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Minireview

Protection against peroxynitrite

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Abstract Peroxynitrite formed in vivo from superoxide and nitric oxide can mediate oxidation, nitration, or nitrosation reactions, leading to impaired function, toxicity, and alterations in signaling pathways. Protection against peroxynitrite is important for defense of normal tissue, especially during inflammation. Biological protection against peroxynitrite is organized in three categories: *prevention*, *interception*, and *repair*. *Prevention* is the control of the formation of peroxynitrite precursors, nitric oxide and superoxide. *Interception* is by direct reaction with peroxynitrite, leading to non-toxic products. In this regard, organoselenium compounds, metalloporphyrin derivatives, and peroxidases (e.g. glutathione peroxidase and myeloperoxidase) exhibit high second-order rate constants with peroxynitrite. Ebselen, like glutathione peroxidase, protects in a catalytic fashion utilizing glutathione as reductant in the peroxynitrite reductase reaction. Protection by metalloporphyrins can be maintained through glutathione or ascorbate. *Repair* processes remove damaged products and restitute intact biomolecules.

Key words: Peroxynitrite; Oxidation; Nitration; Protection; Selenium; Glutathione peroxidase

1. Peroxynitrite, an oxidizing and nitrating/nitrosating agent

Peroxynitrite[1] is produced by the diffusion-limited reaction of nitric oxide and superoxide anion. Peroxynitrite is stable, but upon protonation to peroxynitrous acid (pK_a 6.8), it decays to nitrate with a rate constant of 1.3 s^{-1} at 25°C. Peroxynitrous acid is highly reactive, yielding oxidizing and nitrating species (see [1–5]). *Oxidation* reactions of peroxynitrite include DNA damage, leading to base modification (Fig. 1) [6] and mutation as well as single- and double-strand breaks [7,8]. Peroxynitrite also causes one- or two-electron oxidations of sulfhydryls [9], leading to thiyl radical formation, radical chain reactions, and depletion of thiol pools. Peroxynitrite can also induce lipid peroxidation [10] and may play a critical role in atherosclerosis [11]. Other oxidations include hydroxylation of phenols [12]. *Nitration* reactions are predominantly nitration of phenols, such as nitration of tyrosine residues in proteins (Fig. 1). Protein tyrosine nitration by peroxynitrite may interfere with phosphorylation/dephosphorylation signaling pathways [13,14] or alter protein function. Peroxynitrite can also cause *nitrosation* reactions (Fig. 1) [15,16].

At the level of the whole organism, the reactive chemistry of peroxynitrite can be considered beneficial, because of its cytotoxicity to bacteria [17] or other invading organisms. Inflammatory cells, such as macrophages and neutrophils, produce large amounts of both nitric oxide and superoxide, which in turn rapidly form peroxynitrite [18–20]. However, excessive production of peroxynitrite can damage normal tissue. Indeed, the formation of protein 3-nitrotyrosine in vivo has been shown in a number of inflammatory conditions in humans and experimental animals [21]. The physiological and pharmacological strategies for protection against peroxynitrite are organized in three categories: *prevention*, *interception*, and *repair* (see [22]).

2. Prevention

Table 1 lists some possibilities for the prevention of the formation of peroxynitrite. During inflammation, the expression of inducible nitric oxide synthase (NOS II) is often upregulated, concomitant with an increase in NOS activity. Specific inhibition of nitric oxide synthase can block generation of nitric oxide (see Table 1). In addition to exogenous scavengers of nitric oxide (see Table 1), hemoglobin is a good scavenger of nitric oxide and plays a role in decreasing nitric oxide levels in blood. Inhibitors of xanthine oxidase or of NADPH oxidase decrease superoxide production. Superoxide dismutase and mimics (e.g. metalloporphyrins; Fig. 2) can decrease superoxide levels and thereby decrease peroxynitrite formation. Lastly, anti-inflammatory agents, such as glucocorticoids, block excessive nitric oxide and superoxide formation by counteracting the inflammatory response.

