

Nitric Oxide Biochemistry: Pathophysiology of Nitric Oxide-Mediated Protein Modifications

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Abstract Nitric oxide (NO) is a pluripotent signaling molecule, which has been proposed to be critically important in both physiological and pathological processes of the brain. The wide-ranging functionality of NO is in opposition to its relatively simple chemical structure. In this chapter we attempt to summarize the functional involvement of NO within the neurological system and then discuss how such complex signaling may be achieved via the differential post-translational modification of protein targets. It is our contention that the redox properties of NO allow this molecule to modify proteins in a variety of ways with physiological or pathological consequences. In this way the effects of NO production are dependent on the quantity produced, the redox environment in which it is synthesized, and the presence of reactive targets. A summary of known post-translational modifications is given as well as the functional consequences of their formation.

Keywords Nitric oxide · Nitrosothiol · Nitration · Nitroalkene · Thiol · Nitrosylation

1 Introduction

Nitric oxide (NO) plays a variety of physiological roles in the nervous system, including respiratory and blood flow control, immune defense, intracellular signaling, and neurotransmission. It is synthesized by all brain cells including neurons, endothelial cells, and glial cells and under physiological conditions, approximately 20 times more NO is produced in the brain than in the entire vasculature. The enzymes responsible for the production of NO are collectively known as nitric oxide synthases (NOS) with three distinct isoforms: endothelial (eNOS), inducible (iNOS), and neuronal (nNOS) [1]. Transient increases in

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intracellular calcium (Ca^{2+}) result in the release of nanomolar fluxes of NO by the Ca^{2+} /calmodulin-dependent nNOS and eNOS isoforms, which are essential for neurotransmission and the control of cerebral blood flow. However, iNOS (which is constitutively active) induces the release of fluxes of a higher order of magnitude of NO by glial and vascular cells [2]. iNOS function is principally controlled by its expression and degradation. The role of NO is paradoxical as it is not only critical in modulating immune function but also appears to play a role in mediating tissue damage. Indeed, a variety of neuropathological events including stroke and several neurodegenerative diseases are marked by elevated levels of NO [3]. Therefore, whether NO is protective or detrimental depends on the conditions under which it is released, including its flux and the cell environment. In order to provide a basis for understanding this complexity of NO-based mechanisms, this chapter will consider some of the basic biology surrounding NOS and NO within the brain and then provide an overview of the chemistry that underlies this biology.

2 NOS, NO, and the Brain

The nNOS isoform can be considered ubiquitous within the brain as it is found in a variety of neural structures including the cerebral cortex [4], the olfactory bulb [5], the nucleus accumbens, the striatum, the amygdala [6], the hippocampus (especially the CA1 and the dentate gyrus), the hypothalamus [7], the thalamus [8], and the cerebellum [4]. It is important to note that despite this generalized expression the distribution of nNOS is far from uniform but rather has areas of concentration. eNOS expression is also widespread as it is found in cerebral endothelial cells, but its expression in neurons appears to be limited to the hippocampus, where it is found in the granule cells of the dentate gyrus as well as those of the CA1, CA2, and CA3 regions [9]. Under physiological conditions, iNOS levels in the brain are low but are increased in response to glial activation. The mechanisms controlling iNOS induction within glial cells appear to be similar to those in other inflammatory cells, being responsive to toxins, such as lipopolysaccharide, and cytokines, such as interferon- γ . iNOS function is turned off either by its own degradation or by apoptosis of the induced cell. It is important to remember that the function of NOS is in fact more complicated even than just the production of NO. It is dependent on a number of cofactors including, NADPH, FMN, and tetrahydrobiopterin. In addition, substrate supply, namely, both oxygen and arginine, can affect both the products and rate of enzyme activity.

