cells (**852**, **1372**). These functions are all disrupted during circulatory shock, leading to impaired blood flow regulation and reduced oxygen supply to vital organs.
Villa et al. (**1328**) were the first to show that infusion of authentic peroxynitrite in isolated perfused hearts resulted in a severe impairment of endothelial-dependent relaxation in coronary vessels. Seminal works by Szabo et al. (**1233**) then provided evidence that peroxynitrite-dependent endothelial dysfunction was consecutive to activation of PARP: aortic vascular rings exposed ex vivo to peroxynitrite, as well as vascular rings taken from endotoxemic rats, exhibited reduced endothelium-dependent relaxant responses to acetylcholine that were significantly ameliorated by the PARP inhibitor 3-aminobenzamide. In support of the peroxynitrite/PARP mechanism of endothelial dysfunction, several studies reported an improved endothelial function by pharmacological blockade of peroxynitrite generation (**265**, **278**, **1457**) and PARP activation (**623**,**1046**, **1183**) in rodent septic shock. Peroxynitrite and PARP can trigger multiple cooperating mechanisms to induce endothelial dysfunction in shock. First, peroxynitrite limits endothelial NO production by inactivating eNOS through oxidation of its zinc thiolate center (**1469**). Second, it oxidizes the NOS cofactor tetrahydrobiopterin (BH_4), resulting in eNOS uncoupling (**725**). Third, peroxynitrite potently inactivates PGI_2 synthase by

tyrosine nitration, resulting in failing prostacyclin synthesis and secondary formation of vasoconstricting prostaglandins such as thromboxane A_2 (**1469**, **1472**). The latter mechanism has been shown to promote vasospasm of coronary vessels treated by endotoxin in vitro (**39**). Finally, PARP-dependent reduction of cellular NAD may also suppress NO formation by depleting endothelial stores of NADPH, an essential cofactor of NOS (**430**).

C) MYOCARDIAL DEPRESSION.

Impaired myocardial contractile function is a well-documented feature of circulatory shock. It may be triggered by a myriad of mechanisms, including microvascular dysfunction, infiltration by activated leukocytes, and the generation of inflammatory mediators, mainly TNF-α and IL-1β, which lead to an overproduction of NO with subsequent cardiodepressive effects. The role of NO as an inducer of myocardial failure in shock is however controversial, in view of conflicting results indicating either deleterious or beneficial effects of NO on cardiac function in this setting (**729**). In fact, sound experimental evidence supports that peroxynitrite might be the link between NO and cardiac depression in shock (**384**, **604**, **670**, **729**). Overproduction of NO, superoxide, and peroxynitrite occurs in the myocardium during the first 4 h of endotoxemia, and such changes are correlated with significant reductions of cardiac work, oxygen consumption, and cardiac efficiency (**670**). In a model of isolated working hearts perfused with TNF-α and IL-1β, Ferdinandy et al. (**384**) reported a steady decline of myocardial contractile function accompanied by enhanced perfusate nitrotyrosine and dityrosine levels. These alterations were markedly attenuated by the peroxynitrite decomposition catalyst FeTPPS. More recently, Lancel et al. (**729**) showed that rats challenged with endotoxin disclosed myocardial nitrotyrosine formation as well as a severe impairment of cardiac contractile performance, which were almost suppressed by FeTPPS. Although not addressed in these studies, one may speculate that the mechanisms underlying the cardiodepressive effects of peroxynitrite in shock are similar to those reported in other cardiac conditions (heart failure, myocardial infarction, cardiomyopathy), and which include the inhibition of calcium pumps, creatine kinase, mitochondrial enzymes, and α-actinin, as well as the activation of MMPs, as detailed in the specific sections on these topics. Additional evidence favoring the role of myocardial PARP activation as an important contributor of peroxynitrite-mediated cardiodepression has been presented. The severe depression of systolic and diastolic left ventricular functions induced by endotoxin in mice is virtually suppressed in mice genetically deficient in PARP (**983**), and there is a direct correlation between the degree of myocardial PARP activation and the severity of cardiac dysfunction in humans with septic shock (**1184**).

D) SYSTEMIC INFLAMMATION.

Whatever its primary mechanism, circulatory shock rapidly evolves to a state of systemic inflammation, manifested by the de novo generation of an array of proinflammatory and vasoactive mediators, including inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), chemokines (e.g., IL-8), enzymes (e.g., iNOS, COX2), coagulation proteins, and lipid mediators, to name but a few (**380**, **544**, **569**, **662**). A key mechanism underlying the upregulation of these mediators lays in the activation of the transcription factor NFκB, triggered by microbial products (e.g., LPS), inflammatory cytokines, and, supposedly, oxidants and free radicals (**759**). Peroxynitrite has been proposed to function, in vitro, as an NFκB activator, especially in leukocytes, where it was found to stimulate the expression of TNF-α and IL-8 (**391**, **640**, **851**, **1476**). In vivo, two

studies suggested a similar function of peroxynitrite in shock, since the peroxynitrite decomposition catalyst FeTPPS attenuated the activation of NFκB in the intestine (**803**) and the heart (**729**) of endotoxemic rats. The concept of peroxynitrite-mediated NFκB activation has however recently been challenged by results indicating that peroxynitrite inhibited instead of activated NFκB (**749**, **1006**, **1007**). Further work must therefore be engaged before any conclusions can be drawn regarding this particular issue. An alternate mechanism whereby peroxynitrite might activate NFκB and downstream inflammatory pathways is dependent on PARP. Oliver et al. (**973**) first demonstrated that the absence of functional PARP suppressed the activation of NFκB in immunostimulated cells and that PARP-deficient mice did not exhibit NFκB nuclear translocation when challenged with endotoxin, an effect associated with a markedly reduced release of inflammatory cytokines. These observations have since been confirmed by other investigators (**502**, **649**) and recently extensively reviewed (**520**, **1331**). Overall, the above-presented studies support the contention that peroxynitrite may act to foster inflammatory responses in shock by playing complex roles on the regulation of NFκB, but additional studies are needed to more precisely assess this point.

E) TISSUE LEUKOCYTE SEQUESTRATION.

In addition to its potential roles in the upregulation of NFκB, peroxynitrite can also participate to the perpetuation of inflammation by enhancing neutrophil activation. In vitro, both exogenous and endogenously synthesized peroxynitrite increased the biosynthesis of IL-8, a major chemoattractant cytokine, by human leukocytes (**641**, **674**, **1476**). Peroxynitrite also enhanced leukocyte endothelial interactions by increasing β_2-integrin at the surface of leukocytes (**1477**), by stimulating the expression of P- and E-selectins, as well as ICAM-1 in endothelial cells (**272**, **1118**,**1178**, **1447**), and by impairing endothelial formation of NO and PGI_2 (see above), which are essential for the antiadhesive phenotype of the endothelium. In models of shock elicited by endotoxin or zymosan, the accumulation of neutrophils in tissues such as the heart (**729**), lung, gut (**258**, **259**), peritoneum (**259**), and kidney (**1418**) was dramatically reduced by uric acid (**1418**), FeTPPS (**729**), MnTBAP (**259**), and NAC (**258**), supporting a similar role of peroxynitrite in vivo. Scavenging peroxynitrite with uric acid also suppressed liver neutrophil accumulation and prevented liver injury in a model of hemorrhagic shock in rats (**1296**).

F) GUT MUCOSAL BARRIER FAILURE.

The loss of the normal barrier function of the gut mucosa is a critical event in shock states. The resulting translocation of microbial products and inflammatory mediators towards the circulation has been proposed as a triggering mechanism of remote organ damage in this setting (**944**). A contributing role of peroxynitrite to gut barrier failure in shock has been proposed by Salvemini et al. (**1109**), who showed that various peroxynitrite decomposition catalysts reversed the mucosal injury evoked by the administration of endotoxin to the rat, an effect associated with the suppression of microvascular injury and lipid peroxidation within the intestines. These effects might either reflect direct toxicity of peroxynitrite, or indirect effects related to the activation of PARP. In support of the latter hypothesis, several in vitro studies showed that exposure of human enterocyte monolayers to peroxynitrite was followed by the occurrence of DNA strand breakage and PARP activation. The ensuing functional loss of intestinal barrier function, evaluated by the hyperpermeability to a fluorescent marker, was totally prevented by pharmacological inhibitors of PARP (**202**, **666**, **867**). These conclusions were further supported by the in vivo demonstration

that pharmacological inhibition of PARP (1225) or its genetic suppression (767, 768) abrogated the intestinal damage and the mucosal hyperpermeability complicating endotoxic (1225) and hemorrhagic shock (767), and suppressed the occurrence of bacterial translocation (1263).

In summary, circulatory shock is a leading cause of death in intensive care units. Considerable improvement in our understanding of the molecular and cellular mechanisms of shock over the past 20 years makes it now a reasonable expectation that novel, efficient mechanism-based therapies will emerge in the near future. Considerable evidence now exists that overproduction of NO and superoxide, triggering the generation of large amounts of peroxynitrite, is a central aspect of shock pathophysiology. In addition to direct cytotoxic effects such as the peroxidation of lipids, proteins, and DNA, peroxynitrite also occupies a critical position in a positive feedback loop of inflammatory injury, by (directly or indirectly, via PARP activation) activating proinflammatory signaling and by triggering the recruitment of phagocytes within injured tissues, leading to further NO, superoxide, and peroxynitrite production, which will progressively amplify the initial inflammatory reactions (see sect. VI*D*, Fig. 14). These various observations support the view that future strategies reducing peroxynitrite or its precursors might have a considerable therapeutic impact in clinical circulatory shock.

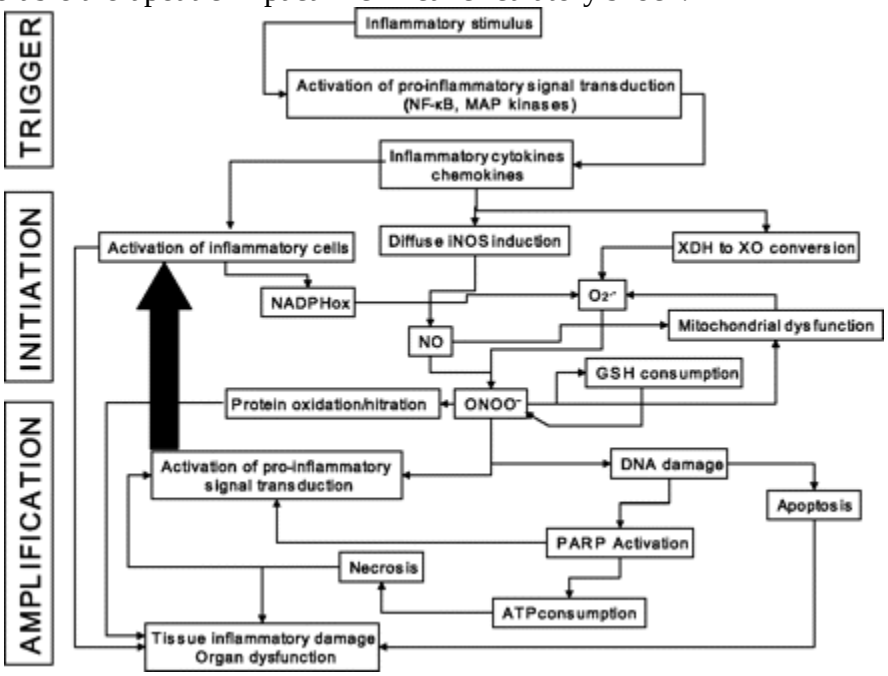

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FIG. 14.

Mechanisms of amplification of inflammation by peroxynitrite. Inflammation is triggered by the activation of multiple signaling cascades culminating in the upregulated production of an array of proinflammatory cytokines and chemokines. Those initiate a more complex inflammatory reaction characterized by the activation of inflammatory cells and the stimulated activity of enzymes, including inducible NO synthase (iNOS), which produces high amounts of NO, and the superoxide ($O_2^{\bullet-}$)-producing enzymes NADPH oxidase (NADPHox) and xanthine oxidase (XO). The simultaneous production of NO and $O_2^{\bullet-}$ results in the generation

of peroxynitrite ($ONOO^-$), which in turn damages target molecules including proteins, glutathione (GSH), mitochondria, and DNA. DNA damage can initiate apoptotic cell death and is also the obligatory trigger for the activation of poly(ADP-ribose) polymerase (PARP), which may induce cell necrosis by ATP depletion. Both $ONOO^-$ and PARP further participate to the upregulation of proinflammatory signal transduction pathways, thereby producing a self-amplifying cycle of inflammatory cell injury, as indicated by the black arrow.

D. Nitric Oxide and Peroxynitrite in Local Inflammation

Multiple lines of evidence, gathered in the past 15 years, indicate that enhanced NO production due to induced expression of iNOS by proinflammatory cytokines is instrumental in the pathophysiology of inflammation. Experimentally, the simplest model used to investigate inflammation is the paw edema triggered by the intraplantar injection of the phylogogenic agent carrageenan in rodents, which induces vascular hyperpermeablity and intense infiltration by polymorphonuclear leukocytes (**1110**). Implication of NO in these changes was initially established by Ialenti et al. in 1992 (**592**), reporting a marked reduction of edema and vascular hyperpermeability when carrageenan was coinjected with the NOS inhibitors L-NAME or L-NMMA. These early observations were then confirmed by the significant prevention of carrageenan-induced paw inflammation in iNOS knockout mice (**1352**), as well as in rats treated with the selective iNOS inhibitors aminoguanidine and *N*-iminoethyl-L-lysine (L-NIL) (**1110**). These studies also indicated that carrageenan triggered the formation of nitrotyrosine, which was suppressed by iNOS inhibition, supporting a role for locally produced peroxynitrite in the pathophysiology of inflammation in this model (**1110**). This hypothesis was elegantly confirmed by Salvemini et al. (**1111**), who showed that FeTPPS was able to prevent the formation of paw edema and the release of lactate dehydrogenase, a marker of cell necrosis, in rats injected with carrageenan. The key role of iNOS-derived peroxynitrite in this prototypical inflammatory model was then established as a central component of inflammation in more complex paradigms of inflammation, and especially chronic arthritis and inflammatory bowel diseases, as summarized below.

1. Chronic arthritis

Inflammation stands in the foreground of a large number of chronic conditions that have the joints as one of their principal targets. These conditions include rheumatoid arthritis (RA), juvenile chronic arthritis, ankylosing spondylitis, and systemic lupus erythematosus. The most prevalent is RA, which exists in ~1% of the adult population (**1116**, **1222**). The pathogenesis of RA involves the early invasion of the synovial membrane by T lymphocytes, which activate resident cells (monocytes and synovial fibroblasts) to produce large amounts of proinflammatory cytokines, mainly TNF-α and IL-1β, leading to proliferation and neovascularization of the synovial membrane, activation of osteoclasts, and generation of oxidants and free radicals, eventually resulting in the progressive destruction of cartilage (**396**).
Several lines of evidence indicate that an overproduction of NO contributes to the pathogenesis of chronic arthritis (**537**, **876**, **955**). In rodent models of arthritis (e.g., induced by Freund adjuvant or type II collagen), increased levels of nitrite/nitrate in plasma (**227**, **256**, **398**, **857**) and in articular fluid (**1203**, **1354**), as well as a high expression of iNOS in hyperplastic synovium (**227**, **856**) and chondrocytes (**1419**), have been demonstrated. In humans, increased

circulating levels of nitrate/nitrite are present in arthritic patients (377), and the synovial tissues of patients with RA express iNOS (860, 1103) and produce abnormally high amounts of NO (227). The pathogenic role of the increased production of NO in arthritis has been attested by pharmacological studies evaluating the effects of NOS inhibitors. In rat adjuvant arthritis, development of the disease was ameliorated by the nonselective inhibitors L-NAME or L-NMMA (592, 979), by the iNOS selective inhibitors L-NIL or aminoguanidine (227), and trimethoxy-trifluoromethylchalcone (AEITU) (1419), by PPA250, which suppresses the activity of iNOS by preventing its dimerization (970), and by aminoethyl-isothiourea (ttCH), which downregulates iNOS expression (1082). Similar beneficial effects have been obtained in mouse collagen-induced arthritis with the use of GW274150, a highly potent and long-acting selective inhibitor of iNOS (256) and PPA250 (970). Interestingly, one study reported that the partially selective nNOS inhibitor 7-nitroindazole was beneficial in rat adjuvant arthritis (1039), suggesting a pathological role of this NOS isoform, in addition to iNOS, in the development of joint inflammation in this animal model. Further confirming the pharmacological studies, iNOS knockout mice were found to be relatively resistant to collagen-induced arthritis, as shown by reduced joint inflammation and paw swelling, and by less structural damage of large joints, both radiographically and histologically (256).