3. Interception

A number of compounds have been shown in vitro to react with peroxynitrite and were suggested to be useful protectants in vivo. For determining the detoxifying capacity of the reaction of a given compound with peroxynitrite, it is useful to consider the rate constant of this reaction and the achievable concentrations, as well as the ability of this reaction to be catalytically maintained. For homogeneous systems, multiplication of the concentration of a given compound with the corresponding second-order rate constant for the reaction with peroxynitrite yields the rate of disappearance of peroxynitrite. This first-approximation approach was used previously considering the reaction of peroxynitrite with CO_2, hemoglobin, and peroxidases [23,24]. Table 2 lists the apparent second-order rate constants of the reaction of peroxynitrite with some

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[1] The term peroxynitrite is used sometimes to refer to both the peroxynitrite anion proper ($ONOO^-$) and peroxynitrous acid (ONOOH); the IUPAC names are oxoperoxonitrate(1−) and hydrogen oxoperoxonitrate, respectively. The systematic names of nitric oxide ($NO^\bullet$) and nitrosoperoxycarbonate ($ONO_2CO_2^-$) are nitrogen monoxide and 1-carboxylato-2-nitrosodioxidane, respectively.

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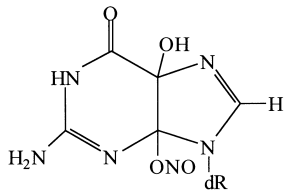
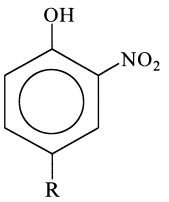
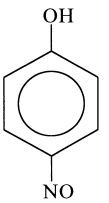


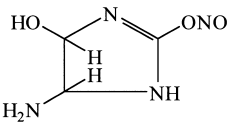
4,5-Dihydro-5-hydroxy-4-(nitrosooxy)-deoxyguanosine



3-Nitrotyrosine in Proteins



p-Nitrosophenol



Nitrated/nitrosated uric acid product

Fig. 1. Examples of products formed by oxidizing and nitrating/nitrosating reactions of peroxynitrite.

endogenous compounds, their concentrations in vivo, and the expected rate of disappearance of peroxynitrite. The rate constants for some exogenous compounds are also listed.

3.1. Low-molecular-weight compounds

3.1.1. Carbon dioxide. When one considers the concentration of carbon dioxide in vivo (~1 mM) and the rate constant of its reaction with peroxynitrite [25,26], the formation of the adduct, nitrosoperoxycarbonate ($ONO_2CO_2^-$), is most likely a major route of peroxynitrite reactivity in vivo. However, whether the carbon dioxide/peroxynitrite reaction is a detoxication pathway in vivo is unclear [23]. For example, carbon dioxide enhances protein tyrosine nitration by peroxynitrite [27]. Further, while carbon dioxide decreases two-electron oxidation of thiols by peroxynitrite [26], one-electron oxidation reactions are enhanced [28]. The latter pathway would lead to thiyl radical formation and subsequent radical chain reactions. Thus, it may be appropriate to call carbon dioxide a modifier of peroxynitrite reactions rather than a detoxifier.

3.1.2. Ebselen and organoselenium compounds. Selenium-containing amino acids and the organoselenium compound ebselen (Fig. 2) rapidly react with peroxynitrite [29–31] and protect against DNA damage caused by peroxynitrite more effectively than their sulfur analogs [32]. The reaction scheme depicted in Fig. 3 applies generally to ebselen or to selenocysteine in free or protein-bound form, such as in glutathione peroxidase (see below). Peroxynitrite is reduced by these compounds to nitrite; the resulting selenoxide is subsequently reduced by GSH, establishing a catalytic cycle so that the defense can be maintained in a peroxynitrite reductase reaction. Organotellurium compounds also protect against oxidation and nitration reactions caused by peroxynitrite [33,34]; bis[4-aminophenyl] telluride (Fig. 2) protects against peroxynitrite-mediated oxidation of dihydrorhodamine 123 more efficiently than its selenium analogue or ebselen [33].

