Review

Nitric oxide and thiol groups

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Abstract

S-Nitroso(sy)lation reactions have recently been appreciated to regulate protein function and mediate ‘nitrosative’ stress. S-Nitrosothiols (SNOs) have been identified in a variety of tissues, and represent a novel class of signaling molecules which may act independently of homolytic cleavage to NO – and, indeed, in a stereoselective fashion – or be metabolized to other bioactive nitrogen oxides. It is now appreciated that sulfur–NO interactions have critical physiological relevance to mammalian neurotransmission, ion channel function, intracellular signaling and antimicrobial defense. These reactions are promising targets for the development of new medical therapies. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Nitric oxide; S-nitrosothiol; S-nitrosoglutathione; S-nitrosylation

Contents

1. Introduction .......................................................... 324
2. Nitrosative chemistry and the chemistry of related NO groups ................. 324
3. S-Nitrosothiol measurement ........................................... 325
4. S-Nitrosothiol reservoirs ................................................ 326
5. Sulfur nitros(yl)ation in biological systems .................................. 326
6. S-Nitrosothiol breakdown in biological systems .................................. 327
7. Bioactivities resulting from S-nitro(sy)lation reactions ........................... 328
   7.1. Protein S-nitrosylation reactions .................................... 328
   7.2. Extracellular SNOs: potential mechanisms of action ...................... 329
   7.3. Intracellular signaling ................................................ 329
   7.4. Antimicrobial cytotoxicity ............................................. 330
8. Summary .................................................................... 330

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1. Introduction

Ignarro et al. demonstrated that reactions with cellular thiols contributed to the bioactivities of certain pharmacological nitrogen oxide (NO\textsubscript{x}) donors in 1981 [1], several years before making the observation that nitric oxide (NO) is synthesized endogenously in mammalian cells [2]. Kowaluk and Fung later showed that S-nitrosothiols (SNOs) – thiol–NO adducts – exerted bioactivities independent of breakdown to NO [3]. However, there was little general interest in thiol–NO interactions until Stamler and coworkers focused attention on SNOs as nitrosyl (NO\textsuperscript{+}) and nitroxyl (NO\textsuperscript{3}) donors with chemical reactivities distinct from those of NO [4] (Fig. 1) which were: (1) capable of forming in – and modifying – proteins; and (2) present in mammalian tissue [5,6]. It is now evident that thiol–NO chemistry is relevant to immune, antimicrobial, smooth muscle relaxant and neuronal bioactivities, and that NO\textsubscript{x}, like Marines carried in an amphibious task force, may be protected from harm, transported to the point of attack, and act with enhanced effectiveness following reaction with carrier thiol groups. Here, we will review: (1) nitrosative chemistry as it applies to sulfhydryl groups in biological systems; (2) current measurement techniques for SNOs; (3) the location and composition of known SNO reservoirs in mammalian species; (4) SNO metabolism, specifically including both formation and catabolic fate; and (5) recent insights regarding the mechanisms by which thiol–NO interactions may exert bioactivities.

2. Nitrosative chemistry and the chemistry of related NO groups

The reactivity of NO with sulfhydryl (R–SH) groups depends on the electron configuration of its 2p-\Pi antibonding orbital, as recently reviewed [4]. The presence of one (radical) electron in this orbital does not ordinarily confer reactivity with R–SH groups (Fig. 1), though it clearly allows reaction with thiyl radical species. On the other hand, loss of this electron to form NO\textsuperscript{+} confers strong electrophilicity and reactivity towards most biological R–SH species [4,7]. A second electron in the 2p-H orbital, forming NO\textsuperscript{3}, may under certain circumstances confer reactivity with relatively electropositive R–SH species, particularly in the presence of ferrous ion or other transition metals [4,7,8]. Of note, nitric oxide synthase (NOS) may produce nitrous oxide (N\textsubscript{2}O) and hydroxylamine (NH\textsubscript{2}OH) from NO\textsuperscript{–} [9]. Further, coproduction of NO and superoxide may form peroxynitrite (ONOO\textsuperscript{–}). This is a potent nitrosating species, especially in the presence of excess NO.