A series of experiments have indicated that peroxynitrite may represent the final executioner of NO-dependent cytotoxicity and inflammation in arthritis. Increased nitrotyrosine formation has been observed in cartilage and subchondral bone of rodents suffering from adjuvant and collagen-induced arthritis (256, 1241, 1419). The critical role of iNOS-derived NO has been proven by the finding of a complete absence of nitrotyrosine in articular tissues of iNOS-knockout mice challenged with collagen (256). Furthermore, the SOD mimetics M40403 also reduced nitrotyrosine formation and joint inflammation in a rat model of collagen-induced arthritis (1108). There is additional evidence of protein nitration in joints from rheumatoid patients, who disclose increased levels of nitrotyrosine in plasma and synovial fluid, and nitrotyrosine formation localized within macrophages and vascular smooth muscle in the inflamed synovium (842, 1115).

An early pharmacological study using mercaptoethylguanidine, an anti-inflammmatory compound with combined mechanism of action as a selective iNOS inhibitor and peroxynitrite scavenger, showed an almost complete reversal of collagen-induced arthritis in mice receiving the drug (129). A more thorough investigation of the role of peroxynitrite has been brought up by Mabley et al. (819), who evaluated the effects of FP-15, a novel porphyrin-base peroxynitrite decomposition catalyst, in a mouse model of collagen-induced arthritis. Treatment with FP-15, started at the time of the second collagen injection, markedly reduced both arthritis incidence and severity, as shown by decreased joint swelling and redness of the paws. FP-15 alleviated malondialdehyde accumulation (a marker of lipid peroxidation) and myeloperoxidase activity (indicative of neutrophil infiltration) in affected joints, together with a significant reduction of the local concentrations of the Th1 cytokine IL-12 and of the chemokine MP-1alpha. Importantly, reduced inflammation was also noted, although to a lesser extent, when FP-15 was started 7 days after collagen injection, indicating that NO, superoxide, and peroxynitrite generation represent delayed phenomena in the immunologic and inflammatory series of events associated with arthritis (819).

An important mechanism whereby peroxynitrite may sustain inflammatory changes in arthritis has been proposed to rely on the induction of DNA oxidative damage and subsequent activation of PARP (see sect. IV). In support of this hypothesis, a human study performed in patients with

RA reported a significant elevation of DNA strand breaks in peripheral mononuclear cells compared with healthy subjects (**99**). A strong activation of PARP has been demonstrated in joint tissues from rodents with collagen-induced arthritis, and this activation was suppressed when peroxynitrite formation was blocked by treatment with a selective iNOS inhibitor or by genetic iNOS suppression (**256**). Further evidence for a pathogenic role of PARP has been given by the considerable reduction of joint inflammation provided by various PARP inhibitors, including nicotinamide (**875**), 5-iodo-6-amino-1,2-benzopyrone (**1241**), and PJ-34 (**818**) in different rodent models of arthritis. Overall, these different sets of data clearly implicate NO, peroxynitrite, and PARP in the pathophysiology of arthritis and indicate that novel, potent peroxynitrite decomposition catalysts and PARP inhibitors might become important therapeutic agents for the treatment of chronic joint inflammation in years to come.

2. Inflammatory bowel diseases

The second major chronic inflammatory process deserving discussion here is represented by the inflammatory bowel diseases (IBDs), which encompass two entities, ulcerative colitis and Crohn's disease (**1123**). IBD pathogenesis relies on dysregulated interactions of the host mucosal intestinal immunity with the huge antigenic load represented by the microorganisms present in the gut lumen (**395**), a concept supported by the fact that inflammation does not develop in a germ-free environment in animal models of IBD. The importance of proinflammatory cytokines in IBD has been highlighted by the therapeutic successes obtained with anti-TNF antibodies in patients with Crohn's disease (**513**). A major mechanism underlying the deleterious effects of cytokines in IBD is represented by the induction of iNOS and subsequent overproduction of NO in the injured intestine. In chemically induced models of IBD in rodents, triggered by the intrarectal administration of trinitrobenzene sulfonic acid (TNBS) or acetic acid in ethanol, as well as by the addition of high-molecular-weight dextrans to the drinking water, increased expression and activity of iNOS (**562**, **1426**) have been documented in the inflamed colon. Also, in rhesus monkeys spontaneously developing symptoms and histopathological features close to those of human ulcerative colitis, there is a high expression of iNOS and high NO production in the colic mucosa (**105**). Similarly, in humans, increased expression or activity of iNOS, as well as elevated levels of luminal nitrite have been detected in patients suffering from ulcerative colitis and Crohn's disease (**801**, **874**).

A number of studies using NOS inhibitors with differing isoform selectivity have helped to understand the roles of NO in experimental IBD. In rat models of TNBS-induced colitis, nonselective NOS inhibitors (which block the activity of all NOS isoforms) produced contrasting results, with improvements of local inflammation and morphological mucosal damage in some studies, but with opposite results (i.e., increased mucosal inflammation and injury) in others (**322**,**683**, **1401**). Importantly, in the latter studies, treatment was started before or simultaneously with colitis induction. In contrast, NOS inhibition was beneficial when treatment was started after the induction of colitis (**557**, **683**, **929**). In dextran-induced colitis in mice, inflammation was also exacerbated by the prophylactic administration of a massive, nonselective, dose of aminoguanidine (**956**), while administration of the highly selective iNOS inhibitor 1400W (**714**) was protective. It is also important to mention that iNOS knockout mice were largely protected against colitis induced by dextran (**562**, **714**) and TNBS/ethanol (**1464**). In the latter study, iNOS knockout mice showed a smaller loss of body weight, an attenuated morphological damage to intestinal epithelium, less mucosal immunostaining for nitrotyrosine, and a lower colic content in

malondialdehyde, indicative of a reduced level of nitrative and oxidative stress in the colon of knockout animals. Overall, these various results suggest an important protective role of NO generated by the constitutive isoforms of NO at the early stage of colitis, possibly through the preservation of mucosal perfusion and/or mitigation of leukocyte recruitment. Alternatively, the strong induction of iNOS that occurs at a more advanced stage contributes to inflammation and mucosal damage in this model.

Supporting a role for iNOS-dependent generation of peroxynitrite in the pathogenesis of IBD, biochemical evidence of peroxynitrite generation (formation of nitrotyrosine) has been shown both in experimental models of colitis (**885**, **1170**, **1464**) and in human samples of active Crohn's lesions, in which massive nitrotyrosine immunostaining has been reported (**1170**). The formation of peroxynitrite in such circumstances is largely favored, since not only NO but also superoxide are being formed in the inflamed intestines (**268**, **321**), which explains the beneficial effects of SOD mimetics in experimental colitis (**268**). In addition, it is noteworthy that the direct application of authentic peroxynitrite within the gut elicits a severe, colitis-like, inflammatory response (**1052**). The pathogenic role of peroxynitrite has been firmly established by studies using pharmacological approaches to reduce peroxynitrite in the inflamed colon. Thus treatment of rats with the iNOS inhibitor and peroxynitrite scavenger mercaptoethylgaunidine markedly alleviated colonic injury induced by intrarectal instillation of TNBS (**1456**). Also, the peroxynitrite decomposition catalyst FP-15 exerted potent protective effect in mice fed with 5% dextran sulfate sodium (**819**). Treatment with this compound, when started simultaneously with dextran, largely reduced colon damage and inflammation, as assessed by histological evaluation, and reduced rectal bleeding, weight loss, and colon shortening. Furthermore, FP-15 reduced the colitis-induced increase in colonic malondialdehyde levels, indicative of the ability of the drug to attenuate oxidative stress, and reduced colonic infiltration by activated phagocytes, as determined by reduced myeloperoxidase levels (**819**).

As in the case of arthritis, there is large evidence that a common final pathway of peroxynitrite-dependent inflammatory changes in IBD depends on the activation of PARP. First, PARP is strongly activated in various rodent models of colitis, and second, pharmacological inhibition of PARP or PARP genetic suppression provided significant resistance against the development of colitis in these models (see Ref. **1230** for recent review). In addition to preventing cell necrosis by inhibiting ATP depletion, it has also been established that the absence of PARP exerted direct anti-inflammatory effects in TNBS-induced colitis as well as in the spontaneous colitis that develop in IL-10-deficient mice, as shown by decreased neutrophil infiltration, reduced release of pro-inflammatory cytokines and chemokines, and smaller increases in colon permeability (**634**, **818**,**1461**). In a recent work in mice challenged with intrarectal TNBS, reduced colon ulceration and apoptotic mucosal cell death were noted in PARP knockout mice and could be correlated with a reduced activation of the MAPK JNK. This was followed by a depressed activity of the transcription factor AP-1 in the colon, together with an enhanced expression of the antiapoptotic protein Bcl-2 (**1458**). These results represent a further illustration of the very complex interactions occurring in vivo between PARP, cell death, and inflammation, as exposed in detail in section IV.

3. Tissue inflammation from toxic origin

In addition to its involvement in the pathophysiology of well-characterized acute and chronic inflammatory diseases, peroxynitrite is also suspected to play an important role in the

development of organ damage and inflammation triggered by various drugs and chemical agents. A detailed description of these emerging roles of peroxynitrite in drug-dependent toxicity is beyond the scope of this review, and further informations can be obtained in an extensive review on this topics recently published by Denicola and Radi (**311**). Two drugs deserve here some discussion, in view of their widespread use in clinical medicine, namely, doxorubicin (DOX) and acetaminophen.

DOX is an anthracycline antibiotic used as an antitumor agent, whose major side effect is significant cardiotoxicity (**985**). DOX forms a complex with cardiolipin within the mitochondrial inner membrane of cardiomyocytes, where it is reduced by NADH dehydrogenase from the respiratory chain to form a semiquinone radical, which is then oxidized back to the parental compound by passing the electron received onto molecular oxygen, forming a superoxide radical (**843**). The superoxide formed during the redox cycling of DOX rapidly combines with NO to generate peroxynitrite, as indicated by the intense nitrotyrosine staining demonstrated in rodents treated with DOX (**985**, **1355**) (**Fig. 13*C***). Importantly, a direct correlation between the degree of myofibrillar protein nitration and the severity of DOX-induced heart failure has been established in these models (**1355**). The critical role of peroxynitrite downstream in DOX-mediated myocardial dysfunction has been firmly established by Pacher et al. (**985**), who found that accelerating peroxynitrite decomposition with FP-15 produced a significant protection against the protein nitration, lipid peroxidation, MMP activation, and cardiac dysfunction triggered by DOX treatment in mice.

Acetaminophen (AAP), a widely used analgesic drug, can cause severe liver injury in the overdose setting (**622**). AAP toxicitiy is mainly related to its metabolic activation to the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI), which consumes hepatic glutathione and subsequently covalently binds to cellular proteins, notably within mitochondria (**622**). These early events are rapidly followed by disturbances of Ca^{2+} homeostasis (**235**), inhibition of mitochondrial respiration (**620**), overproduction of $O_2^{\cdot-}$ and NO (due to iNOS expression; Ref. **432**) and subsequent generation of peroxynitrite (**622**). A strong immunoreactivity for nitrotyrosine, mainly in the mitochondria, has been detected in dying hepatocytes after acetaminophen overdose (**239**,**690**). Furthermore, administration of GSH (**46**) or NAC (**1071**) to restore endogenous GSH stores has been shown to reduce nitrotyrosine staining and to attenuate liver injury upon AAP overdose in animals. According to our current understanding, mitochondrial peroxynitrite formation in response to AAP triggers massive hepatocyte cell death by inducing membrane permeability transition, collapse of the mitochondrial membrane potential, and depression of ATP biosynthesis (**622**). Additional studies with peroxynitrite decomposition catalysts are needed to further precisely define these possible roles of peroxynitrite in AAP overdose.

In summary, studies performed in animal models of inflammatory diseases have highlighted the crucial role of the NO-superoxide-peroxynitrite-PARP activation pathway as a mechanism of progressive amplification of inflammation in these conditions. Such a role is certainly not limited to arthritis and colitis, as similar roles of peroxynitrite and PARP have been documented in many other localized inflammatory paradigms, recently reviewed by Szabo (**1230**). These include inflammation of the CNS, such as allergic encephalomyelitis, meningitis, and multiple sclerosis; ocular inflammation (uveitis); asthma; and periodontal inflammation (gingivitis), as well as the systemic inflammatory responses observed during circulatory shock (see sect. VI*C* for specific discussion). As summarized in **Figure 14**, it is currently envisioned that the generation of peroxynitrite initiates oxidative DNA damage and DNA strand breaks formation in all these

conditions. In turn, injured DNA triggers PARP activation in cells exposed to toxic concentrations of peroxynitrite. Activation of PARP depletes cellular NAD^+ and ATP, leading, in the worst case, to irreversible damage and necrotic cell death. Simultaneously, PARP acts as a coactivator of multiple crucial proinflammatory cascades, including MAPKs, AP-1, and NFκB (**361**, **1230**). This results in a greater expression of proinflammatory cytokines, chemokines, enzymes (e.g., iNOS), and adhesion molecules. Inflammatory cells are sequestered in the tissues, enhancing the production of oxidants and free radicals, generating further DNA damage and PARP activation, thereby fueling a continuous cycle of progressive inflammation. The different events set in motion by the initial generation of peroxynitrite indicate that potent peroxynitrite decomposition catalysts and PARP inhibitors might represent useful therapeutic agents for debilitating chronic inflammatory diseases.

E. Nitric Oxide and Peroxynitrite in Cancer

A relationship between chronic inflammation and tumorigenesis has long been suspected. It is well known that malignant tissues are infiltrated by leukocytes, which locally secrete cytokines, chemokines, matrix-degrading enzymes, growth factors, free radicals, and oxidants. This creates a microenvironment that may enhance cell proliferation, survival, and migration, as well as angiogenesis, thereby promoting tumor development (**238**). A particularly important role of increased NO generation in this microenvironment is now well recognized as an essential step initiating neoplastic transformation (**418**). Importantly, not only immune cells infiltrating the tumor, but also tumor-associated stromal fibroblasts and the tumor cells themselves, notably in lung, breast, thyroid, stomach, and colon cancers, are able to produce large amounts of NO due to induced expression of iNOS (see Ref. **418** for review). The latter can be triggered in cancer cells via cytokine-dependent NFκB signaling, or via a signaling cascade involving activation of the transcription factor HIF-1 under the hypoxic conditions which may prevail in rapidly growing tumors. In addition to iNOS, several types of tumor cells, for example, from breast, brain, or lung origin, also express eNOS or nNOS, while endothelial cells in the tumor vasculature produce eNOS-derived NO (**418**).

