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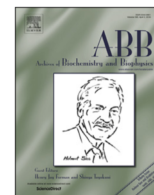

Peroxynitrite: From interception to signaling

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ABSTRACT

Peroxynitrite is a strong oxidant and nitrating species that mediates certain biological effects of superoxide and nitrogen monoxide. These biological effects include oxidative damage to proteins as well as the formation of 3-nitrotyrosyl moieties in proteins. As a consequence, such proteins may lose their activity, gain altered function, or become prone to proteolytic degradation – resulting in modulation of cellular protein turnover and in the modulation of signaling cascades. In analogy to hydrogen peroxide, peroxynitrite may be scavenged by selenoproteins like glutathione peroxidase-1 (GPx-1) or by selenocompounds with a GPx-like activity, such as ebselen; in further analogy to H_2O_2, peroxiredoxins have also been established as contributors to peroxynitrite reduction. This review covers three aspects of peroxynitrite biochemistry, (i) the interaction of selenocompounds/-proteins with peroxynitrite, (ii) peroxynitrite-induced modulation of cellular proteolysis, and (iii) peroxynitrite-induced modulation of cellular signaling.

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1. Introduction

Soon after the identification of peroxynitrite as a product of the near-diffusion-controlled reaction of superoxide with nitrogen monoxide (nitric oxide, NO) that is capable of oxidizing biomolecules in a fashion similar to the hydroxyl radical [1], its potency not only as an oxidizing, but also as a nitrating species was recognized [2,3]. Considering the early hypothesis that peroxynitrite formation might be a major mediator of superoxide and NO toxicity, it was asked whether there might be a way not only of preventing its formation (e.g., by dismutation of superoxide or by inhibiting NO formation) but also of interfering with peroxynitrite action. This would, of course, have the benefit of leaving other biological functions of superoxide or NO unimpaired.

The formation and action of peroxynitrite has been extensively reviewed elsewhere [4,5]. As this issue of ABB is dedicated to Helmut Sies, this overview will focus on three aspects of peroxynitrite biochemistry that Helmut and his laboratory have been interested in, and contributed to. First, some aspects of interfering with peroxynitrite action will be presented. Then, damage to proteins elicited by peroxynitrite and consequences of this damage for protein degradation will be reviewed, followed by a short overview on stress signaling cascades stimulated by peroxynitrite and how peroxynitrite may initiate these signaling processes.

2. Selenoproteins and selenocompounds as peroxynitrite reductases

Peroxynitrite formation can be prevented at the level of attenuating NO or superoxide generation, or by spatially separating their formation, but interference with peroxynitrite itself would require means of scavenging peroxynitrite, e.g. by reduction.

In some analogy to hydrogen peroxide, peroxynitrite/peroxynitrous acid ($ONOO^-$/ONOOH) was suggested to interact with peroxidase mimetics with iron/heme [6] or selenium moieties [7], rendering such compounds peroxynitrite reductases ("peroxynitritases") in the presence of suitable reductants. In fact, the earliest low-molecular mass compounds demonstrated to stimulate peroxynitrite decomposition include porphyrins containing iron [6] or manganese [8] that had been known to catalyze the dismutation of superoxide or hydrogen peroxide. Similarly, selenium-containing peroxidase mimetics, such as ebselen, were identified as compounds harboring significant peroxynitrite reductase activity [9–11] and to block peroxynitrite-induced oxidation and nitration reactions *in vitro* in cell-free systems and in cultured cells exposed

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to peroxynitrite [7] – both by direct interaction with peroxynitrite, and indirectly by stimulating nuclear factor erythroid 2-related factor 2 (Nrf2) signaling to enhance endogenous antioxidant defense [12].

In parallel, the respective peroxidase proteins were tested for their peroxynitrite reductase activities, and heme peroxidases, such as myelo- and lactoperoxidases, certain catalases [13,14], as well as the selenoenzyme glutathione peroxidase (GPx-1) [15] were demonstrated to catalyze peroxynitrite reduction. Despite its obvious peroxynitrite reductase activity *in vitro*, the *in vivo*-relevance of GPx-1 in the cellular defense against peroxynitrite is unclear.

One problem in attributing a biological effect to the action of peroxynitrite, and thus in attributing any protective GPx-1 action to its interaction with peroxynitrite, is based on the mere fact that no clear peroxynitrite-specific fingerprint exists in complex systems. Oxidation of biomolecules with similar product spectra may be elicited by other reactive oxygen species in cells. Even protein nitration to yield 3-nitrotyrosine moieties, which was initially assumed to be a suitable marker of peroxynitrite action [3] (and is still frequently taken as such), has since been demonstrated to be stimulated by other mechanisms, including exposure of proteins to nitrite and hypochlorous acid [16] or to heme peroxidases in the presence of nitrite and H_2O_2 [17].

In many of the studies referred to later on, the involvement of peroxynitrite in a biological effect was based on three pieces of evidence, i.e. the formation of 3-nitrotyrosine moieties in proteins, the abrogation of the effect observed upon inhibition of superoxide formation (e.g. by inhibition of NADPH oxidases), and the attenuation of the biological effect upon inhibition of NO generation (e.g. by NO synthase inhibition).