Clinically, ebselen has been found to be protective in patients with delayed neurological deficits and aneurysmal subarachnoid hemorrhage [35], in acute ischemic stroke [36], and in acute middle cerebral artery occlusion [37]. Since increased nitrotyrosine levels were found to be associated with such neurological disorders, these protective effects of ebselen could be due in part to peroxynitrite defense.

3.1.3. Metalloporphyrins. In addition to mimicking superoxide dismutase, synthetic metalloporphyrins have been shown to react with peroxynitrite at second-order rate constants similar to that of ebselen [38,39] (Table 2). The metal in the porphyrin shown in Fig. 2 can be manganese(III) or iron(III). Both compounds catalyze the isomerization of peroxynitrite to nitrate. It is proposed that peroxynitrite attacks the metal, and the manganese(IV) can be rereduced by thiols or ascorbate [39,40], while the iron(IV) compound catalyzes its own reduction [38,41]. Synthetic porphyrins have been shown to be cytoprotective against peroxynitrite in vitro [42] and to alleviate some of the toxic effects of endotoxic shock in rats [41,43]. It should be mentioned that nitrogen dioxide can be released during the reaction process [39,41] and that these compounds may enhance nitration reactions of peroxynitrite [44].

3.1.4. Thiols and ascorbate. The interaction of peroxynitrite with free thiols in proteins or in glutathione is also rapid enough, in view of their in vivo concentrations, to make this reaction significant [2]. While the bulk of the reaction is a two-electron reduction of peroxynitrite to nitrite, at least a portion of peroxynitrite is reduced via a one-electron pathway, leading to a sulfur-centered radical [9]. Ascorbate has a low second-

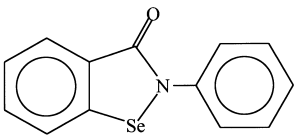
Table 1
Prevention of pathways leading to peroxynitrite formation

Compound	Example	Protective effect
Inhibitors of nitric oxide synthases	N^G-Monomethyl-L-arginine (L-NAME)	Protects against myocardial reoxygenation injury in piglets [65]
Inhibitors of superoxide production from xanthine oxidase or NADPH oxidase	Allopurinol	Partially restores acetylcholine-elicited vasorelaxation in isolated aortic rings from cholesterol-fed rabbits [66]
Inactivators of nitric oxide	2-Phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (carboxy-PTIO)	Delays onset and severity of experimental allergic encephalomyelitis in mice [67]
Inactivators of superoxide	Superoxide dismutase	Partially restores acetylcholine-elicited vasorelaxation in isolated femoral rings from cholesterol-fed rabbits [68]
Anti-inflammatory agents	Budesonide (glucocorticoid)	Decreased protein nitrotyrosine formation and increased breathing performance in asthmatic patients [69]

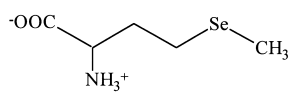
order rate constant for the reaction with peroxynitrite [45], and even with millimolar concentrations in cells, it is unlikely that ascorbate plays a significant role in direct reactions with peroxynitrite (Table 2); however, in the reduction of the oxidized metalloporphyrin compounds, it becomes important in peroxynitrite defense [39,40].

3.2. Proteins

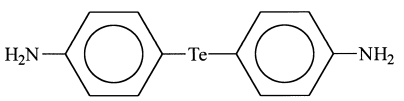
3.2.1. Myeloperoxidase and horseradish peroxidase. The mammalian heme peroxidases (e.g. myeloperoxidase) also react with peroxynitrite (Table 2) [46]. Although the concentration of myeloperoxidase in blood is low relative to more abundant biomolecules that react with peroxynitrite (e.g. CO_2) [24], concentrations are much higher in inflammatory cells (e.g. neutrophils). Further, localized extracellular concentrations near inflammatory cells during respiratory bursts may be high enough to react with peroxynitrite. In plants, the reaction between horseradish peroxidase and peroxynitrite may also be significant; the rate constant is 3.2×10^6 M^{-1} s^{-1} at pH 6.8, 25°C [46]. The reaction of horseradish peroxidase can be catalytically maintained using chlorogenic acid as a reductant [47]. However, both myeloperoxidase and horseradish peroxidase increase formation of nitrotyrosine by peroxynitrite [48].