Evidence for a role of NO overproduction as a mechanism initiating and promoting tumorigenesis has come from studies showing reduced tumor formation by genetic deletion of iNOS in several mouse models of cancer. For instance, iNOS knockout mice had an 80% reduction of urethane-induced lung tumor formation (**682**). Similarly, mice with a mutation of the adenomatous polyposis coli (Apc) gene, who spontaneously develop multiple polyps in the intestines, are protected from polyp development when bearing an iNOS knockout genotype, or when treated with a selective iNOS inhibitor (**9**). Several mechanisms accounting for the tumor-promoting influence of NO have been identified. First, NO can stimulate tumor angiogenesis, by inducing angiogenic and lymphangiogenic factor expression, most significantly vascular endothelial growth factor (VEGF) (**18**, **19**, **631**), by inhibiting the expression of endogenous antiangiogenic factors such as thrombospondin-1 (**1076**), and by stimulating blood vessel maturation via the recruitment of perivascular cells (pericytes) (**657**, **1423**). Second, NO has been associated with enhanced migration and invasion of tumor cells through mechanisms depending on guanylyl cyclase and MAPK signaling, notably in breast and colon cancer cells (**619**, **975**, **1163**). Third, NO can induce DNA damage, potentially leading to DNA mutations and clonal transformation (**418**). As discussed below, evidence is emerging that peroxynitrite most

probably represents the major species responsible for such DNA mutations linking NO overproduction with carcinogenesis.

Studies pointing to a tumor-promoting role of NO must be weighted by the contrasted results of studies that showed instead a tumor-suppressing activity of NO. Indeed, several reports indicated prevention of intestinal tumorigenesis, as well as sarcomagenesis and lymphomagenesis in iNOS knockout mice (**314**, **585**, **1140**). It is currently considered that these contrasted influences of NO depend on the duration and level of NO exposure, the type of iNOS-expressing cell (tumor vs. stromal or inflammatory cells), the cellular sensitivity to NO's cytotoxic activity, and the status of the p53 tumor suppressor gene in the tumor cell (**418**). Obviously, more studies will be necessary to precisely delineate the role of NO in specific forms of tumors, especially when considering the potential clinical application of strategies aimed at either inhibiting, or enhancing, NO generation, as an adjuvant therapy in human cancer. A detailed discussion on the multifaceted actions of NO in cancer, as well as possible future therapeutic implications, is beyond the scope of this article but can be found in an extensive review recently published by Fukumara et al. (**418**). In the next paragraphs, we limit our focus on the evidence favoring a potential role of peroxynitrite in carcinogenesis.

As discussed in section IV, there are abundant demonstrations of the toxic consequences of peroxynitrite towards DNA. Peroxynitrite triggers oxidative modifications within nucleobases, most significantly guanine (**945**), generating 8-oxoguanine, which is at least 1,000-fold more reactive with peroxynitrite than parent guanine, yielding further oxidation products such as spiroiminodihydantoin, guanidinohydantoin, cyanuric acid, and oxazolone (**945**, **1124**). In addition to oxidative damage, peroxynitrite can also nitrate guanine, to form 8-nitro-guanine and 5-guanidino-4-nitroimidazole (**945**, **1124**). Overall, the guanine modifications introduced by peroxynitrite have been shown to result in a series of potential mutations in both viral (**939**) and mammalian (**1219**) DNA (G to A, G to T, and G to C mutations). Peroxynitrite further damages DNA by producing DNA single-strand breaks, due either to endonuclease-dependent cleavage of abasic sites created by peroxynitrite, or to direct oxidation of the deoxyribose moiety, which opens the sugar ring (**160**, **945**, **1422**). Peroxynitrite-mediated guanine oxidation and single-strand breaks have been identified as powerful mechanisms of homologous recombination in DNA (**684**), which is recognized as a critical step in the induction of genomic lesions associated with carcinogenesis. In addition to directly targeting DNA, peroxynitrite may promote DNA damage by inactivating DNA repair enzymes, e.g., OGG1 (8-oxoguanine DNA glycosylase), a key base excision repair enzyme responsible for base excision repair of 8-oxoguanine (**625**), as well as by inhibiting (through tyrosine nitration) the transcription factor p53 (**222**, **223**), which serves as an essential mechanism to remove cells having sustained significant DNA damage.

The considerable genotoxic potential of peroxynitrite detected in cell culture studies and purified DNA supports the contention that intense and prolonged peroxynitrite-dependent oxidative and nitrative stress prevailing under inflammatory conditions might foster the development of cancer. This hypothesis has been strengthened by the in vivo demonstration of 8-nitroguanine formation in chronic infections and inflammatory diseases known to be associated with greater risk of cancer. These include chronic infection of the bile ducts with the liver fluke in hamster (a risk factor for cholangiocarcinoma) (**1029**), chronic gastric infection with *H. pylori* in humans (which may precede gastric carcinoma) (**813**), human oral leukoplakia (a precancerous state) (**814**), and chronic colitis in mice (associated with the development of colon carcinoma) (**324**). In the latter study, the important finding was made that 8-nitroguanine formation in colon epithelial cells colocalized with the expression of proliferating cell nuclear antigen, a marker of cell

proliferation, indicating that nitrative DNA damage induced in colon epithelial cells during chronic colitis is associated with proliferation of these cells, which may contribute to colon carcinogenesis (**324**). More direct evidence of the tumor-promoting role of peroxynitrite was recently described in mice with *Apc* gene mutation (*Apc^{min}* mice). A considerable reduction in the spontaneous development of intestinal polyps (evaluated at 12 wk of age) occurred when *Apc^{min}* mice were treated by the peroxynitrite decomposition catalyst FP15, given orally from the fifth week of life. FP-15 also resulted in significant reduction of malondialdehyde accumulation in intestinal tissues, pointing to a key role of peroxynitrite-related oxidative stress in tumor initiation in this particular model (**820**).

In summary, available evidence indicates that NO plays dichotomous roles (promotion vs. suppression) in tumor initiation and progression. The activation of angiogenesis and the induction of DNA mutations represent key aspects of the procarcinogenic effects of NO. Peroxynitrite is emerging as a major NO-derived species responsible for DNA damage, mainly through guanine modifications and the inhibition of DNA repair enzymes. In chronic inflammatory states, the identification of 8-nitroguanine in tissues indicates that nitrative DNA damage consecutive to overproduction of NO and peroxynitrite may represent an essential link between inflammation and carcinogenesis.

F. Nitric Oxide and Peroxynitrite in Stroke and Other Forms of Reperfusion Injury

1. Stroke

Acute ischemic stroke is the second leading cause of death in industrialized countries and the leading medical cause of acquired adult disability. In the United States, ~600,000 new strokes occur annually, representing an economic burden of $40 billion in direct and indirect costs. Ischemic stroke results from the reduction of cerebral blood flow in the territory of a major cerebral artery due to its transient or permanent occlusion by local thrombosis or embolus. A complex cascade of molecular events is set in motion during cerebral ischemia and culminates in neuronal cell death. Improving our understanding of these events might help devise novel therapies to limit neuronal injury in stroke patients, a concept termed “neuroprotection” (**741**,**1363**).

In both animal models of focal cerebral ischemia [e.g., induced by middle cerebral artery (MCA) occlusion] and in human stroke, two distinct ischemic regions can be identified: the core, which is served primarily by the occluded artery, and the penumbra, where residual blood flow (<40% of normal flow) persists (**326**, **1363**). The earliest consequence of ischemia is a significant fall in tissue ATP levels, which is considerably more pronounced in the core than in the penumbra. The immediate consequence is the dissipation of ionic gradients normally maintained by Na^+-K^+-ATPases, resulting in the rapid depolarization of neurons and glia, followed by the activation of voltage-dependent Ca^{2+} channels and Ca^{2+} overload (**778**). These events induce the accumulation of excitatory neurotransmitters, especially glutamate, within the extracellular space, triggering the activation of two distinct ionotropic receptors, the NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors. NMDA receptor opens a Ca^{2+} channel and thus amplifies Ca^{2+} overload, whereas AMPA receptor opens a Na^+ channel, leading to accumulation of intracellular Na^+ and brain edema (**326**, **778**). The pathological alterations elicited by the actions of glutamate on these receptors are referred to as “excitotoxicity.”

The massive increase in intracellular Ca^{2+} activates various enzymes (e.g., phospholipases, cyclooxygenases, NO synthase, and proteolytic enzymes) and stimulates the release of cytotoxic oxidant species and free radicals, which provoke lipid peroxidation, DNA injury, and mitochondrial damage, and also contribute to the breakdown of the blood-brain barrier and the development of brain edema (**326**, **778**, **1079**). Furthermore, tissue anoxia, calcium overload, and oxidant stress foster the activation of various transcription factors, including NFκB, hypoxia-inducible factor 1, and STAT3. This, in turn, triggers the production of inflammatory cytokines (TNF-α, IL-1β), enzymes (iNOS, COX-2), adhesion molecules (ICAM-1, selectins), and the recruitment of activated phagocytes (**326**, **587**). These changes evolve over several days after the initial ischemic insult, resulting in progressive inflammatory changes spreading from the core into the ischemic penumbra and characterized by the migration of activated microglial cells, macrophages, and neutrophils within the site of injury, where they produce large quantities of oxidants and free radicals. Ultimately, Ca^{2+} overload, glutamate excitotoxicity, oxidant-mediated injury, and inflammatory changes induce neuronal cell death, which occurs predominantly by necrosis within the core of the lesion, and by apoptosis within the penumbra (**326**).

A) ROLE OF NO IN NORMAL BRAIN PHYSIOLOGY AND DURING ISCHEMIC STROKE.

In the brain, NO is physiologically produced by two Ca^{2+}/calmodulin-dependent NOS isoforms present in endothelial cells (eNOS, type III NOS) and neurons (nNOS, type I NOS), which produce small (nanomolar) amounts of NO for short periods in response to transient increases in intracellular Ca^{2+}. NO generated by eNOS and nNOS is essential for the control of cerebral blood flow, whereas nNOS-derived NO also functions as a neurotransmitter and is involved in synaptic plasticity, modulation of neuroendocrine functions, memory formation, and behavioral activity (**491**, **1229**). Under various pathological conditions, including cerebral ischemia, large amounts of NO are produced in the brain as a result of the induced expression of iNOS, related to enhanced iNOS gene transcription in response to locally produced inflammatory cytokines. Expression of iNOS in brain tissue has been localized in infiltrating phagocytes, vascular cells, and glial cells (astrocytes, oligodendrocytes, and microglia) (**39**, **491**).
A number of experimental investigations have shown that NO production is upregulated and plays opposite (protective vs. deleterious) effects in stroke. In both focal and global cerebral ischemia models in rodents, a burst of NO generation, occurring in the first minutes of ischemia, was demonstrated by EPR spectroscopy (**834**, **1282**) and the determination of NO-decomposition products (nitrites and nitrates) (**1156**; see Refs. **110** and **906** for review). In the rat forebrain, NO levels up to 11 μM have been determined following global ischemia induced by bilateral carotid occlusion (**1282**). Ischemia-induced NO overproduction has been correlated with glutamatergic-mediated increases in intracellular Ca^{2+} concentrations, resulting in a calmodulin-dependent upregulation of nNOS and eNOS activities in the infarcted tissues (**110**, **906**). This increased activity is short lasting (~1 h), declining rapidly to <25% of control activity after a few hours in both transient and permanent ischemia (**466**, **588**). Importantly, this reduced activity persists for at least 10 days after the induction of focal ischemia (**466**), a phenomenon supposed to reflect the loss of nNOS-expressing neurons, the degradation of nNOS within the infarct (**101**), and the inhibition of nNOS activity by iNOS-derived NO in the late phase of ischemia (**907**). In addition to stimulated NOS activity, there is a transient increase in the expression of both nNOS (**1443**) and eNOS (**1444**) in the ischemic area, which might contribute to the initial burst of NO in stroke (**907**).

Following this early and transient rise in NO formation, a secondary wave of NO overproduction starts to develop several hours after the initial ischemic insult and is sustained for up to 4–7 days (**466**, **588**). This enhanced and prolonged NO release can be entirely ascribed to the induced expression of iNOS, which has been detected in infiltrating neutrophils, cerebral blood vessels (**589**), and glial cells, especially astrocytes (**101**), in rodent models of transient or permanent ischemia (reviewed in Refs. **111**, **906**). In humans, it is likely that a similar scenario takes place, in view of the increase in the levels of nitrates and nitrites in blood and cerebrospinal fluid of stroke patients (**181**, **346**, **716**), together with the demonstrated expression of iNOS in neutrophils and blood vessels in autopsy brain specimens (**404**).

Using both pharmacological (administration of NOS inhibitors with various isoform specificity) and genetic approaches (using mice with targeted deletions of the eNOS, nNOS, or iNOS gene), the role of each NOS isoform in cerebral ischemia has been investigated. It has thus been clearly demonstrated that NO plays both neuroprotective and neurotoxic roles in stroke, depending on the NOS isoform from which it is produced (**491**). Thus eNOS-derived NO produces beneficial effects, as demonstrated by the larger infarcts measured 24 h after MCA occlusion in mice lacking the eNOS gene (**575**). Vascular NO production dependent on eNOS has been proposed to protect against stroke mainly by increasing collateral blood flow to the ischemic penumbra (**1106**, **1432**), but additional mechanisms have also been suggested. These include the enhancement of endothelium-dependent vasorelaxation, the prevention of inflammation and oxidative damage, the inhibition of platelet aggregation and thrombosis formation, the prevention of neuronal apoptosis, the reduction of NMDA receptor activation, the mobilization of stem and progenitor cells, and the improvement of neovascularization, as recently reviewed by Endres et al. (**358**). In line with the beneficial effects attributed to eNOS-derived NO, numerous studies reported that administration of the eNOS substrate L-arginine increased regional cerebral blood flow in the ischemic territory, improved functional recovery, and conferred protection against stroke (reviewed in Ref. **1374**). Similarly, the enhancement of eNOS expression by the administration of statins (**357**, **1173**) or corticosteroids (**505**), as well as treatment with various NO donors (**672**, **1374**), have been associated with neuroprotective effects in rodent models of transient or permanent MCA occlusion.

In marked contrast to the beneficial effects afforded by eNOS, both nNOS and iNOS have been associated with deleterious, neurotoxic effects in stroke. Mice lacking either the nNOS (**390**, **576**) or iNOS (**590**) gene are protected against ischemic damage after both transient or permanent ischemia, and similar beneficial effects have been obtained with pharmacological NOS inhibitors exhibiting selectivity towards nNOS, e.g., 7-nitroindazole (**1421**), ARL17477 (**1445**), and BN80933 (**193**) or iNOS, such as aminoguanidine (**591**) or 1400 W (**1008**). Importantly, the therapeutic window for administration of selective iNOS inhibitors in these studies was much longer than that for nNOS inhibitors, given the time course of iNOS expression after brain ischemia. iNOS inhibitors still provided protection when given as late as 24 h after MCA occlusion (**907**). Of note, treatment with nonselective NOS inhibitors (e.g., L-NAME or N^G-nitro-L-arginine) yielded much more variable outcomes in experimental stroke, due to their inherent inhibitory action on eNOS. Studies with these agents reported either beneficial, neutral, or detrimental effects, depending on the experimental model (transient vs. permanent ischemia) and the timing of administration (before or after the induction of ischemia), as reviewed recently (**1373**).

In summary, the different studies listed above indicate that small amounts of NO produced by eNOS in the vasculature during the early phase of brain ischemia are essential to limit the extent

of cerebral damage, whereas higher concentrations of NO, generated initially by nNOS and later by iNOS, exert essentially neurotoxic effects in the ischemic brain. Evidence that such toxicity depends, in large part, on the rapid reaction of NO with locally produced superoxide to generate peroxynitrite will be now exposed (see also **Fig. 15**.)