The third-order reactivity of NO with oxygen under physiological conditions (rate constant in aqueous phase $\sim 6.6 \times 10^6 \text{M}^{-2} \text{s}^{-1}$) [10] predicts relatively slow production of dinitrogen trioxide (N\textsubscript{2}O\textsubscript{3}) as a nitrosating agent as (NO\textsuperscript{+}…NO\textsubscript{2}). Of note, the reaction is accelerated 300-fold in the hydrophilic core of biological membranes [11]. Reactions of NO with superoxide, on the other hand, are so rapid as to be diffusion limited ($k = \sim 7 \times 10^9 \text{M}^{-1} \text{s}^{-1}$) [12]. Both amines and sulfhydryl groups are highly

![Fig. 1. Interconversion of the redox-related forms of NO. Three pathways of potential biological significance are shown, involving metal (M) nitrosyl complexes, charge transfer to electron acceptors (A), and coupling to thiol/disulfide redox reactions. Reproduced with permission from [4].](image-url)
susceptible to reactions with N₂O₃ and ONOO⁻[9,11,13,14]. Thiol nitrosylation is preferred under physiological conditions, both because of the tendency of amines to be more basic and because, unlike deamination of primary amines after NO⁻-induced diazotization[4,13], loss of the SNO group thiolate does not generally occur rapidly. Reactivity of these nitrosating species toward carbon groups is less than toward amino groups and sulfhydryl groups. It is therefore not surprising that S-nitrosylation of proteins has been demonstrated to be preferred over N- and C-nitrosation under physiological conditions[15] and that large, stable reservoirs of SNO, but not N-NO or C-NO, species have been identified in tissues[5,6,16–18].

3. S-Nitrosothiol measurement

Several techniques are now available for SNO assay. Traditional spectrophotometric assays, which are sensitive to approximately 500 nM, include both: (1) measurement of the characteristic absorbance of the S-NO bond at 340 nm[5,6]; and (2) heterolytic cleavage of the bond using excess mercuric chloride (HgCl₂) with subsequent assay for nitrite (NO₃⁻) formed from NO⁺ in water[5,6,19]. Formation of diamino naphthalene with assay by fluorescence is more sensitive than colorimetric assays, but both reactions may be inhibited in the presence of proteins[18]. The lower limit of sensitivity of S-NO assays may be improved upon, and S-nitrosoproteins more reliably assayed, using reactions which cause homolytic cleavage of the S-NO bond and subsequent assay for NO by chemiluminescence. Classically, this cleavage is carried out by photolysis[5,6], though these assays may be expensive and cum-