The importance of NO in signaling cannot be underestimated as NO can modify receptors and can activate intracellular messengers, ultimately affecting neurotransmitter release. Classically, NO interacts with soluble guanylyl cyclase (sGC, a cytosolic heme-containing enzyme that catalyzes the conversion of GTP into cGMP) ultimately affecting protein kinase G (PKG) and cyclic

nucleotide-gated channels, both of which are important for neuronal transmission. For example, stimulation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate results in the influx of Ca^{2+} with the subsequent activation of nNOS (which is physically associated with the NMDA receptor at the NR2B subunit) and the release of NO. The release of NO, in turn, results in the activation of nearby glutamatergic neurons that stimulate the release of acetylcholine from the nucleus accumbens [10]. NO also modulates the release of norepinephrine and glutamate in the hippocampus. NO donors increase norepinephrine and glutamate release, while NO scavengers (e.g., hemoglobin) inhibit the release of norepinephrine and glutamate. The effects on the GABAergic system also depend on NO concentration. Basal concentrations of NO reduce the release of GABA, whereas higher levels result in an increase of GABA [11]. Dopamine and serotonin release from the medial preoptic area in rats are similarly affected by NO levels [12].

Long-term potentiation (LTP), which is a cellular model of synaptic plasticity and purportedly a model of learning and memory, also appear to be modulated by NO. NO-mediated modulation of synaptic plasticity is an sGC-dependent mechanism: LTP is inhibited by the addition of an sGC inhibitor to hippocampal and amygdala slices, and potentiated when sGC is added [13]. It has been proposed that when produced post-synaptically, NO affects pre-synaptic transmission as a retrograde diffusible messenger in hippocampal and cortical LTP. One of the roles that NO plays in the mesencephalon is its involvement in the sleep–wake cycle [14]. Administration of L-arginine (the precursor of NO) into the pedunculopontine tegmentum during the light phase results in an increase in slow-wave sleep in rats [15], a result that was also corroborated in cats administered an NO donor [16].

The presence of nNOS in the PVN and the supraoptic nucleus of the hypothalamus attests to its involvement in the stress response. Both neural groups secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). In response to stress, CRH and AVP are released in the median eminence where they stimulate the release of adrenocorticotropin-releasing hormone into the general circulation and, ultimately, stimulate the secretion of glucocorticoids from the adrenal gland. NO seems to exert diverging effects on different components of the stress response: the upregulation of CRH and AVP expression in response to a neurogenic stressor is decreased when rats are administered the NOS inhibitor L-NAME, and increased in response to intracerebroventricular administration of NO, but, basal levels of both CRH and AVP are unaffected by NO administration in rats [17]. Interestingly, the administration of L-NAME downstream of the PVN increases the release of ACTH from the pituitary gland suggesting that NO plays an inhibitory role possibly starting at the level of the median eminence [17].

NO plays an important role in neuroprotection, as it has been shown that inhibition of NO in cultured cerebellar granule cells results in enhanced apoptosis via activation of caspase-3, which can be reversed by the addition of NO donors [18]. In models of neurotoxicity where prolonged stimulation of NMDA

receptors results in cell death by Ca^{2+} overload, NO has been shown to reduce the Ca^{2+} burden by S-nitrosylating the NR1 and NR2 subunits of the NMDA receptor [10]. A second mechanism by which NO might be neuroprotective is via the induction of heme oxygenase-1, which is an early marker of oxidative stress and has been shown to play a role in antioxidant protection pathways [19].

In contrast to its potential neuroprotective function, NO production in excess, potentially in response to inflammation, has been implicated in neurodegenerative diseases. For example, patients afflicted by either Alzheimer's (AD) or Parkinson's disease show an increase in nitrotyrosine, a marker of nitrative stress [20–22]. NO release also activates cyclooxygenase, which is found in brain cells during the inflammatory state. The upregulation of cyclooxygenase, and other peripheral inflammatory signals, are potential biomarkers for the progression of AD [23, 24]. Postmortem examination of AD patients also reveals nitration of mitochondrial proteins implying a role for NO in energetic dysfunction [25, 26]. The finding that both eNOS and iNOS expression is promoted by α -amyloid expression has been confirmed in autopsied AD patients, where increased NOS levels are observed [27]. It has also been suggested that nNOS expression is significantly altered in neurodegenerative disease [28]. Another neurodegenerative disorder where NO appears to play a central role is multiple sclerosis (MS), which is characterized by demyelinating lesions in the central and the peripheral nervous system. The cerebrospinal fluid of MS patients has elevated levels of nitrite [29]. Elevated levels of NO have also been confirmed in experimental autoimmune encephalomyelitis (EAE), an animal model of MS [30], although inhibition of NOS appears to play a role in inducing the disease [31]. This connection between NO production and neurodegeneration may stem from NO's function as a cell death mediator in neurodevelopment. During normal neurodevelopment, many more neurons are produced than those that survive. Programmed cell death or apoptosis is an important mechanism for the normal development of the central nervous system and in this regard NO has been shown to play an instrumental role. Peak levels of NOS in rats and guinea pigs are observed immediately before the period of maximal synaptogenesis, whereas both nNOS and iNOS expression is several fold higher during early postnatal development [32]. And, although nNOS is expressed in less than 4% of neurons, these cells are capable of killing neighboring cells.