It should be noted that many of the experiments on biological (e.g. signaling) effects of peroxynitrite referred to in the later sections were based on an exposure of cultured cells to exogenous peroxynitrite or a nitrogen monoxide/superoxide donor, such as 3-morpholinosydnonimine (SIN-1). These conditions are of course far from reflecting an actual *in vivo*-situation and should always be considered as just a first hint in the number of steps to be taken to confirm the role of peroxynitrite in a biological phenomenon. Nevertheless, such *in vitro* data are of some relevance when investigating the role of peroxynitrite in a certain biological effect: we have no clear and unambiguous *in vivo*-marker of peroxynitrite formation and action, but when eliciting an effect using exogenous peroxynitrite we can at least be sure of its involvement.

Early on, there were attempts to exploit the cellular stress response as a result of a complex endogenous machinery potentially capable of distinguishing different stimuli, and translating them into a stimulus-specific response. Stimulus-specific stress kinase activation patterns were initially shown to differ between oxidants employed to elicit the response – e.g. peroxynitrite and singlet oxygen [18] –, but these differences turned out to be cell type-specific and also not applicable to an *in vivo* situation where one type of oxidant will rarely be generated in the absence of competing oxidants. It is, after all, a crucial property of the cellular stress recognition modules to integrate numerous molecular events triggered by exposure to a stressful stimulus such as an oxidant/nitrating agent to quickly mount a signaling response common to multiple stimuli. Hence, in many respects, peroxynitrite-induced signaling is unlikely to significantly differ from signaling elicited by exposure to other oxidants such as hydrogen peroxide (see below).

In line with the peroxynitrite reductase activity of GPx-1, and assuming that protein tyrosine nitration is sufficiently specific in indicating a role of peroxynitrite, GPx-1-deficiency slightly elevated protein nitration in atherosclerotic lesions of apolipoprotein E-knockout mice [19], which was recently demonstrated in these ApoE/GPx-1 double-knockout mice to be rescued by application of the GPx mimetic, ebselen, or by an ebselen-derivative [20]. Nevertheless, cells from GPx-1 knockout mice were less sensitive towards peroxynitrite than wild type cells [21], suggesting that the role of GPx-1 in the cellular response to peroxynitrite is complex. One is tempted to speculate that GPx-1 activity in cells can go both ways with respect to peroxynitrite reduction *vs.* enhancing peroxynitrite toxicity (e.g. by preventing peroxynitrite-induced protective signaling), implying that GPx-1 levels need to be carefully controlled (Fig. 1). In line with such a need for careful control of GPx-1 levels, its overexpression in a transgenic mouse model resulted in hyperinsulinemia and impaired insulin signaling in target tissues, rendering aged mice insulin resistant [22].

Other selenoproteins were tested for their interaction with peroxynitrite, and peroxynitrite reducing activity was indeed identified for selenoprotein P [23–25] and thioredoxin reductase [26].

3. Peroxynitritases based on other chalcogens: sulfur and tellurium

Sulfur analogs of selenium-based compounds with a peroxynitrite reductase activity were less active peroxynitritases than the corresponding selenocompounds – for example, ebsulfur was less active than ebselen in various *in vitro* assays testing for oxidation or nitration reactions by peroxynitrite [7]. In contrast, tellurium-based peroxidase compounds generally turned out to be similarly or even more active than the selenium-based analogs [27].

In further analogy to hydrogen peroxide, however, whose intracellular concentrations are now known to be fine-tuned by sulfur/thiol-based peroxidases, the peroxiredoxins [28], peroxynitrite was soon identified as a substrate of peroxiredoxins [29]. Based on its known avid interaction with thiols [30], peroxiredoxin/peroxynitrite interaction is now assumed to be a major sink of peroxynitrite in mammalian cells [31].

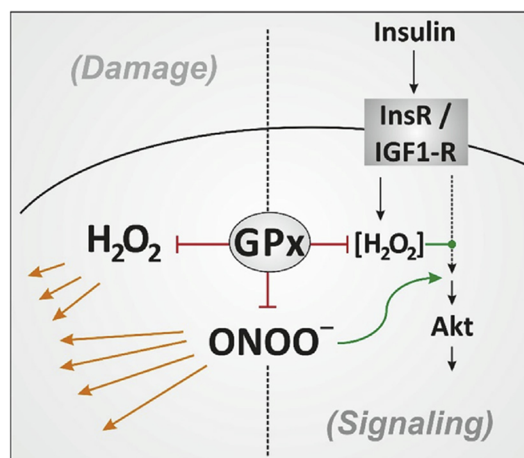

Fig. 1. Dual role of glutathione peroxidase-1 (GPx) in modulating hydrogen peroxide and peroxynitrite effects. GPx catalyzes hydrogen peroxide and peroxynitrite reduction. Both H_2O_2 and peroxynitrite may imitate insulin action by stimulating phosphoinositide 3′-kinase/Akt-dependent signaling [67,112]. Moreover, exposure of cells to insulin results in endogenous generation of hydrogen peroxide, which is required for proper insulin-dependent stimulation of Akt (green line) [113]. On the other hand, H_2O_2 and peroxynitrite (at higher concentrations, orange arows) may cause oxidative/nitrative damage to cellular components. GPx, by lowering H_2O_2 and peroxynitrite concentrations, may protect cells against this damage (left side of diagram), but may also impair signaling processes triggered by, or relying upon either of these reactive species (right side of diagram).

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