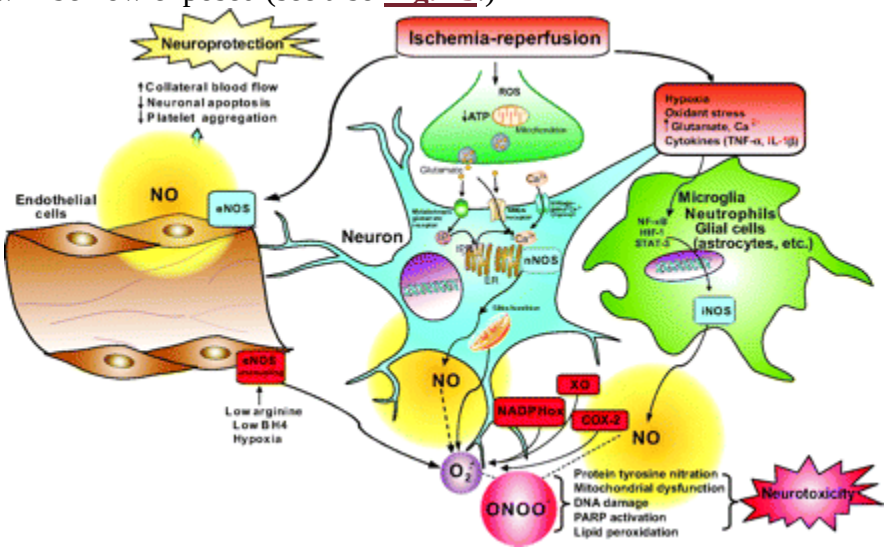

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FIG. 15.

Roles of NO and peroxynitrite in the pathophysiology of stroke. Brain ischemia and reperfusion leads to transient stimulation of the activity of endothelial NO synthase (eNOS), resulting in brief increases in endothelial NO generation, associated with neuroprotective actions in stroke. In parallel, ischemic energy depletion and oxidant (ROS) production triggers the release of glutamate, which results in neuronal calcium overload from extracellular (activation of calcium channels) and intracellular (phosphoinositol-3-kinase-endoplasmic reticulum signaling) sources. Calcium overload results in prolonged synthesis of NO, due to stimulated activity of the neuronal isoform of NO synthase (nNOS). Enhanced NO generation also depends on the induced expression of inducible NOS (iNOS) in various types of reactive inflammatory cells, upon the activation of several cell signaling pathways (HIF-1, STAT-3, and NFκB) in response to hypoxia, cytokines, oxidants, and glutamate. During the same period of time, superoxide production is enhanced due to uncoupling of eNOS, mitochondrial dysfunction, and the stimulated activity of NADPH oxidase, xanthine oxidase, and cyclooxygnease-2 (COX-2). Formation of peroxynitrite is then markedly favored, damaging lipids, proteins, DNA, and triggering the activation of poly(ADP-ribose) polymerase (PARP), which all contribute significantly to neurotoxicity in stroke.

B) ROLE OF PEROXYNITRITE IN NO-DEPENDENT NEUROTOXICITY IN STROKE.

Seminal studies on the possible neurotoxic role of NO were conducted in the late 1980s by Bredt and Snyder (**134**), who showed that exposure of cerebellar slices to the excitotoxic neurotransmitters glutamate and NMDA triggered the formation of NO. Two years later, Dawson

et al. (295) definitely identified NO as the mediator of glutamate and NMDA-dependent neurotoxicity, by showing that NOS inhibitors prevented NMDA-dependent neuronal cell death in vitro. The toxic role of NO did not appear straightforward, however, as NO was simultaneously found to exhibit protective effects, by inhibiting responses mediated by NMDA receptors in rat cortical neurons (746). This paradox was resolved in 1993 by Lipton et al. (779), who showed that NO-mediated neurotoxicity was engendered by its reaction with superoxide to form peroxynitrite, whereas its protective effects resulted from the downregulation of NMDA receptor activity by *S*-nitrosylation of thiol group(s) in the receptor's redox modulatory site.

In vivo, the generation of peroxynitrite in ischemic stroke is largely favored, due to the simultaneous increase of both NO (see above) and superoxide production. The upregulated formation of superoxide in ischemic stroke has been attested by methods such as cytochrome *c* oxidation (374), lucigenin enhanced chemiluminescence (1025), and hydroethidine oxidation (677), which showed that levels of superoxide start to rise during the ischemic phase, followed by a much larger increase during the early reperfusion period, both in neurons and in endothelial cells. In focal ischemia, this increase was much sharper in the ischemic penumbra than in the core, reaching up to 25 μM/min (374). The pathogenic importance of superoxide in ischemic stroke has been highlighted by studies using transgenic mice with either deletion or overexpression of the various SOD isozymes. Thus mice deficient in Cu/Zn-SOD (701) or Mn-SOD (677, 915) disclosed larger infarcts after transient focal ischemia, whereas mice overexpressing Cu/Zn-SOD were protected (1410). By the same token, pharmacological compounds exhibiting properties as SOD mimetics were reported to exert significant protection against brain ischemic damage in rodents (1153, 1158, 1266).

Many different sources act in concert to produce such high concentrations of superoxide in stroke. The most important is probably the mitochondrion (1169), which produces superoxide via the partial reduction of molecular oxygen by electrons leaking from the electron transport chain under conditions of respiratory block, a phenomenon amplified by cellular hypoxia and NO-mediated inhibition of cytochrome oxidase (143, 533). The central role of mitochondria in generating toxic levels of superoxide during stroke is attested by the demonstration that mice lacking the mitochondrial isoform of SOD (Mn-SOD) experience much larger infarcts than their wild-type littermates after transient MCA occlusion (677, 915). Superoxide also arises from the activity of cyclooxygenase enzymes (COX), especially COX-2, present in glutamatergic neurons and which catalyzes the conversion of arachidonic acid to prostaglandin G_2 (PGG_2) and then to PGH_2, with the concomitant liberation of superoxide (661). In brain pathologies associated with glutamate excitotoxicity, and notably stroke, COX-2 is markedly upregulated and becomes a significant generator of superoxide, especially in the ischemic penumbra (1448). NADPH oxidase, expressed by neurons (1147, 1310), endothelial cells (8), and infiltrating neutrophils (778), represents a further source of superoxide during ischemia, and its blockade, either by pharmacological inhibition or genetic suppression (1337), produces significant reductions of brain infarct volume in experimental stroke. Finally, superoxide may also be generated by the hypoxic-dependent conversion of xanthine dehydrogenase into xanthine oxidase, during the metabolism of the breakdown products (xanthine and hypoxanthine) of adenine nucleotides (778), as well as by the uncoupling of eNOS, due to deprivation of its cofactor tetrahydrobiopterin or its substrate L-arginine, caused by the reduced blood supply (358). In such conditions, eNOS may function as a superoxide generator instead of an NO generator.

Evidence for the generation of peroxynitrite from NO and superoxide in stroke has been obtained by the concomitant demonstration that *1*) nitrotyrosine rapidly accumulates in the brain

following transient or permanent ischemia and *2*) the nitrotyrosine accumulation is markedly prevented by strategies blocking NO or superoxide generation, as well as by treatments aimed at directly scavenging peroxynitrite. Although nitrotyrosine can be formed independently from the generation of peroxynitrite, via the reaction of hydrogen peroxide with myeloperoxidase (see sect. IV), this mechanism is highly unlikely to occur in stroke, as shown in a recent study using myeloperoxidase-deficient mice exposed to transient focal cerebral ischemia. Absence of myeloperoxidase did not reduce the accumulation of nitrotyrosine in the infarcted tissue, nor did it reduce the lesion size, indicating that the peroxynitrite pathway, but not the myeloperoxidase pathway, is responsible for the nitration reaction occurring in the ischemic brain (**1258**).

nNOS plays the predominant role in the formation of nitrotyrosine in the early phase of ischemia and reperfusion, as demonstrated by the suppression of nitrotyrosine generation by 7-nitroindazole, a selective nNOS inhibitor administered in the acute phase (15 min before occlusion) of focal brain ischemia reperfusion in mice (**550**). Also, the accumulation of nitrotyrosine found in cortical neurons and vascular endothelium after 3 h of permanent ischemia was absent in nNOS knockout mice, supporting an essential role of nNOS in this early nitrotyrosine accumulation (**348**). Comparable results were obtained in transient ischemia in rats, where nitrotyrosine formed in cortical neurons could be eliminated by tamoxifen, a compound with nNOS inhibitory activity (**976**). NMDA receptor activation appears as the major trigger of this early, nNOS-dependent nitrotyrosine formation, in view of the suppression of the latter afforded by MK-801, a NMDA receptor antagonist, in focal transient ischemia (**551**).

Interestingly, although eNOS has generally been attributed a neuroprotective function in stroke, it might also be responsible for the generation of peroxynitrite by triggering a surge of NO at the onset of reperfusion, as recently proposed by Gursoy-Ozdemir et al. (**495**). These investigators demonstrated that the accumulation of nitrotyrosine in blood vessels after reperfusion was not influenced by the nNOS inhibitor 7-nitroindazole, whereas it was suppressed by the eNOS inhibitor nitro-L-arginine (**494**,**495**). These data indicate that, although NMDA-dependent nNOS activation represents the major source of peroxynitrite in neurons, eNOS may play this role in the vascular endothelium during the early reperfusion phase.

At later stages of stroke, formation of peroxynitrite is totally dependent on the expression of iNOS. In a model of transient MCA occlusion in mice, strong nitrotyrosine immunoreactivity was demonstrated within the vascular wall in the peri-infarct region, peaking 15 h after reperfusion. Nitrotyrosine staining was totally absent in iNOS knockout mice (**552**). In rats exposed to 2 h of MCA occlusion followed by 22–70 h of reperfusion, nitrotyrosine peaked at 48 h within vascular walls and then progressively declined. The time course of nitrotyrosine paralleled the infiltration of neutrophils within the ischemic region, suggesting a major role of iNOS and superoxide derived from infiltrating phagocytes in the formation of peroxynitrite in this model (**1218**). Similarly, Bidmon et al. (**101**) found that nitrotyrosine formation in blood vessels from the border of focal cortical ischemic lesions in rats occurred simultaneously to the induced expression of iNOS. The latter was detected after 1 day in neutrophils, accumulating in injured blood vessels and infiltrating the perilesionnal cortex, and after 3 days in microglia, astrocytes, and layers V and VI pyramidal neurons (**101**). The formation of nitrotyrosine can be considerable, as indicated in a study by Takizawa et al. (**1260**). Using HPLC techniques, these authors found that the ratio of nitrotyrosine to tyrosine reached 0.95% in the penumbra and 0.5% in the core of infarct at 1 h after the onset of reperfusion after MCA occlusion in rats. These elevated levels persisted for 48 h and were suppressed by the iNOS inhibitor aminoguanidine (**1259**). The induced expression of iNOS, leading to peroxynitrite formation in the

microvasculature, glia, and neurons after transient brain ischemia appears to depend in large part on the local generation of the inflammatory cytokine IL-1, as evidenced by the marked attenuation of iNOS and peroxynitrite observed in mice lacking the IL-1 gene (**968**). Increased nitrotyrosine staining of brain tissue in asphyxiated neonates was also recently demonstrated, suggesting that peroxynitrite toxicity might play a role in hypoxic-ischemic brain injury at term (**481**).

Once formed in the ischemic brain, peroxynitrite may exert its toxic effects through multiple mechanisms, including lipid peroxidation, mitochondrial damage, protein nitration and oxidation, depletion of antioxidant reserves (especially glutathione), and DNA damage followed by the activation of the nuclear enzyme PARP, as summarized in **Figure 15**. A series of in vivo experimental studies have specifically addressed the neurotoxicity elicited by peroxynitrite in stroke, by using various pharmacological strategies to remove peroxynitrite in rodent models of brain ischemia.

Dhar et al. (**315**) investigated the neuroprotective effects of peroxynitrite decomposition catalyst FeTMPyP on global cerebral I/R injury produced by 5 min of occlusion of both common carotid arteries followed by reperfusion of 96 h in the adult male Mongolian gerbils. FeTMPyP administered 30 min prior to ischemia improved the neurological functions, reduced the hyperlocomotion and memory impairment, attenuated neuronal loss from the pyramidal layer of the CA1 region, and inhibited lipid peroxidation in I/R-challenged gerbils (**315**). Thiyagarajan et al. (**1273**) found that when peroxynitrite decomposition catalysts FeTMPyP and FeTPPS were given at the time of reperfusion in rats exposed to 2-h MCA occlusion followed by 70-h reperfusion, both compounds reduced cerebral infarction by ~70%. Importantly, the drugs were still very effective while given at 6 h after reperfusion, with a 35% decrease in infarct size. These beneficial effects were related to the reduction of nitrotyrosine generation in the ischemic brain and to the prevention of apoptotic cell death in neurons within the ischemic penumbra (**1273**). An additional important finding of this study was the striking reduction (70%) of postischemic brain edema afforded by FeTPPS and FeTMPyP, pointing to an important role of peroxynitrite in the rupture of the blood-brain barrier in the ischemic brain. Such observations are consistent with the recent findings that peroxynitrite injures cerebral microvessels and increases vascular permeability in brain by mechanisms involving F-actin depolymerization in vascular smooth muscle (**841**) and the activation of MMP-9 in brain microvessels (**495**).

In a similar model of transient MCA occlusion in rats, Yu and co-workers (**1425**) evaluated the therapeutic potential of uric acid, a natural antioxidant with very effective properties at preventing nitration by peroxynitrite (notably, it does not directly scavenge peroxynitrite). Uric acid was given either 24 h before MCA occlusion or 1 h after reperfusion. In both conditions, uric acid reduced ischemic damage to cerebral cortex and striatum by >70% and significantly improved behavioral outcome of the animals. The mechanisms underlying uric acid neuroprotection were then evaluated in an in vitro model of hippocampal cell culture exposed to excitotoxic concentrations of glutamate. Glutamate induced the formation of peroxynitrite, mainly localized within the mitochondria, and triggered delayed (6 h) calcium overload, mitochondrial depolarization, lipid peroxidation, and massive neuronal cell death. Peroxynitrite generation was suppressed by uric acid, which alleviated the mitochondrial damage, lipid peroxidation, and calcium overload produced by glutamate, resulting in an almost complete protection against neuronal death (**1425**).

Two additional compounds, NAC and ebselen, which enhance endogenous defenses against peroxynitrite, and which may also directly scavenge peroxynitrite, were also recently found to

exert potent protection in experimental stroke. Cuzzocrea et al. (264) determined the neuroprotective effects of NAC in a model of global transient ischemia in gerbils, produced by a 5-min bilateral occlusion of the common carotid arteries, followed by reperfusion for up to 48 h. NAC almost suppressed nitrotyrosine formation within neurons and endothelial cells from the ischemic area. There was a concomitant reduction of lipid peroxidation, neutrophil infiltration, and brain edema, with a considerable prevention of histological damage in animals treated with NAC (264). Ebselen is a selenium-containing organic antioxidant which acts as a mimic of glutathione peroxidase and thus favors the maintenance of cellular reduced glutathione pools, which represent one of the major defense mechanisms against peroxynitrite. In rat permanent MCA occlusion, infusion of ebselen, starting 45 min before and maintained 4 h after the occlusion, reduced cerebral cortical damage by 28%. This effect correlated with a significant prevention of lipid peroxidation and DNA oxidation, implying that these two events may represent key mechanisms of peroxynitrite-dependent neuronal damage in stroke (599). Whereas peroxynitrite may directly injure neurons by inhibiting mitochondrial respiration, oxidizing membrane lipids, structural proteins and enzymes, as well as by consuming intracellular antioxidants such as GSH, evidence is growing that a major action of peroxynitrite (and other oxidants) in stroke is to injure DNA and activate PARP, a subject extensively reviewed in Reference 214. Accumulation of poly(ADP-ribose), as a marker of PARP activation, has been identified not only in animal models of transient (923) and permanent (1281) ischemia, but also in the infarcted human brain. Indeed, immunohistochemical evidence of PARP activation has been demonstrated in autopsy specimen, occurring in neural cells during the first 24 h after stroke, and in infiltrating macrophages between 3 days and 3 wk after the episode of acute ischemia (794). Accumulation of poly(ADP-ribose) has also been detected in neurons after global cerebral ischemia due to cardiac arrest, located in regions of ischemic damage and immediately adjacent neocortex (793). The essential role of nNOS-derived peroxynitrite on PARP activation in stroke has been attested by the significant prevention of PARP activation provided by genetic deletion (359) or pharmacological inhibition (1281) of nNOS. The activation of PARP induces major neurotoxicity, as evidenced by the extreme protection against brain damage in PARP knockout mice subjected to transient MCA occlusion (up to 80% reduction of infarct volume) (349, 360). A similar high degree of protection could be reproduced by a series of pharmacological inhibitors of PARP, such as 3-aminobenzamide (360), PJ-34 (1), or INO-1001 (624). Importantly, these agents remained effective even when given several hours after the ischemic insult, which indicates that these drugs might be clinically useful. Regarding mechanisms, PARP-dependent neurotoxicity appears multifactorial, involving the depletion of NAD/ATP leading to neuronal necrosis (360), the upregulation of transcription factors (AP-1, NFκB) enhancing postischemic brain inflammation (697), and the activation of AIF (see sect. IV), activating caspase-independent apoptosis (294).