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Fig. 2. S-Nitrosoglutathione: detection in tracheal aspirates. In the presence of cuprous ion, CSNO, but not GSNO, decomposes rapidly to NO. The transnitrosation reactions which convert GSNO and other SNOs to CSNO in the presence of excess cysteine may therefore be exploited, in the presence of CuCl₂ to measure SNOs as NO. (a) GSNO (100 µM), in phosphate-buffered saline (PBS), slowly liberates NO as measured by chemiluminescence in a helium (He) stream (open arrow). Addition of excess cysteine (1 mM) and CuCl₂ (100 µM) (closed arrow) results in liberation of all SNO-bound NO (presented in mV as the raw signal from the photoelectric response). Assays that follow represent addition of SNO to 1 mM cysteine and 100 µM CuCl₂ (50°C in He) (CSNO/Cu) as described. S-Nitrosohomocysteine (HCSNO), CSNO and GSNO assays were linear to 5 nM, were strongly correlated with standard spectrophotometric assays[1,13] in the range of spectrophotometric sensitivity (>1 µM; r² > 0.9) and were highly specific, failing to detect ten µM NO₃⁻, NO₂⁻ and 3-nitrotyrosine. (b) S-Nitrosothiols were assayed at 1-min intervals after C-18 reverse phase HPLC separation (mobile phase 20% methanol, 80% sodium phosphate buffer, 1 mM 1-octanesulfonic acid by CSNO/Cu). These observations confirm that: (1) SNOs may be distinguished by HPLC followed by copper reduction as reported[20]; (2) GSNO is the principal SNO in human ALF; and (3) this GSNO peak is missing in asthmatic ALF.
bersome. More recently, reaction with excess (1 mM) cysteine and cuprous chloride (100 μM) (CuCl/cysteine) has been shown to provide a linear assay for SNOs to 5 nM [20] (Fig. 2). With both homolytic cleavage-based assays, it is important to demonstrate that NO signal is lost by pre-incubation with excess HgCl₂ [5,6] because each can detect contaminating nitrite (NO₃⁻). Of note, NO₃⁻ detection using the CuCl/cysteine method is eliminated if the reaction is carried out at pH 6–8 (unpublished observations). Cupric chloride has been used to assay SNOs by heterolytic cleavage, with subsequent colorimetric NO₃⁻ assay [21]. This assay is sensitive, but is largely unproven with regard to biological samples. Each of these general classes of assays may be coupled with high pressure liquid phase chromatography (HPLC) for separating SNO species. Several different HPLC systems have been developed for this purpose [21–25] (Fig. 2). Theoretical concerns exist regarding artifactual formation of SNOs in the presence of NO₃⁻ at low pH in mobile phase, which may require pretreatment of the sample with ammonium sulfamate [6,17], and these systems have not been formally compared with one another. Finally, SNOs may be definitively identified by mass spectrometry and characterized in biochemical pathways using ¹⁵N labeling [15,17].

4. S-Nitrosothiol reservoirs

Unlike NO, tissue concentrations of which may be limited to the low nM range by considerations of diffusion and reactivity [26], SNO concentrations in general, and S-nitroso glutathione (GSNO) concentrations in particular, may be in the μM range [6,17]. Endogenous GSNO was first described in human airways, and airway levels are now known to be elevated in patients with pneumonia and to be depleted in patients with asthma [6,20]. S-Nitroso glutathione and other SNOs have also been identified in erythrocytes, polymorphonuclear leukocytes, brain tissue, platelets and plasma [16,18,20,27–30]. Of note, intracellular SNOs may be responsible for the nitrinergic photorelaxation response of smooth muscle cells originally described in 1989 [31]. S-Nitroso glutathione may be favored over other SNOs in these reservoirs, except in plasma and erythrocytes, because of: (1) its stability (relative, for example, to S-nitrosocysteine (CSNO) [5,32]); (2) favorable kinetics and thermodynamics for its formation in transnitrosation reactions from other endogenous low mass (LM) SNOs [33,34]; and (3) the high endogenous substrate reduced glutathione (GSH) concentrations in many tissues [30,35]. However, CSNO, S-nitrosocysteinyl glycine and S-nitrosated proteins have been identified in plasma and cell systems, and high nM concentrations of S-nitrosohemoglobin are present in oxygenated erythrocytes [16]. The role of these pools of GSNO and other SNOs would appear to be cell- and tissue-specific and to be regulated, at least in part, by specific metabolic pathways.

5. Sulfur nitros(yl)ation in biological systems

Electrophilic reactions of NO⁺ with cysteinyl sulfhydryl moieties is now appreciated to be responsible for a wide range of protein modifications. These may be thought of as being analogous to serine, threonine, and tyrosine phosphorylation. While reactions of nitronium (NO₂⁺) may result in tyrosine nitration under physiological conditions, particularly in the presence of carbon dioxide [12,36,37], reactions of NO⁺ equivalents with sulfhydryl groups are favored over those with nitrogen and carbon in most circumstances. In this regard, it should be observed that tyrosine nitration reactions may not be regulatory, while cysteine nitrosylation reactions are. As noted above, these nitrosating reactivities may be conferred upon NO by inorganic reactions with oxygen species. Additionally, SNO formation is facilitated through electron transfer in iron nitrosyl groups (Fe (S) NO) in vitro [8], and this process may be relevant in vivo as well.