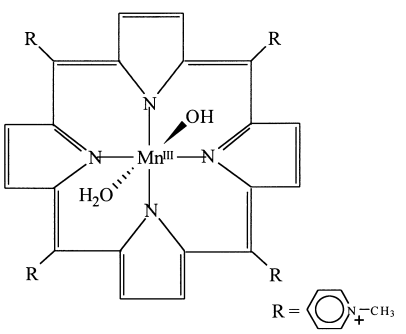
Ebselen



Selenomethionine



bis(4-Aminophenyl) telluride



5,10,15,20-Tetrakis(*N*-methyl-4′-pyridyl)porphine manganese(III) complex

Synthetic metalloporphyrin

Fig. 2. Structures of some low-molecular-weight compounds with high second-order rate constants for the reaction with peroxynitrite, including organoselenium, organotellurium, and synthetic metal porphyrin compounds (see Table 2).

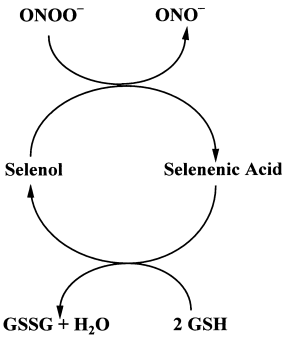


Fig. 3. Proposed catalytic mechanism of selenoperoxidases in the reduction of peroxynitrite to nitrite (or peroxynitrous acid to nitrous acid). The mechanism is based on that established for glutathione peroxidases and the mimic, ebselen, which use ROOH and ROH as substrate and product, respectively (see [29,51]). Selenomethionine can also react with peroxynitrite, with the resultant methionine selenoxide being reduced by glutathione in a catalytic cycle [57].

3.2.2. Hemoglobin. In addition to reacting with nitric oxide, hemoglobin reacts rapidly with peroxynitrite and is suitable for efficient protection of erythrocytes. However, hemoglobin is not able to fully protect the plasma membrane of erythrocytes; when peroxynitrite was generated outside the cells, hemolysis was found to occur [49]. Oxyhemoglobin reacts with nitric oxide to methemoglobin and nitrate via a short-lived intermediate peroxynitrite complex [50].

3.2.3. Glutathione peroxidase and selenoproteins. The selenocysteine-containing glutathione peroxidase (GPx) can act as a peroxynitrite reductase, preventing both oxidation and nitration reactions caused by peroxynitrite [51]. GPx inactivates peroxynitrite in a catalytic reaction at the stoichiometry known for that of hydroperoxide reduction, i.e. the classical GPx reaction (Fig. 3), similar to that described above for ebselen, and also for selenomethionine. Increases in nitrite during exposure to peroxynitrite were observed with GPx [51], indicating two-electron reduction of peroxynitrite; however, the nitrite yield was less than complete ($\sim$50%). The second-order rate constant for the reaction of glutathione peroxidase (tetrameric) with peroxynitrite is 8.0×10^6 M^{-1} s^{-1} (Table 2) [52]. Further, there is no net loss of GPx activity when GPx is maintained in the reduced state by supplying reductants [51,52]. These data suggest that inside the cell, GPx outcompetes thiols for the reaction with peroxynitrite and can compete with carbon dioxide (Table 2). Thus, the reaction of GPx with peroxynitrite is considered a biologically efficient detoxication pathway in vivo.

Selenoprotein P in human plasma also protects against peroxynitrite [53], suggesting that it may serve as a protectant against peroxynitrite in human blood. The heparin binding domains of selenoprotein P enable surface coating of cellular membranes (e.g. endothelial cells) [54,55]; this may serve as a protective barrier against peroxynitrite. Furthermore, the selenoprotein thioredoxin reductase can function in the reduction of peroxynitrite by selenocysteine or ebselen [55a].