2. Other forms of reperfusion injury

Although most experimental effort investigating NO and peroxynitrite's actions in reperfusion injury has so far been focused on the brain and heart (see above and sect. VI*A*), evidence also exists that theses species are involved in other reperfusion paradigms. In such conditions, the mechanisms underlying the formation of NO, superoxide, and peroxynitrite, as well as their cellular targets, are similar to those exposed in detail in the sections on stroke and myocardial I/R. Therefore, here we only provide a brief summary of the major relevant studies implying

NO/peroxynitrite generation as key players of reperfusion injury in organs such as the gut, the liver, the lung, and the kidney.

A) KIDNEY.

As in many other conditions, NO plays both beneficial and detrimental effects in kidney I/R (KIR), depending on the rate and timing of its formation as well as the isoform from which it is produced as extensively reviewed by Goligorsky et al. (**454**). Crucial in vitro experiments demonstrated that proximal renal tubules isolated from mice with a targeted deletion of iNOS were resistant to hypoxia, contrasting with the lethal damage produced by the same degree of hypoxia in tubules prepared from mice lacking eNOS or nNOS (**774**). In vivo, iNOS inactivation by selective iNOS pharmacological inhibitors (**200**, **1429**), or iNOS antisense oligodeoxynucleotides (**948**), protected kidneys from KIR injury, while nonselective NOS inhibitors did not provide protection (**454**). Importantly, evidence for peroxynitrite generation in injured tubules has been reported in KIR, where injury was reduced by anti-iNOS strategies (**200**). It has also been shown that an NO donor given before the induction of ischemia reduced nitrotyrosine and exerted beneficial influence, while it enhanced nitrotyrosine formation and increased renal damage when given 6 h after reperfusion (**928**). These data all point to a protecting role of eNOS-dependent NO formation in the early phase of KIR, and a detrimental action of iNOS-derived NO and peroxynitrite at later stages (for review, see Ref. **454**). The latter assertion has been confirmed by a series of studies showing that strategies directly preventing peroxynitrite generation or accelerating its degradation prevented the generation of nitrotyrosine in injured tubular cells, ameliorated renal histological damage, and reduced functional renal alterations (evaluated by the increase of plasma creatinine and urea, and the development of proteinuria) in KIR. Strategies aimed at limiting peroxynitrite in these studies involved uric acid (**1418**), MnTBAP (**1429**), and various compounds extracted from plants with documented peroxynitrite scavenging activity in vitro, e.g., (−)-epicatechin 3-*O*-gallate (**1418**), Coptidis Rhizoma (**1417**), and sanguiin H-6 (**1416**).

B) GUT.

An abundant literature has implicated NO in the pathophysiology of gut I/R (GIR) injury. Basal NO production dependent on constitutive NOS (nNOS or eNOS) is essential in minimizing mucosal and microvascular barrier dysfunction associated with reperfusion of the postischemic intestine (**717**). Several NO donors have thus been shown to exert beneficial effects on mucosal and microvascular function in this setting (**648**, **831**). Alternatively, increased NO production due to the expression of iNOS in the intestinal mucosa is detrimental to intestinal integrity: mice with genetic deletion of iNOS exhibited resistance against reperfusion-induced mucosal injury and bacterial translocation (**1220**), whereas administration of selective iNOS inhibitors such as aminoguanidine (**787**) and ONO-1714 (**926**) prevented the hemodynamic collapse, intestinal microcirculatory derangements, lipid peroxidation, and neutrophil infiltration in rat models of GIR. There is additional evidence implicating the formation of free radicals, most notably superoxide, as a critical mechanism of intestinal damage and dysfunction related to ischemia. Thus both the SOD mimetics M40401 (**267**) and the broad-spectrum antioxidant tempol (**270**, **271**, **273**) attenuated gut inflammation and damage in rodents.

There are many indications that peroxynitrite generation is the ultimate mechanisms underlying NO and $O_2^{\cdot-}$ toxicity in GIR. Massive nitrotyrosine staining is evident in the ileum of rats

exposed to GIR and can be reduced by strategies blocking either the formation of NO (274) or superoxide (267). In addition, the peroxynitrite decomposition catalyst FeTMPS reversed tissue injury, reduced lipid peroxidation, and alleviated neutrophil infiltration in the reperfused bowel (272). The latter effect was associated with an attenuation of reperfusion-induced upregulation of the adhesion molecules P-selectin and intracellular adhesion molecule-1. Similar results were obtained when peroxynitrite generation was inhibited with NAC (263) or melatonin (260). Finally, experiments performed either with pharmacological inhibitors or genetic suppression of PARP showed an almost complete protection against the development of mesenteric barrier failure complicating GIR (277, 768). These different studies support the contention that peroxynitrite formation due to NO and superoxide overproduction in the reperfused intestine induces gut damage and inflammation, notably by stimulating the mechanisms recruiting activated phagocytes, and also results in gut barrier failure by triggering the activation of PARP within the gut mucosa.

C) LIVER.

Liver I/R (LIR) is a significant clinical problem involved in the liver failure associated with circulatory shock, vascular exclusion during surgery, and liver transplantation. An important early mechanism of liver failure in such conditions is the marked sinusoid vasoconstriction that develops during reperfusion, as a consequence of an imbalance between vasoconstrictors, especially endothelins, and vasodilators, essentially NO (621). In the liver, NO is normally produced exclusively by eNOS expressed by sinusoid endothelial cells (207). In LIR, a significant reduction of eNOS activity has been demonstrated both in humans (1319) and animals (1146), precipitating sinusoidal vasoconstriction (621). These microcirculatory disturbances can be alleviated by the administration of NO donors (335, 722), while they are seriously aggravated by the administration of nonselective NOS inhibitors (904) or by eNOS gene deletion (660), which have been associated with significant enhancement of LIR-induced liver injury. LIR also rapidly activates Kupffer cells, which then produce proinflammatory cytokines, free radicals, oxidants, and large amounts of NO due to iNOS expression (207, 621). These events result in the activation of neutrophils, endothelial cells, and hepatocytes, which further release toxic levels of oxidant species and iNOS-derived NO in the delayed phase of LIR (207, 621). The pathogenic role of oxygen-centered radicals in this setting has been well established by the significant reduction of liver damage provided by various antioxidant strategies (1361, 1400).

Despite the increased generation of NO and the ensuing formation of peroxynitrite, evidenced by nitrotyrosine formation in LIR (1146, 1319), the pathogenic role of these abnormalities remains largely debated. On the one hand, selective iNOS inhibitors such as FK330 (1295) and ONO-1714 (863, 1257) reduced nitrotyrosine formation and ameliorated liver injury and dysfunction by reducing leukocyte trafficking, cytokine expression, as well as hepatic apoptosis and necrosis. One study in iNOS-deficient mice also indicated that these mice experienced a slight protection against LIR (739). On the other hand, studies also revealed that selective iNOS inhibitors could impair hepatic blood flow and increase liver injury, suggesting that iNOS, in a way similar to eNOS, exerts an essential role in maintaining liver sinusoidal perfusion in LIR (570, 1347). Furthermore, a significant aggravation of LIR-mediated damage has been documented in a second study performed in iNOS knockout mice (548), although the relevance of these findings is questionable, given the absence of iNOS expression in wild-type control mice in this particular study.

It has been suggested that any peroxynitrite formed during LIR would be effectively scavenged by the high intrahepatic stores of reduced glutathione, which would thereby mitigate any potential toxic effects of peroxynitrite (621). It is also worth noting that peroxynitrite might even exert beneficial effects in LIR, as proposed by Liu et al. (782). In a model of rat LIR, the exogeneous administration of 2 μmol/kg peroxynitrite at 0, 60, and 120 min postreperfusion reduced neutrophil accumulation and liver damage (782). Clearly, the studies summarized above have highlighted the controversial roles of NO and peroxynitrite in LIR. Further studies using well-designed selective iNOS inhibitors and peroxynitrite decomposition catalysts should be performed to gain more precise insights into their actions in this condition.

D) LUNG.

Lung I/R injury (LIRI) develops in as much as 25% of patients after lung transplantation and is a major cause of primary graft dysfunction and early postoperative mortality. The donor alveolar macrophages appear to play a critical role in the initiation of lung damage upon reperfusion, by secreting inflammatory cytokines, resulting in the secondary recruitment of recipient activated neutrophils, with ensuing inflammation, epithelial and endothelial damage leading to reperfusion lung edema (397). The role of NO in LIRI is unclear at present. Many animal studies have reported beneficial effects of inhaled NO therapy in models of LIRI induced by transient pulmonary artery occlusion, or by lung transplantation. In pigs, short pretreatment with inhaled NO (15–20 ppm for 10–30 min) either before lung ischemia (1338) or before lung harvest in the donor animal (455), significantly reduced reperfusion pulmonary damage, via mechanisms involving reduced IL-8 production and decreased neutrophil infiltration (455), as well as a reduced formation of free radicals (1338). Comparable beneficial effects were reported in rabbit models of LIRI and lung transplantation, where inhaled NO was found to improve endothelial integrity and to reduce apoptotic cell death of pulmonary cells (1139, 1406). There are further indications that intravenous administration of nitroglycerin can alleviate lung damage induced by LIRI in pigs and rats (341, 788). In humans, a recent prospective study has evaluated inhaled NO therapy (20 ppm, initiated 10 min after reperfusion) in lung transplant recipients (862). Unfortunately, this strategy did not confer significant protection, although it tended to reduce the duration of mechanical ventilation. This negative study has however been criticized as being largely underpowered to detect any significant effects of inhaled NO.

At variance with the above-mentioned results, studies demonstrating cytotoxic roles of NO in LIRI have also been presented. Schutte et al. (1138) showed that the NOS inhibitor L-NMMA protected against lung damage induced by reperfusion, only if the ischemic phase was accompanied by hypoxic, but not normoxic, ventilation. In this condition, a surge of NO production occurred in early reperfusion, which was abrogated by L-NMMA. Furthermore, SOD also produced significant protection, suggesting an essential role of superoxide and NO-derived peroxynitrite formation in mediating lung damage in LIRI (1138). In line with these findings, LIRI has been associated with significant expression of iNOS (977) and with the abundant formation of nitrotyrosine in lung tissue (607, 977), and a selective iNOS inhibitor, 1400W, reduced reperfusion-induced lung damage in a model of LIRI in the rabbit (977). Finally, accelerating the decomposition of peroxynitrite with FP-15 was recently found to exert major benefits in rats exposed to 90 min of lung ischemia/anoxia followed by 60 min of reperfusion (925). FP-15 reduced nitrotyrosine formation and the expression of the chemokines MIP-1α, CINC, and MIP-2. It also limited neutrophil infiltration, lung edema, and significantly ameliorated histological changes (924, 925).

In summary, I/R is a crucial pathophysiological mechanism of organ damage in many different clinical conditions, including myocardial infarction, stroke, circulatory shock, surgery, or organ transplantation. In most of these instances, a dual role of NO, protective and deleterious, has been established. Protection has generally been attributed to the actions of eNOS-derived NO, due to its vasodilating, anti-inflammatory, and antithrombotic effects. In contrast, enhanced NO production consecutive to iNOS induction (and, in the brain, to the stimulated activity of nNOS), has been associated with detrimental consequences, mostly related to the secondary generation of peroxynitrite. In line with these observations, ample experimental evidence shows significant benefit of therapeutic strategies aimed at manipulating peroxynitrite formation/degradation in the pathological paradigm of I/R.

G. Nitric Oxide and Peroxynitrite in Neurodegenerative Disorders

NO is produced by all brain cells including neurons, endothelial cells, and glial cells (astrocytes, oligodendrocytes, and microglia) by Ca^{2+}/calmodulin-dependent NOS isoforms. Physiologically NOS in neurons (nNOS, type I NOS) and endothelial cells (eNOS, type III NOS) produce nanomolar amounts of NO for short periods in response to transient increases in intracellular Ca^{2+}, which is essential for the control of cerebral blood flow and neurotransmission and is involved in synaptic plasticity, modulation of neuroendocrine functions, memory formation, and behavioral activity (**491**, **890**, **1229**). The brain produces more NO for signal transduction than the rest of the body combined, and its synthesis is induced by excitatory stimuli. Consequently, NO plays an important role in amplifying toxicity in the CNS. Indeed, under various pathological conditions associated with inflammation (e.g., neurodegenerative disorders and cerebral ischemia), large amounts of NO are produced in the brain as a result of the induced expression of iNOS (type II NOS) in glial cells, phagocytes, and vascular cells, which can exert various deleterious roles (**39**, **491**, **890**). Thus NO may be a double-edged sword, exerting protective effects by modulating numerous physiological processes and complex immunological functions in the CNS on one hand and on the other hand mediating tissue damage (**446**, **491**, **890**). The detailed discussion of the role of NO in the pathophysiology of various neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), just mentioning a few, is the subject of numerous excellent recent overviews (**77**, **145**, **194**, **219**, **491**, **890**, **1003**, **1205**, **1433**) and beyond the scope of this paper. Here we cover only the role of peroxynitrite and protein nitration, which are likely responsible for most deleterious effects of NO in neurodegenerative disorders. A common feature of neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, MS, and ALS is extensive evidence of oxidative stress, which might be responsible for the neuronal dysfunction and death contributing to pathogenesis of these disorders (reviewed in Refs. **20**, **33**, **59**, **63**, **173**, **608**, **686**, **900**, **901**, **1037**, **1038**, **1251**). Because neurons are incapable of division, the consequences of severe oxidative stress killing neurons makes sustained damage irreversible. Yet, it is important to look beyond damage to neurons as oxidants may also have more subtle roles in compromising the integrity of the blood-brain barrier and in producing reactive changes in astrocytes. Oxidants induce distinct pathological consequences that amplify and propagate injury and eventually cause irreversible degeneration. Moreover, oxidative stress appears to provide a critical link between environmental factors such as exposure to pesticides, herbicides, and heavy metals with endogenous and genetic risk factors in the pathogenic mechanisms of neurodegeneration, particularly in Parkinson's disease (**63**, **608**, **632**). The

discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity leads to Parkinson's-like disease provided strong evidence that complex I within mitochondria may be a major source of superoxide that initiates the disease (**1043**). More recently, paraquat, a commonly used pesticide and a well-known inhibitor of complex I, has also been identified as a potential cause of Parkinson's disease (**700**, **1114**). Both of these compounds are capable of transferring electrons from complex I to oxygen, producing superoxide (**419**). Simultaneously increased NO (see above) and oxidative superoxide production associated with neurodegenerative disorders favors the in vivo generation of peroxynitrite (**608**, **1119**, **1284**). Peroxynitrite formation has been implicated in Alzheimer's disease, Parkinson's disease, Huntington's disease, MS, ALS, and traumatic brain injury (reviewed in Refs. **194**, **608**, **1119**,**1284**). Nitrotyrosine immunoreactivity has been found in early stages of all of these diseases in human autopsy samples as well as in experimental animal models. Increased nitrite, nitrate, and free nitrotyrosine has been found to be present in the cerebral spinal fluid (CSF) and proposed to be useful marker of neurodegeneration (**168**; reviewed in Refs. **608**, **1119**, **1284**). Once formed in the diseased brain, peroxynitrite may exert its toxic effects through multiple mechanisms, including lipid peroxidation, mitochondrial damage, protein nitration and oxidation, depletion of antioxidant reserves (especially glutathione), activation or inhibition of various signaling pathways, and DNA damage followed by the activation of the nuclear enzyme PARP (**608**, **1119**, **1284**).