Importantly, hemoglobin may serve as a catalyst for SNO formation under conditions of high oxygen affinity, in which S-nitrosylation of the single β-chain reduced cysteine (93) is favored [16,38]. The resulting SNO–hemoglobin synthesis in the lung allows for LM SNO formation through transnitrosation reactions [16] (Fig. 3). The circulatory system may thus provides end organs with a steady supply of LM SNOs which can diffuse out of the erythrocyte and into tissues [16]. Furthermore, NOS activation itself may form SNOs, perhaps through intermediate
ONOO⁻ in the presence of thiol [9,14]. Additional SNO synthetic reactions may occur in vivo, such as protein nitrosylation by nitrous acid (HNO₂) in acidic organelles, but these remain to be clarified.

6. S-Nitrosothiol breakdown in biological systems

In many tissues, SNO concentrations, sites of action and bioactivities may be regulated more by catabolic processes than by synthesis. In this regard, several enzymes have been described to break down LM SNO in vitro [39–44] (Table 1). The relative distribution of these enzymes in different tissues could dramatically alter S–NO bioactivities. In the lung, for example, γ-glutamyl transpeptidase, which converts GSNO to S-nitroso-cysteinyl glycine [25], may confer greater membrane permeability for submucosal/smooth muscle bioactivity, while xanthine oxidase, in the presence of xanthine, has the potential to catalyze CSNO breakdown to cytotoxic ONOO⁻ [39]. Furthermore, glutathione peroxidase (GSPX) theoretically may produce NO [40,41] with the net effect of inactivating GSNO and eliminating NOx through NO expiration and/or reaction of NO with heme iron(II) (Fig. 4). Of note, additional catabolic enzymes have been proposed to exist in platelets [28], airway epithelial cells [45], neutrophils [46], and Escherichia coli [47]. However, none of these processes have yet been shown to be physiologically relevant, and many of the $K_m$ values for these enzymes are out of the normal range for endogenous SNO substrate.

Inorganic reactions also cause SNO breakdown. Intermediate Fe(S)NO formation involving LM thiol groups may contribute to SNO catabolism [8]. Inorganic reactions with copper are highly relevant to S-nitrosocysteine breakdown in vitro [33]. These may theoretically be less relevant in vivo, where

Table 1

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Nitrogen oxide product</th>
</tr>
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<tbody>
<tr>
<td>(Thioredoxin) thioredoxin reductase [22]</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Glutathione peroxidase [40]</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase [25,43]</td>
<td>S-Nitroso-cysteinyl glycine</td>
</tr>
<tr>
<td>Xanthine Xanthine oxidase [39]</td>
<td>Peroxynitrite</td>
</tr>
<tr>
<td>Glutathione-dependent formaldehyde dehydrogenase [42]</td>
<td>Hydroxylamine*</td>
</tr>
</tbody>
</table>

*Under conditions of excess reduced thiol.
free copper(I) concentrations are low. However, Cu(I) chelation results in inhibition of bioactivities which are proposed to be related in GSNO catabolism in platelets [28] and cardiac myocytes [48]. Of note, the SNO catabolic effects of other biological transition metals are minimal compared with those of Cu and Fe [49]. Finally, O$_3$ has been shown to cause CSNO and GSNO breakdown with second order (in SNO) rate contents [50,51]. These reactions are apparently first-order in O$_3$ (overall $k \sim 3-6 \times 10^8$ M$^{-2}$ s$^{-1}$). Therefore, μM SNO concentrations would be degraded only very slowly (pM min$^{-1}$ range) by these reactions in the presence of nM O$_3^-$ concentrations. However, in the presence of activated neutrophils, SNO catabolism could be significantly accelerated by those inorganic processes, perhaps explaining low levels of SNOs observed in the airways of patients with cystic fibrosis [52].