Selenomethionine is oxidized to the selenoxide by peroxynitrite with a second-order rate constant approximately 100-fold higher than for the reaction of methionine with peroxynitrite [56]. Methionine selenoxide is effectively and rapidly reduced to selenomethionine by glutathione, permitting a catalytic re-

Table 2
Interception of peroxynitrite

Addition	Rate constant[a] (M^{-1} s^{-1})	In vivo conc. (M)	Disappearance of $ONOO^-$ (s^{-1})	Remarks
Spontaneous decay	–	–	0.4	
Low-molecular-weight compounds				
Carbon dioxide	3.0×10^4 [26]	1×10^{-3}	30	Enhances tyrosine nitration and thiyl radical formation [27,28]
Glutathione	5.8×10^2 [39]	1×10^{-2}[b]	5.8	Formation of thiyl radicals [9]
Ascorbate	5.0×10^1 [45]	1×10^{-2}[c]	0.5	–
Ebselen	2.0×10^6 [30]	–	–	–
Metalloporphyrins	2.0×10^6 [38,39]	–	–	–
Proteins				
Myeloperoxidase	4.8×10^6 [46]	5×10^{-4}[d]	2400	Enhances tyrosine nitration [48]
Hemoglobin	2.5×10^4 [70]	5×10^{-3}[e]	125	–
Glutathione peroxidase[f]	8.0×10^6 [52]	2×10^{-6}[g]	16	–
Albumin	5.6×10^3 [60]	6×10^{-4}[h]	3.4	Formation of thiyl radicals [28]

[a]Second-order rate constants are for pH 7.4, 25°C, with the exception of myeloperoxidase, which was at 12°C, and hemoglobin and albumin, which were at 37°C.
[b]Concentration in hepatocytes.
[c]Concentration in neutrophils.
[d]Concentration in neutrophils. The concentration is calculated from the amount of myeloperoxidase per neutrophil ($\sim1.5\times10^{-16}$ mol) [71] and neutrophil volume ($\sim$300 fl) [72].
[e]Concentration in erythrocytes.
[f]Rate constant for the reduced form of glutathione peroxidase. The rate constant for oxidized glutathione peroxidase is 7.4×10^5 M^{-1} s^{-1} at pH 7.4, 25°C [52].
[g]Concentration in hepatocytes. The concentration is calculated from the amount of selenium in liver ($\sim$2.6 mg/l) [73], assuming 23% to be present as GPx [74].
[h]Concentration in serum.

action by selenomethionyl residues in proteins [57]. In contrast, methionine sulfoxide is not reduced by glutathione; the enzyme methionine sulfoxide reductase is necessary for the reduction of methionine sulfoxide to methionine [58]. Since selenomethionine can occur in proteins such as hemoglobin [59], these residues may play a defensive role against peroxynitrite.

3.2.4. Albumin. The high concentration of albumin in plasma makes its reaction with peroxynitrite significant (Table 2). The reaction of peroxynitrite with albumin is largely due to the one free cysteine residue [60]. Further, human albumin contains six tyrosine residues adjacent to glutamate residues, which are preferentially nitrated by peroxynitrite [3]. Indeed, oxidized [28] and nitrated [51,53] products of albumin are observable when peroxynitrite is added to plasma.

4. Repair

Protection from the effects of peroxynitrite can be by repair of damage once it has occurred. As prevention and interception processes are not completely effective, damage products could continuously form in low yields during excessive peroxynitrite generation and may accumulate. As discussed above, damaged biomolecules include DNA, occurring as modified bases or in the form of single- or double-strand breaks [8], or membranes, occurring as phospholipid oxidation and nitration products, or proteins, occurring as oxidized and nitrated amino acid side-chains. Correspondingly, there are biological systems involved in DNA repair [8,61], modified lipid turnover [62,63], and proteolysis [64] that are capable of providing the functions of restitution or replenishment. The emerging and active field of research on repair of peroxynitrite-induced damage is not reviewed in detail here.

5. Concluding remarks

Defense against peroxynitrite occurs at various levels; defense strategies can vary between tissues and between subcellular compartments. The damaging potential of peroxynitrite is mediated by reactive oxidizing and nitrating species formed during the reaction of peroxynitrite with biomolecules. Therefore, cellular strategies of antioxidant defense not specific to peroxynitrite may also play a role in defense against damage due to peroxynitrite.

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