Tyrosine nitration represents a major cytotoxic pathway in the nervous system, possibly contributing to neurodegenerative disorders. Mitochondria are particularly vulnerable targets of oxidative stress and protein nitration in neurodegeneration (**1135**). Increased superoxide production in mitochondria should render them vulnerable when exposed to NO (**532**). Consistently, mice deficient in NOS1 are resistant to MPTP toxicity, and NOS inhibitors are protective (**1348**). Peroxynitrite also readily damages complex I in the mitochondria (**919**, **1062**) and might further amplify injury. One of the major consequences of peroxynitrite production within mitochondria is nitration and inactivation of mitochondrial Mn-SOD (**826**, **827**, **830**). In vivo, nitration of Mn-SOD has been detected in cerebrospinal fluid of patients with ALS, Alzheimer's disease, and Parkinson's disease (**27**). Serious consequences arise from the genetic knockout of Mn-SOD, which is generally lethal in the neonatal period. In addition to causing cardiac failure, the mitochondrial Mn-SOD knockout mouse suffers CNS pathology that includes mitochondrial vacuolization and oxidized lipid deposits. Conversely, genetically induced increased expression of mitochondrial Mn-SOD or induction of the enzyme during stress has been shown to protect mitochondria and cells from oxidative stress. The inactivation of Mn-SOD by peroxynitrite will make mitochondria more vulnerable in neurodegeneration.

Another major group of targets for nitration in neurodegeneration are various structural proteins. These are particularly abundant proteins in cells and tend to have a higher proportion of tyrosine. Tyrosine is moderately hydrophobic and can be buried within the contact regions between subunits and yet also can form hydrogen bonds with water when subunits are disassembled. Often these tyrosines are located near acidic and basic residues that can increase their susceptibility to nitration (**72**). Nitration of structural proteins can have major functional consequences. Addition of the bulky nitro group will increase steric interference and introduce a partial negative charge. If a tyrosine involved in subunit contacts is nitrated, it could seriously compromise the formation of a large structure. The nitration of the structural protein has a dominant effect interfering with the proper assembly and function of the entire structure. Tyrosine radical intermediates may also cause covalent cross-links between structural proteins

that will also interfere in their proper assembly and function. Disruption of structural proteins might also have a major impact on mitochondrial function in neurons, because mitochondria moving along axons are far removed from nuclear protein synthesis (2). Over 99% of the proteins in the mitochondria are encoded in the nucleus and imported. In neurons, mitochondria could potentially be several days to months away from the cell soma, making replacement of key components difficult to maintain.

The CNS intermediate filament proteins, neurofilament-L (NFL) and glial fibrillary acid protein (GFAP) were among the very first proteins to be identified as endogenously nitrated in vivo (247,459, 531). SOD was also shown to be very efficient at catalyzing nitration by peroxynitrite of disassembled NFL subunits in vitro, particularly when the SOD is zinc deficient (246, 247). The most likely sequences to be nitrated were in the coiled-coil rod domain that is crucial for the initial dimerization, but not in the head domain where 10 of its 100 residues are tyrosine. Nitration of a small percentage (<10%) of NFL is sufficient to substantially disrupt the assembly of neurofilaments. The nitration of NFL may be particularly important in ALS where motor neurons contain massive concentrations of neurofilament proteins needed to support the enormous axons that can be a meter in length. Over 99% of the volume of motor neurons is contained in the axon plus the neuromuscular junction and hyperphosphorylated neurofilaments found in inclusions are an early marker of motor neuron pathology in ALS. Neurofilament proteins also have a high affinity and binding capacity for zinc (1028), which may favor the formation of zinc-deficient SOD. As described below, the loss of zinc from SOD may be a key factor in understanding why motor neurons are vulnerable in ALS.

Subsequent studies have found numerous other proteins that may lead to aberrant structures when nitrated. Mutations to α-synuclein have been linked to a small fraction of Parkinson's cases. Wild-type α-synuclein is a major component in Lewy bodies as well as other filamentous protein inclusions in sporadic PD and several other pathologies (22, 443, 1042, 1191). The use of specific antibodies for nitrated α-synuclein revealed that the majority of the Lewy bodies and protein inclusions contain nitrated and oxidized α-synuclein (443). Cellular systems and biochemical studies have shown that nitrative stress promotes the formation of α-synuclein aggregates in a manner that is resistant to proteolysis (608, 1191, 1288). Nitration of other structural proteins such as synaptic proteins (synaptophysin, Munc-18, SNAP25) (317), Tau protein (1073, 1074,1442), and tubulin (54, 199, 730, 1269; see also Table 1) may also be involved in the pathophysiology of various neurodegenerative disorders and stroke.

1. Multiple sclerosis (MS)

MS is an immune-mediated, inflammatory disease causing focal damage to the white matter attacking different regions of the CNS apparently at random. The ability of neurons to conduct impulses becomes compromised through the loss of their myelin sheath, and through the secondary axonal loss (1187). The disease affects 2–3 million people worldwide and most commonly shows an unpredictable, relapsing-remitting course and a range of clinical symptoms (e.g., tremor, ataxia, visual loss, double vision, weakness or paralysis, difficulty in speaking, loss of bladder control and constipation, cognitive impairment, and painful muscle spasms) depending on where the demyelination and axonal loss have occurred (226). Although numerous drugs targeting the immune system slow down the progression of the disease, the treatment of MS remains mostly symptomatic and far from satisfactory (675, 1036).

Inflammatory plaques in MS patients showed increase immunoreactivity for iNOS and nitrotyrosine (**41**, **123**, **139**, **241**, **242**, **445**, **546**, **780**, **1154**, **1312**) accompanied by elevated levels of nitrate and nitrite in CSF, urine, and serum (**447**, **448**, **1407**). Tyrosine nitration may contribute to the blood-brain barrier damage (allowing the influx of inflammatory cells) which is a cardinal feature of active MS (**296**, **567**, **972**). Furthermore, iNOS expression decreases in demyelinated plaques from MS patients when inflammation is reduced (**780**). Inhibition of iNOS in experimental allergic autoimmune encephalomyelitis (EAE; mouse model of MS) yielded controversial results, since both reduction (**242**, **1142**) or enhancement (**644**) of inflammation were reported. Peroxynitrite scavengers, mercaptoethylguanidine (MEG) and guanidinoethyldisulphide (GED), protected only against the induction phase of EAE, but did not prevent disease progression (**1142**).
Uric acid has proven to be a useful inhibitor of tyrosine nitration (although it is not a direct peroxynitrite scavenger) (**1271**) and has been shown to protect the blood-brain barrier and largely prevent the entry of inflammatory cells into the CNS (**566**, **567**). Additionaly, it also prevented CNS injury after inflammatory cells have already migrated into the CNS (**1141**). Urate has also proven beneficial in reducing the morbidity associated with viral infections (**710**, **1141**). Interestingly, in humans there is an inverse correlation between affliction with gout and MS (**710**, **1195**). Numerous studies have reported lower levels of uric acid in MS patients favoring the view that reduced uric acid in MS is secondary to its “peroxynitrite scavenging” activity during inflammatory disease, rather than a primary deficiency (reviewed in Ref. **694**). These studies have also suggested that serum uric acid levels could be used as biomarkers for monitoring disease activity in MS (reviewed in Ref. **694**).

2. Parkinson's disease

Parkinson's disease (PD), the second most common neurodegenerative disease of adult onset, is characterized by progressive loss of dopaminergic neurons within substantia nigra pars reticulata (SNr), resulting in reduced dopamine levels and a loss of dopaminergic neurotransmission in the striatum, which interferes with the function of the basal ganglia critical to motor function and coordination. Even though oxidative stress, inflammation, excitotoxicity, mitochondrial dysfunction, and hereditary and environmental factors have all been implicated in the pathogenesis of PD, the exact cause of the loss of dopaminergic neurons remains obscure (**362**, **522**).
Post mortem studies have demonstrated ROS- and peroxynitrite-mediated oxidative and/or nitrosative damage in PD (reviewed in Refs. **337**, **338**, **632**, **1119**, **1284**). Increased nitrotyrosine accumulation has been found in Lewy bodies (characteristic feature of PD; Ref. **456**) and polymorphonuclear cells of PD patients (**437**). In the latter, the accumulation of nitrotyrosine-containing proteins was accompanied by overexpression of nNOS (**437**). In a mouse model of PD induced by intraperitoneal administration of a selective neurotoxin of dopaminergic nigrostriatal neurons MPTP elevated levels of both free and bound 3-NT were demonstrated in ventral midbrain and in the striatum (**1020**). Consistent with the pathogenetic role of NO in PD, nNOS knockout mice or mice or primates treated with nNOS inhibitors are more resistant to neurotoxicity induced by MPTP (**68**, **1044**).
Peroxynitrite may induce nitration of tyrosine hydroxylase, the initial and rate-limiting enzyme in the biosynthesis of dopamine, leading to inhibition of enzyme activity and consequent failure in the synthesis of dopamine (**28**). Importantly, the nitration of tyrosine residues in tyrosine

hydroxylase paralleled the decline in dopamine levels in mouse striatum following MTPT administration (**28**). Tyrosine residues are also pivotal for the substrate specificity of monoamino oxidase B (MAO B) leading to impaired dopamine metabolism once nitrated (**440**). Peroxynitrite has been implicated to contribute to the loss of intracellular glutathione from substantia nigra (an early event in PD) by inactivating glutathione reductase, the enzyme responsible for the regeneration of glutathione from its oxidized form (**60**, **97**), and to induce apoptosis in dopaminergic neurons in PD (**930**). Recent evidence suggests that mitochondrial complex I inhibition may be the central cause of sporadic PD and that derangements in complex I lead to α-synuclein aggregation, which contributes to the demise of dopamine neurons (**293**). Accumulation and aggregation of α-synuclein may further facilitate the death of dopamine neurons through impairments in protein handling and detoxification (**293**). As already mentioned above, both mitochondrial complex I and synuclein can be targets for peroxynitrite-induced protein nitration (see also **Table 1**).

3. Alzheimer's disease

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is characterized by the formation of neuritic plaques rich in β-amyloid (Aβ) peptide, neurofibrillary tangles rich in hyperphosphorylated tau protein, gliosis, and a neuroinflammatory response involving astrocytes and microglia, inevitably leading to progressive global cognitive decline, and accounting for the vast majority of age-related dementia (**1357**).
Increased oxidative stress is present and appears to be an early event in the process of neurodegeneration associated with AD (**162**, **356**, **564**, **845**, **872**, **900**, **1167**, **1278**). It appears that both neuronal and glial NOS may play a role in the pathogenesis of AD and peroxynitrite formation. Increased expression of nNOS was reported in neurons with neurofibrillary tangles in the hippocampus and enthorinal cortex of AD patients as well as in reactive astrocytes near amyloid plaques (**1166**, **1276**). Presence of neuritic plaques has also been associated with increased expression of iNOS and eNOS in astrocytes (**297**, **298**, **804**–**806**, **1340**).
Dysfunctional neurons and neurofibrillar tangles frequently display various markers of nitrative stress, including 3-NT, the hallmark of peroxynitrite formation. Indeed, increased nitrotyrosine levels were demonstrated in hippocampus, neocortical regions, and ventricular fluid and CSF of AD patients (**538**, **1176**, **1279**). Importantly, the high levels of 3-NT in cerebrospinal fluid correlated with the decrease in cognitive function in AD patients (**1279**). In contrast, a study found no difference in 3-NT levels in CSF of patients with AD (**1095**). Immunohistochemical staining for 3-NT is more intense around Aβ depositions, and chronic intracerebroventricular infusion of Aβ can also cause ROS and peroxynitrite formation and subsequent tyrosine nitration of proteins (**1119**, **1285**). Nitration of a variety of proteins including synaptophysin, proteins involved in glucose metabolism, cytoskeletal integrity, antioxidant defense, just naming a few, was also reported in AD (**180**, **225**, **1285**).

4. Amyotrophic lateral sclerosis (ALS)

ALS (also known as Lou Gehrig's disease or motor neuron disease) is the most common adult-onset human motor neuron disease, which is characterized by rapid, progressive degeneration of motor neurons in the motor cortex, brain stem, and spinal cord. This ultimately leads to progressive weakness, paralysis, and premature death within 3–5 years after the onset of

symptoms (152, 1088). Patients are cognitively intact and thus completely aware of their progressive disability. Only ~10% has familial inheritance, usually with an autosomal dominant pattern, while most ALS cases are sporadic with no genetic basis. Although various mechanisms, including neuroinflammation, oxidative stress, autoimmunity, a defect in neuronal glutamate transport and glutamate toxicity, neurofilament accumulation, exogenous factors (viruses, toxins), mitochondrial dysfunction, and mutations in the SOD gene were implicated to play a role, the pathogenesis of ALS is incompletely understood (63, 91, 152, 872, 1088, 1168, 1309, 1359). Tragically, available treatment options do not prevent disease progression and death and extend life by only a few weeks (1088).

In 1993, an international collaboration identified 13 missense mutations to SOD in ~2–3% of ALS patients (1086). Further screening has identified over 120 different missense mutations occurring at about 45 different places that are linked to ALS (a current list is maintained at www.alsod.org). The disease caused by the SOD mutations is generally not clinically or pathologically distinguishable from the sporadic cases of ALS. The mutations to SOD are dominant, and almost all the mutants result in the expression of an active SOD protein. Overexpression of many but not all of the ALS mutations in transgenic mice or rats results in the development of motor neuron disease, which strongly supports a toxic gain of function in SOD induced by the mutations (493). The disease is clearly not the result of losing SOD scavenging activity, because knockout mice for this gene do not develop motor neuron disease (1070).

Because SOD could catalyze tyrosine nitration by peroxynitrite, Beckman et al. (76) proposed that the mutations may result in greater nitration activity. A number of investigators have since found increased tyrosine nitration in both human ALS patients (3, 4, 69, 217, 218, 457, 1280, 1384) and in transgenic mouse model of familial ALS (animals overexpressing SOD mutants) (151, 176, 388,1121, 1135). More recently, the nitration of proteins in transgenic mice has been directly confirmed using mass spectrometry (176). Protein nitration may have a role in ALS pathogenesis, acting directly by inhibiting the function of specific proteins and indirectly interfering with protein degradation pathways and phosphorylation cascades (176).