7. Bioactivities resulting from S-nitrosylation reactions

7.1. Protein S-nitrosylation reactions

S-Nitrosothiol bioactivities arise partly from protein S-nitrosylation reactions, which may either alter protein structure directly or lead to oxidation of vicinal thiols [7,53]. An example of the former is the structural activation of tissue plasminogen activator [15,53], while an example of the latter is inactivation of Yersinia enterocolitica phosphotyrosine protein phosphatase [54]. These reactions affect the function of a broad spectrum of proteins ranging from NMDA receptors in the central nervous system [55,56] to the transcriptional regulatory proteins, such as E. coli oxyR [47]. In this regard, the motif cysteine–aspartate–glutamate has recently been proposed to predict structural alterations based on cysteine nitrosylation, analogous to those for phosphorylation. Acidic and basic amino acids are also conserved in the N-terminal direction of nitrosylation-sensitive proteins, suggesting that S-nitrosylation signaling and bioactivity may be pH-sensitive [55]. Of note, simple S-nitrosylation and cysteine oxidation may have differing effects on a given protein. For example, progressive poly S-nitrosylation reversibly activates the ryanodine-sensitive canine cardiac Ca$^{2+}$ release channel, while oxidation of vicinal thiols causes irreversible activation [57]. Of note, protein S-nitrosylation reactions may result from nitrosative stress associated with high environmental...
concentrations of NO$^+$ donors, or from signaling fluxes in physiological concentrations, perhaps accounting for the paradoxical concentration-dependent effects on thymocyte apoptosis observed with exposure to GSNO [58].

7.2. Extracellular SNOs: potential mechanisms of action

It was once assumed that bioactivities of extracellular SNOs depended upon their homolytic decomposition to NO and the subsequent diffusion of NO into the cell. Though this mechanism is relevant under certain circumstances, it has now also been demonstrated that a variety of SNO bioactivities (ranging from airway smooth muscle relaxation to neuronal signaling) are unrelated to rate of release of NO and, in fact, are inhibited by SNO breakdown to NO [3,31,59–62]. Of particular interest in this regard are the results of several investigators demonstrating that S-nitroso-L-cysteine, but not the D-isomer, has vascular smooth muscle and central nervous system effects in the rat, though both isomers decompose to NO at the same rate [59,60]. Additionally, large, stable SNOs with low membrane permeability may have bioactivities comparable to those of smaller, less stable molecules under certain circumstances [31,62]. These observations suggest that there may be membrane-based, stereoselective SNO bioactivities. Mechanisms for this activity have been proposed to include reactions with both membrane ion channels and membrane signaling proteins. For example, there is evidence that S-nitrosylation reactions may activate calcium-dependent vascular smooth muscle potassium channels [63] and L-type cardiac calcium channels [64]. Additionally, signaling through thiol nitrosylation of a membrane G-protein (p21$^{ras}$) has been proposed [65]. However, activation of traditional signaling cascades associated with regulated phosphorylation and/or dephosphorylation has not been demonstrated, and there is no direct evidence for the regulation of ion channels or p21$^{ras}$ through control of SNO metabolism.

Because the catabolic products of certain extracellular SNOs, which include NO, ONOO$^-$, NH$_2$OH and S-nitrosocysteineyl glycine [22,25,39,40,42,43], may have a broad range of distinct bioactivities, it is tempting to speculate that SNO catabolic enzymes may regulate the distribution of these species, and thus regulate bioactivity, from the SNO reservoir. For example, soluble guanylate cyclase activation in the rat heart is inhibited by glutathione S-nitrosation, but upregulated in vitro by conditions favoring GSNO catabolism to NO [48]. Indeed, accelerated SNO catabolism to NO has been proposed to account, in part, for low SNO levels, airway smooth muscle narrowing and high expired NO levels in subjects with severe asthma [20].

7.3. Intracellular signaling

Many of intracellular signaling and metabolic proteins are affected by S-nitrosylation. These reactions have effects ranging from inhibition of post-translational protein trafficking in the cell (as in the case of translocation of the p47$^{phox}$ subunit of NADPH oxidase to the neutrophil cell membrane [66]) to transcriptional regulation through I$^\kappa$B nitrosylation [67]. Additionally, metabolic processes may be regulated by S-nitrosylation, including activation of the hexose transporter.

Table 2
S-Nitrosothiols inhibit enzymes in glutathione metabolic pathways

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Inhibition by (S)NO: mechanism</th>
<th>IC$_{50}$/K$_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-Glutamyl-cysteine-synthetase [72]</td>
<td>Decreased (rat hepatocyte) enzyme activity through thiol nitrosylation</td>
<td>NA$^b$</td>
</tr>
<tr>
<td>Glutathione-S-transferase [70]</td>
<td>Competitive inhibition$^a$</td>
<td>~0.015 mM</td>
</tr>
<tr>
<td>Glutathione reductase [69]</td>
<td>Competitive$^c$: active Cys-63 nitrosylation$^c$: S$\to$N rearrangement (irreversible inhibition)</td>
<td>0.5 or (K$_i$) 1 mM</td>
</tr>
<tr>
<td>Glutathione peroxidase [68,71]</td>
<td>Nitrosylation of vicinal thiols (bovine)</td>
<td>2 $\mu$M</td>
</tr>
</tbody>
</table>

$^a$Specific for S-nitrosoglutathione.

$^b$NA, not available.
monophosphate shunt [29], though these pathways are not clearly defined. It is also of interest that GSNO and other SNOs may inhibit enzymes associated with response to oxidative stress in eukaryotic cells (Table 2), including glutathione peroxidase [68,71], glutathione reductase [69], glutathione-S-transferase [70], and \( \gamma \)-glutamyl cysteine synthase [72]. Concentrations required for these activities are, in some cases, in the physiological range, arguing for relevance to routine signaling rather than simply to the nitrosative stress response. Both regulatory and stress-related S-NO-mediated reactions have been demonstrated in prokaryotic cells which are analogous to those described for eukaryotic cells. For example, SNOs upregulate the oxidative stress response transcription factor oxyR in \( E. coli \) [47]. In this regard, it is important to recognize that sensitive intracellular signaling mechanisms in prokaryotic and eukaryotic cells may be overwhelmed by high SNO concentrations under circumstances of inflammation and other types of exogenous nitrosative stress [6,15].

7.4. Antimicrobial cytotoxicity

It has been known for over a decade that SNOs have antimicrobial properties [73]. Indeed, \( Salmonella \) species have developed a specific metabolic pathway involving upregulation of homocysteine production to protect against SNO-mediated cytotoxicity, and expression of the responsible met L gene product is actually a previously unrecognized virulence factor [74]. Additionally, thiol nitrosylation of metabolic enzymes in \( Trypanosoma cruzi \) may be responsible for the inhibitory effect of ONOO\(^-\) on this species [75]. Furthermore, S-nitrosylation of \( E. coli \) ribonucleotide reductase, the rate-limiting enzyme in DNA synthesis, inhibits bacterial replication [76]. High GSNO concentrations in the airway lining fluid [6] in neutrophils [29] may therefore serve, under certain conditions, an antimicrobial role.

8. Summary

Sulfhydryl–NO interactions may serve both to stabilize and to activate NO. In many biological systems, there are SNO reservoirs which may be distributed to different bioactivities, ranging from cell signaling to cytotoxicity – by mechanisms – such as catabolic regulation. S-Nitrosylation reactions activate and inhibit proteins through conformational changes analogous to those occurring with protein phosphorylation. Some of these reactions are independent of homolytic cleavage of the S–NO bond, and, in fact, appear under certain circumstances to involve stereoselective recognition by the protein of the intact SNO species. In vivo, NO without thiol groups may be unprotected and ineffectively delivered to the site of action. These observations add a layer of complexity to our understanding of NO biology, and offer promising targets for the development of new therapies.

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