However, when the SOD proteins were purified and carefully treated to have 100% of their complement of copper and zinc, the ALS mutant SOD proteins behaved identically to wild-type Cu,Zn-SOD, reacting to peroxynitrite with the same efficiency and with equal superoxide scavenging activity. However, the proteins were slightly less stable than wild-type SOD and were often deficient in zinc (246, 247). When the SOD proteins were made zinc deficient, they had decreased scavenging activity for superoxide and reacted more efficiently with peroxynitrite to catalyze tyrosine nitration. In addition, the copper remaining in SOD was much more redox active and quickly reacted with ascorbate or other low-molecular-weight reductants typically found within cells. This aberrant redox activity will deplete cells of their antioxidant defenses. In addition, the copper- and zinc-deficient SOD will be entirely reduced, continuously reacting with oxygen to generate superoxide. In the presence of NO, zinc-deficient SOD will produce peroxynitrite as well as increase tyrosine nitration. The loss of zinc turns SOD into a strongly pro-oxidative enzyme (reviewed in Refs. 77, 608).

Of particular importance, the loss of zinc from wild-type SOD carries the same functional consequences as the loss of zinc from any of the ALS mutant SODs. The mutations simply increased the probability of SOD lacking the essential zinc atom by destabilizing the structure of SOD. As a consequence, the loss of zinc from SOD could be involved in the pathology of the 98% of ALS patients who do not have mutations to the SOD protein.

The toxicity of zinc-deficient SOD to primary cultures of motor neurons was confirmed in vitro by entrapping these proteins into liposomes to allow intracellular delivery (368). The zinc-deficient wild-type SOD was as toxic as any of eight different zinc-deficient ALS mutant SODs (366). The toxicity of all the zinc-deficient SODs was inhibited by copper chelators or by inhibition of NO synthesis. Exposure of motor neurons to exogenous NO itself was not toxic but overcame the protection provided by NOS inhibitors. Zinc-deficient SOD also increased tyrosine nitration in the motor neurons before inducing cell death. In contrast, Cu,Zn ALS-mutant SODs were not toxic to motor neurons and provided equal protection as Cu,Zn wild-type SOD to motor neurons subjected to trophic factor deprivation. Hence, the loss of zinc from SOD provides a compelling hypothesis to explain how mutations to this common "house-keeping" enzyme can cause the selective death of motor neurons in ALS (77).

Trophic factor deprivation of primary cultures of motor neurons initiates the endogenous production of peroxynitrite, which in turn activates apoptosis (369, 371). The mechanism appears to be specific for motor neurons and involves a novel pathway with the activation of FAS and induction of nNOS (1068). This pathway is readily induced in primary cultures of motor neurons isolated from transgenic mice overexpressing mutant SOD but only if they are exposed to an exogenous source of NO (1068). Trophic factor deprivation and other stresses to motor neurons apparently activate an intracellular source of superoxide, which activates apoptosis when NO is also coexpressed (366, 369).

Peroxynitrite can participate in the pathogenesis of ALS, because it can activate spinal cord astrocytes, which normally provide excellent trophic support to motor neurons, to assume a reactive phenotype that induces the death of motor neurons (179). The original methods for culture of motor neurons were to grow them on a feeder layer of astrocytes. A variety of cytokines as well as LPS causes astrocytes to produce peroxynitrite and assume the reactive phenotype (179). The reactive phenotype increases the production of nerve growth factor (NGF) (1018,1322). Normally NGF has no effect on motor neurons. However, motor neurons in culture as well as in ALS induce the expression of p75, which is a low-affinity receptor for neurotrophins such as NGF. When motor neurons express p75, they become sensitive to NGF when an exogenous source of NO is added. Reactive astrocytes synthesize and release both NGF and NO in quantities sufficient to induce the death of motor neurons.

The significance of this intricate interplay may have important ramifications not only for ALS but also for PD and AD (6, 58, 1102). Reactive astrocytes are common hallmark of neurodegeneration, and these results suggest that peroxynitrite may play an important role in promoting this phenotype as well as causing the degeneration of neurons. In ALS, the transformation of astrocytes into a reactive phenotype may explain why ALS is progressive, causing the relentless death of neighboring motor neurons. Interfering in such a cascade to stop the progressive death of motor neurons would not necessarily cure ALS but may keep it from being a death sentence.

5. Huntington's disease

Huntington's disease (HD) is a progressive, autosomal dominant, neuropsychiatric disorder of the midlife, caused by an unstable expansion of a trinucleotide polyglutamine repeat in the NH_2-terminal domain of a protein termed huntingtin on chromosome 4. The disorder is characterized by degeneration of neurons in the basal ganglia and cortical regions, which results in motor disturbances, such as chorea (involuntary movements) and dystonia, psychiatric symptoms, and

dementia (21, 431, 866). The prevalence of HD is much lower than that of most of the other common neurodegenerative disorders discussed above. The therapy of HD is very limited and mostly symptomatic (21, 431, 866).

There is accumulating evidence suggesting that increased oxidative stress and excessive production of NO might contribute to the development of HD by damaging neighboring neurons (reviewed in Refs. 63, 163). Accordingly, increased iNOS expression was observed in neuronal, glial, and vascular cells from brains of HD patients and mouse models of disease (206, 491). Similarly, numerous studies have demonstrated increased 3-NT formation in brain tissues (neurons, glia, and/or vasculature) of mice transgenic for the HD mutation, rats injected into the striatum with quinolinic acid (rat model of HD), and HD patients (300–302, 427, 1022, 1023, 1096,1117). Importantly, both NOS inhibitors and peroxynitrite scavengers decreased neuronal damage, improved disease progression, and also decreased brain 3-NT content in experimental models (301, 1022, 1117). These results suggest that peroxynitrite might be an important mediator of oxidative damage associated with HD.

6. Traumatic brain injury

Traumatic brain injury (TBI), which is characterized by axonal and neuronal cell injury, cerebral edema, increased permeability of blood-brain barrier, and posttraumatic changes in cognitive and neurological function, is one of the leading causes of disability and mortality in young individuals, with very limited treatment options (67, 376, 563, 817). TBI may trigger multiple pathophysiological processes including glutamate-induced excitotoxicity, release of inflammatory cytokines from brain-resident cells (microglia, neurons, and astrocytes), cortical blood flow dysregulation, oxidative and nitrosative stress, and eventually cell death via apoptosis or necrosis (441, 1346).

The pathogenetic role of peroxynitrite in TBI is supported by evidence demonstrating increased brain 3-NT levels following TBI in experimental mouse and rat models (92–94, 423, 507, 508,898, 1171, 1360), and by the beneficial effects of NOS inhibitor and peroxynitrite scavengers in reducing neuronal injury and improving neurological recovery following injury (423, 508, 898).

Collectively, multiple lines of evidence discussed above provide strong support for the important role of peroxynitrite formation and/or protein nitration in neurodegenerative disorders and suggest that the neutralization of this reactive species may offer significant therapeutic benefits in patients suffering from these devastating diseases.

H. Nitric Oxide and Peroxynitrite in Diabetes and Diabetic Complications

Diabetes mellitus is one of the most costly chronic diseases with an estimated worldwide prevalence of 170 million in 2002, which is expected to double by 2030 according to the World Health Organization (1370). Type 2 diabetes, accounting for 90% of diabetes, is characterized by insulin resistance and often is associated with obesity and dyslipidemia. Type 1 diabetes occurring predominantly in children and young adults, accounting for 5–10% of diagnosed cases, is characterized by insulin deficiency as a result of destruction of insulin-producing β-islet cells in the pancreas. Hyperglycemia is the most prominent feature of both types of diabetes. The majority of diabetic complications are associated with pathological alterations in the vascular wall, and the macro- and microvascular diseases are the most common causes of morbidity and

mortality in patients with diabetes mellitus (the global mortality attributed to diabetes is 6% and increasing) (**1370**). Type 2 diabetes is often complicated by numerous components of the metabolic syndrome (a syndrome of cardiovascular risk factors affecting over 50 million people in the United States alone, and has been shown to increase cardiovascular disease-related mortality 3.5-fold) and indeed, ~65% of deaths among people with diabetes are due to cardiovascular disease (**1370**). The most common macrovascular complication of diabetes is atherosclerosis, which increases the risk for myocardial infarction, stroke, and peripheral artery disease, the latter being the leading cause of limb amputation in civilized countries. Microvascular complications consist of retinopathy and nephropathy, the leading causes of blindness and renal failure (reviewed in Ref.**1177**). Diabetes can also lead to the development of diabetic cardiomyopathy, which is characterized by complex changes in the mechanical, structural, biochemical, and electrical properties of the heart, which may underlie the development of an early diastolic and a late systolic dysfunction, or both, and increased incidence of cardiac arrhythmias in diabetic patients (**527**). Recently, diabetes is considered a potent, independent risk factor for mortality in patients hospitalized with heart failure, particularly in females (**1177**, **1370**).

There is accumulating evidence supporting the key role of NO, superoxide, peroxynitrite, and downstream effectors such as PARP in the pathogenesis of diabetes and diabetic complication (reviewed in Refs. **630**, **821**, **958**, **994**, **996**, **997**, **1204**, **1232**; see also below and **Table 5**, **Figs. 16**–**18**).

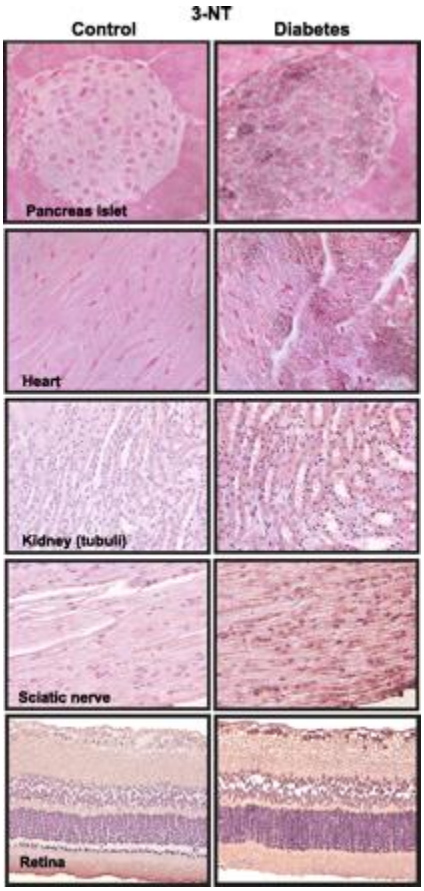

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FIG. 16.

Evidence for nitrotyrosine formation from various tissues of diabetic mice and rats. Immunohistochemical staining for nitrotyrosine (dark brown staining) from control (*left*) and diabetic (*right*) murine tissues. [Derived from Pacher et al. (**994**) and Szabo et al. (**1234**), with permissions from The Feinstein Institute for Medical Research and Bentham Science Publishers.]

1. Primary diabetes

Type 1 diabetes (or insulin-dependent diabetes mellitus) is characterized by autoimmune destruction of the pancreatic islet insulin producing β-cells resulting in prolonged periods of hyperglycemia via reduced uptake of glucose and relative increase in glucagon secretion and gluconeogenesis. Although the actual trigger of the beta-cell destruction is still unknown, various external (chemicals, viruses) or internal factors (free radicals, cytokines) have been proposed to initiate a deleterious chain of events leading to immune cell infiltration, release of immune mediators such as free radicals and cytokines, and eventually the destruction of β-cells.

It appears that NO and various related free radicals and oxidant species are major effectors of β-cell death (**234**, **685**, **1189**, **1215**). Consistently, iNOS is overexpressed in the pancreas of diabetic NOD mice (**1051**), iNOS knockout mice are resistant against streptozotocin-induced diabetes (**399**), and NOS inhibitors are protective in streptozotocin-induced, NOD, and BB models of type I diabetes (**233**, **1210**, **1388**). The sources of high concentrations of NO can be infiltrating macrophages and also various cell types of the islet overexpressing iNOS as a result of exposure to inflammatory cytokines such as IL-1β, TNF-α, and IFN-γ. Exposure of isolated rat, mouse, and human islets of Langerhans (in vitro models of type 1 diabetes) to various combinations of proinflammatory cytokines leads to inhibition of insulin secretion (**233**, **345**, **685**) via NOS induction and subsequent free radical formation (**233**, **685**), DNA damage (**307**, **308**, **378**), and consequent PARP activation and depletion of islet ATP and NAD sources, eventually culminating in apoptosis or necrosis (**109**, **378**, **474**, **651**, **715**, **1063**, **1302**; reviewed in Ref. **1232**). Furthermore, similar effects could be evoked by exposure of rat and human islets to NO, ROS, or peroxynitrite in vitro (**253**, **307**, **308**, **344**, **378**, **504**).
The first evidence on the possible involvement of endogenously formed peroxynitrite in the β-cell destruction came from a study demonstrating more frequent nitrotyrosine staining in islets from diabetic NOD mice (22%) than in islets from normoglycemic NOD mice (7%) and control BALB/c mice (2%) (see also **Fig. 16**). The nitrotyrosine positive cells identified in islets were either macrophages or β-cells. Most of the β-cells in islets from diabetic NOD mice were nitrotyrosine positive, whereas only very few were from control animals (**1210**). Importantly, inhibitors of iNOS and/or scavengers or peroxynitrite prevented development of diabetes and reduced the nitrotyrosine staining in the islets in various experimental models (**822**, **1209**, **1210**, **1234**).

2. Diabetic cardiovascular dysfunction

Diabetes, and even prediabetes, is characterized by endothelial dysfunction, which precedes and predicts, as well as predisposes, for consequent, more severe vascular alteration (165, 169,1242). Considerable evidence suggests that increased oxidative and nitrosative stress in diabetes may play an important role in the development or progression of cardiovascular disease by a number of different mechanisms, including disruption of endothelial function and facilitation of myocardial injury, elevation of acute phase reactants, and impairment of cardiovascular sympathetic nervous system tone and integrity (reviewed in Refs. 630, 994, 996, 997, 1204). Hyperglycemia triggers oxidative stress via multiple mechanisms including activation of the polyol pathway, glucose auto-oxidation, alterations of cellular redox state, increased formation of diacylglycerol and the subsequent activation of PKC, and accelerated nonenzymatic formation of advanced glycation end products (AGE) (150, 184, 500, 946).

Superoxide anion appears to play a particularly important role in the pathogenesis of diabetic cardiovascular dysfunction, and this reactive oxidant was reported to activate many of the above-mentioned pathways (150, 184, 946; Fig. 17). The cellular sources of superoxide anion are multiple and include NAD(P)H and xanthine oxidases, the arachidonic acid cascade (including cyclooxygenase and lipoxygenase), microsomal enzymes, and the mitochondrial respiratory chain, with the latter being the most important source in diabetes (150; Fig. 17). Hyperglycemia-induced superoxide production leads to increased expression of NAD(P)H oxidases, which in turn generate more superoxide anion. Through the activation of NFκB, hyperglycemia favors increased expression of iNOS which can increase the generation of NO (237, 1194).

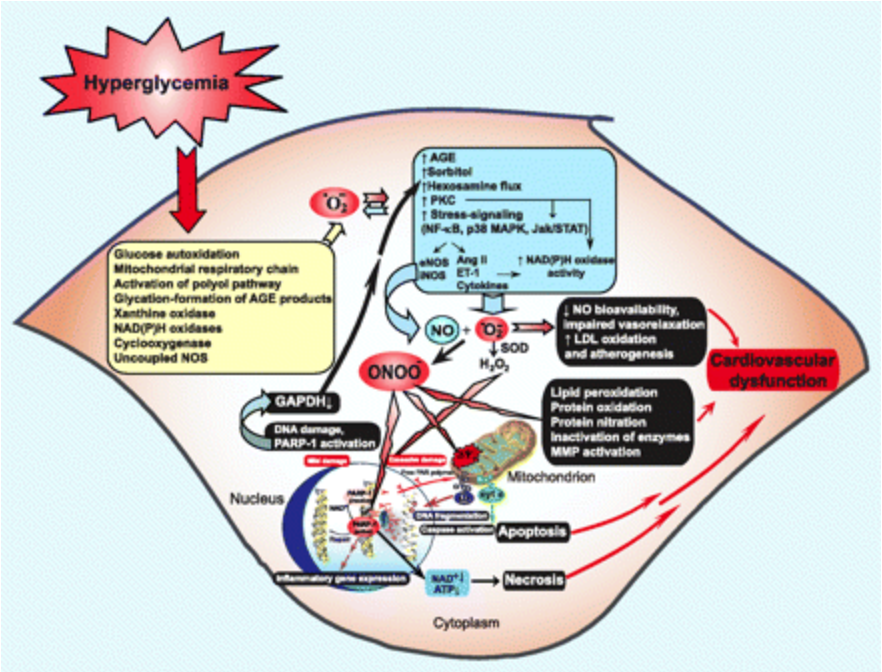

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FIG. 17.

Mechanisms of cardiovascular dysfunction in diabetes: role of superoxide and peroxynitrite. Hyperglycemia induces increased superoxide anion ($O_2^{\cdot-}$) production via activation of multiple pathways including xanthine

and NAD(P)H oxidases, cyclooxygenase, uncoupled nitric oxide synthase (NOS), glucose autoxidation, mitochondrial respiratory chain, polyol pathway, and formation of advanced glycation end products (AGE). Superoxide activates AGE, protein kinase C (PKC), polyol (sorbitol), hexosamine, and stress-signaling pathways leading to increased expression of inflammatory cytokines, angiotensin II (Ang II), endothelin-1 (ET-1), and NAD(P)H oxidases, which in turn generate more superoxide via multiple mechanisms. Hyperglycemia-induced increased superoxide generation may also favor an increased expression of nitric oxide synthases (NOS) through the activation of NFκB, which may increase the generation of nitric oxide (NO). Superoxide anion may quench NO, thereby reducing the efficacy of a potent endothelium-derived vasodilator system. Superoxide can also be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and interact with NO to form a reactive oxidant peroxynitrite ($ONOO^-$), which induces cell damage via lipid peroxidation, inactivation of enzymes and other proteins by oxidation and nitration, and activation of matrix metalloproteinases (MMPs) among others. Peroxynitrite also acts on mitochondria [decreasing the membrane potential (Ψ)], triggering the release of proapoptotic factors such as cytochrome *c* (Cyt *c*) and apoptosis-inducing factor (AIF). These factors mediate caspase-dependent and caspase-independent apoptotic death pathways. Peroxynitrite, in concert with other oxidants (e.g., H_2O_2), causes strand breaks in DNA, activating the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1). Mild damage to DNA activates the DNA repair machinery. In contrast, once excessive oxidative and nitrosative stress-induced DNA damage occurs, overactivated PARP-1 initiates an energy-consuming cycle by transferring ADP-ribose units (small red spheres) from NAD^+ to nuclear proteins, resulting in rapid depletion of the intracellular NAD^+ and ATP pools, slowing the rate of glycolysis and mitochondrial respiration, and eventually leading to cellular dysfunction and death. Poly(ADP-ribose) glycohydrolase (PARG) degrades poly(ADP-ribose) (PAR) polymers, generating free PAR polymer and ADP-ribose, which may signal to the mitochondria to induce AIF release. PARP-1 activation also leads to the inhibition of cellular glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity, which in turn favors the activation of PKC, AGE, and hexosamine pathway leading to increased superoxide generation. PARP-1 also regulates the expression of a variety of inflammatory mediators, which might facilitate the progression of diabetic cardiovascular complications. [From Pacher and Szabo (**996**), with permission from Elsevier.]

Multiple lines of evidence support the pathogenetic role of endogenous peroxynitrite formation in diabetic cardiovascular complications both in experimental animals and in humans (**Table 5**; Refs.**184**, **994**, **996**, **1204**; **Figs. 16** and **18**). First, increased nitrotyrosine levels are detectable in plasma and platelets of diabetic patients (**36**, **186**, **188**, **190**, **553**, **555**, **850**, **1265**), and nitrotyrosine is directly harmful to endothelial cells (**879**). Second, high glucose causes inactivation of human prostacyclin synthase, increased expression of adhesion molecules, and apoptosis via peroxynitrite formation in cultured human aortic endothelial cells (**1473**). In cardiomyocytes grown in culture medium containing elevated glucose, pathophysiological alterations can be attenuated by antioxidants, NOS inhibitors, and peroxynitrite scavengers (**364**). Third, hyperglycemia induces increased nitrotyrosine formation in bovine and human endothelial cells (**236**, **1040**, **1049**, **1473**), in cultured cardiomyocytes (**364**), in the artery wall of monkeys (**1021**), and in diabetic patients during a period of postprandial hyperglycemia (**185**–**189**). Fourth, the degree of cell death and/or dysfunction correlates with levels of nitrotyrosine in

endothelial cells, cardiomyocytes, and fibroblasts from myocardial biopsies of diabetic patients (413), hearts of experimental diabetic rats (413, 646), and hearts perfused with high glucose concentrations (189). Fifth, the nitrotyrosine immunoreactivity is increased in the microvasculature of type 2 diabetic patients and correlates with fasting blood glucose, HbA1c, intracellular adhesion molecule, vascular cellular adhesion molecule, and endothelial dysfunction (1242). Sixth, neutralization of peroxynitrite with peroxynitrite decomposition catalyst ameliorates the endothelial and cardiac dysfunction in streptozotocin-induced murine models of diabetes (1234).

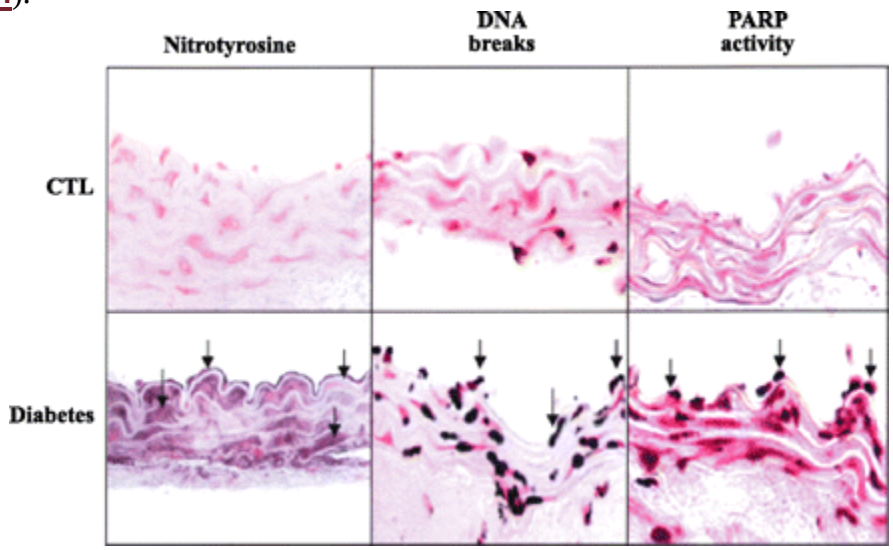

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FIG. 18.

Evidence for nitrotyrosine formation and PARP activation in diabetic vasculature. Immunohistochemical staining for nitrotyrosine, terminal deoxyribonucleotidyl transferase-mediated dUTP nick-end labeling (indicator of DNA breaks), and poly(ADP-ribose) (index of PARP activity) in control rings (top row) and in rings from diabetic mice (bottom row). [Derived from Garcia Soriano et al. (430) with permission from Nature Publishing Group.]

Peroxynitrite has been reported to attack various biomolecules, leading to compromised cardiovascular function in diabetes via numerous mechanisms (Fig. 17). One of these pathways involves DNA strand breakage and consequent activation of the nuclear enzyme PARP, which has been covered by separate overviews (995, 997, 1333). Figure 18 shows increased nitrotyrosine formation, DNA breaks, and PARP activation in aorta of a diabetic mouse. The PARP-1 activation has recently emerged as a crucial process in the development of diabetic cardiovascular dysfunction both in diabetic animals and humans (332, 989, 1185, 1242) and may also contribute to the development of other diabetic complications such as neuropathy, nephropathy, and retinopathy (for recent reviews, see Refs. 959, 997). Recently, a novel mechanism by which PARP activation regulates the development of various pathways related to diabetic complications has been identified (332, 624). According to this concept, high-glucose-induced elevated superoxide generation from the mitochondria (directly or indirectly via

generation of peroxynitrite) induces DNA strand breaks and PARP activation which, in turn, induces the poly(ADP-ribosyl)ation of GAPDH. The resulting metabolic alterations activate NFκB, polyol pathway, and aldose reductase leading to increased oxidative stress (**332**, **624**; **Fig. 17**).

3. Diabetic neuropathy, nephropathy, and retinopathy

Diabetic nephropathy, neuropathy, and retinopathy develop in at least 30–50% of patients with chronic diabetes mellitus (irrespective of the type of the diabetes) and are the major cause of increased morbidity and mortality. The ultimate consequences of diabetic complications may include renal failure, blindness, and foot ulceration and amputation. Numerous studies have suggested that increased oxidative stress, peroxynitrite formation, and downsream effector pathways such as PARP are involved in the pathogenesis of diabetic microvascular injury in nephropathy, retinopathy, and neuropathy, and this topic is covered by numerous recent overviews (**150**, **280**, **630**, **957**, **958**, **994**, **996**, **1204**).

Increased peroxynitrite formation and oxidative stress were demonstrated in kidney biopsies of patients with diabetic nephropathy and in kidneys of diabetic animals (**402**, **615**, **974**, **1277**). Increased eNOS expression and activity as well as increased formation of superoxide anion and peroxynitrite were found in retinal endothelial cells maintained in high glucose (**352**, **354**) and in retinas of diabetic animals (**230**, **231**, **354**, **712**, **713**), and all these alterations could be attenuated with various antioxidants, NOS inhibitors, or peroxynitrite scavengers (**230**, **231**, **352**, **354**, **712**). Furthermore, increased peroxynitrite-mediated VEGF and urokinase plasminogen activator receptor expression were proposed to be responsible for the breakdown of the blood-retina barrier in diabetic animals (**352**, **354**). Increased formation of peroxynitrite has recently been documented in both experimental (**209**, **230**, **231**) and clinical diabetic neuropathy (**554**). Furthermore, a peroxynitrite scavenger FP-15 normalized diabetes-associated decreased sciatic motor nerve and digital sensory nerve conduction velocity and ameliorated the nitrotyrosine formation and poly(ADP-ribose) accumulation in diabetic nerves (**961**). Consistently, several recent studies using PARP-1 knockout mice and/or various PARP inhibitors suggested that PARP activation plays a key role in the pathogenesis of diabetic cardiovascular dysfunction (**332**, **989**,**1185**, **1186**, **1242**), nephropathy (**886**), neuropathy (**598**, **753**, **958**, **960**, **963**), and retinopathy (**962**). Furthermore, some promising antioxidant approaches reduce not only oxidative stress, but also nitrotyrosine formation and PARP activation in diabetic nerves, kidneys and retinas (**331**,**963**).

Collectively, the evidence reviewed above support the view that peroxyntrite-induced damage plays an important role in numerous interconnected aspects of the pathogenesis of diabetes and diabetic complications. Neutralization of RNS or inhibition of downstream effector pathways including PARP activation may represent a promising strategy for the prevention or reversal of diabetic complications.

VII. CONCLUSIONS AND FUTURE PERSPECTIVES

The field of NO has grown immensely from the incredulous proposal as a biological molecule to a field with 80,000 publications and touching all aspects of physiology and pathology. Inhaled NO itself is now routinely administered as a selective pulmonary vasodilator

(53, 411, 412, 593, 680,681, 1143). Drugs affecting the NO pathway have grown into a multibillion dollar business, principally as treatments for male impotence (159, 1066). Yet these indications represent only a small fraction of the potential for both improving medical treatment as well as advancing our understanding of the underlying pathophysiology of many diseases. Understanding the physiology and pathology of NO challenges the paradigms of biological thinking as well as pushes the lower sensitivity limits of analytical chemistry. NO signaling is deceptively simple. In nearly unmeasurable quantities, NO stimulates soluble guanylate cyclase to produce cGMP, which in turn affects intracellular calcium levels to modulate many cellular activities. What is often lost in this simplistic rendition of NO signaling is how the extremely diffusive nature of NO compared with other signaling molecules and moderate half-life allow it to coordinate and integrate physiological responses within small clusters of cells in tissues. A crucial aspect of NO signaling is to act as a shock absorber to dampen physiological responses to prevent parasitic oscillations from overwhelming complex control systems. Its diffusive nature also allows NO to act as a retrograde neuromessenger that can transiently affect thousands of synapses within specific areas of the brain.

Overwhelming evidence has established a role for NO in essentially all major pathological processes affecting humans. But NO itself is unlikely to be the proximal toxin in these processes. It is not highly reactive and is efficiently removed by the reaction with hemoglobin in red blood cells. It takes two oxygen molecules supplied by oxyhemoglobin in red blood cells for NOS to produce each molecule of NO. Because NO diffuses slightly faster than oxygen, it will be able to diffuse back to a red blood cell. Consequently, there will always be an efficient sink to remove NO in blood-perfused tissues that will prevent NO from forming significant amounts of reactive nitrogen species.

However, NO can be quickly converted into a series of powerful oxidants with many biological effects by its diffusion-limited reactions with many free radicals. The major physiological gateway to produce reactive nitrogen species is most likely through the diffusion-limited reaction with superoxide. While a small flux of superoxide is inevitably produced by leakage of electrons to molecular oxygen through the autoxidation of biological molecules, there is growing recognition that cells can be activated to produce large amounts of superoxide by specific NADPH oxidases and other enzymatic sources. Because the rate of peroxynitrite formation rises 100-fold for each 10-fold increase in superoxide and NO production, the production of superoxide offers a dynamic mechanism to redirect NO from being a signaling molecule to an important component of host-defense and innate immunity.

The range of free radical reactions potentially involving NO is bewildering, leading most investigators to retreat into the relative safety of attributing the effects to terms such as “reactive nitrogen species” or more broadly “reactive nitrogen and oxygen species.” But, with this comes a substantial cost in understanding the underlying mechanisms. Once significant amounts of peroxynitrite are produced in a cell, it will produce a shower of other reactive nitrogen species. Peroxynitrite is likely to be the major source of both nitrogen dioxide and possibly nitrite in vivo. When NO is produced more rapidly than superoxide, the excess NO will be consumed to produce a variety of nitroso species, which implies that a modest stimulation of superoxide formation will yield nitrosative rather than nitrative stress.

The broad actions that can be attributed to peroxynitrite in inflammation, cardiovascular disease, neurodegeneration, diabetes, and other pathologies have been reviewed here in some detail. Multiple lines of evidence support the pathophysiological role of peroxynitrite. Its footprints are detectable by using various methods in virtually all diseases both in humans and animals. Potent enzymatic scavenging systems to detoxify peroxynitrite are found in pathogenic microorganisms (**155**, **156**). Selective scavengers of peroxynitrite exert beneficial effects in various animal models of disease, and improvements of many pathophysiological conditions in general are associated with decreased target tissue nitrotyrosine formation. Compounds such as urate and many polyphenolics are protective by acting as alternative targets for tyrosine nitration. Many other therapeutic approaches, such as iNOS inhibitors, superoxide scavengers, NADPH oxidase inhibitors, and broadly effective antioxidants (e.g., vitamin E, ascorbate, melatonin, etc.), may be in part protective by preventing the formation of peroxynitrite or repairing damage initiated by it. Various commonly used medications currently used to treat human disease (e.g., ACE inhibitors, carvediol, etc.) also decrease nitrotyrosine formation in diseased tissues. Peroxynitrite may play an important role in modulating vascular injury as well as proinflammatory responses.

The effects of peroxynitrite are not simply the accumulation of random damage to cells as specific responses determine whether cells activate repair processes or die through apoptosis or necrosis. There is a biological specificity to the effects of oxidants that has been largely ignored. Hence, enormous opportunities remain to reduce human suffering when these subtle actions are better understood.

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