Although NO is governed by the same rules that apply to other neurotransmitters, it appears to be more versatile and can be considered a non-conventional transmitter system. A few important differences between NO and other neurotransmitters include the lower amount of NO needed, the fact that it is not stored in vesicles but directly produced on demand and the lack of a specific receptor, which confers it the ability to act on tissue volume and not necessarily in a defined cellular region [33]. Because of its properties, NO is not limited to any particular cell type or brain region, and, therefore, can potentially affect a variety of structures and functions. Among some of the important functions that have been so far identified are synaptic plasticity [34], neurodevelopment [35], sleep

[36], appetite [37], reproductive behavior [38], sensory [8] and motor involvement [39], thermal regulation [40], pain [41], as well as hormonal secretion [42].

3 Biological Chemistry of NO

A principal question that remains within NO biology is how can a simple diatomic molecule be utilized to obtain such wide-ranging signaling functions. The answer may lie in the unique biological chemistry of NO. Much discussion has been made of NO's gaseous nature, the fact it is a free radical, and that it is highly soluble especially in hydrophobic media. But perhaps the most interesting physical characteristic of NO is its ability to readily undergo redox transitions. This results primarily from the ability of nitrogen to adopt a variety of redox states. Within the field of oxidative stress research one is accustomed to consider partially reduced states of oxygen, such as superoxide, hydrogen peroxide, and peroxy radicals, and the relative facility with which such molecules can react within the biological system. The same can be said for nitrogen, which in its fully oxidized form, nitrate, has a redox state of +5 and its fully reduced form, ammonia, has a redox state of -3. However, like oxygen, nitrogen exists in reactive partially reduced states, such as nitroxyl anion (NO^- , oxidation state +1), nitric oxide (oxidation state +2), and nitrosonium cation (NO^+) or nitrite (oxidation state +3) [43]. Each of these partially reduced, or reactive nitrogen species (RNS), possesses its own particular reactivity [44].

NO and its isoforms are capable of reacting with a number of biological molecules, however, for the purpose of this review we will restrict our discussion to those that have been implicated in cellular signaling within the nervous system. NO reaction with proteins can be divided into three broad and basic pathways, namely reaction with (1) metals, (2) oxides, and (3) thiols. In the following section we will consider the reactivity involved in each of these pathways.

3.1 Metals

NO was first shown to interact with metal centers by Keilin and Hartree in the early 20th century when studying the reactions of various gaseous molecules with hemoglobin and cytochromes [45]. The binding of NO to the heme prosthetic group of soluble guanylate cyclase (sGC) along with the identification of the endothelium-derived relaxing factor raised the possibility of physiological relevance [46, 47]. Although the exact nature of this interaction is still undetermined, the generally accepted principle is that binding of NO to the iron within the heme group of sGC produces a conformational change and enzyme activation [48]. Peculiar to sGC, the binding of NO to the heme is approximately 400-fold faster than the binding of carbon monoxide, implying there are structural constraints, which focus the heme toward NO reactivity [49]. Clearly there

are many other heme-containing proteins that bind NO avidly including hemoglobin [50]. Indeed, the possibility has been raised by recent research that redox interaction of hemoglobin with NO and its related oxides is an essential part of the hypoxic vasodilator response of the systemic vasculature [51–55]. The relevance of such reactions within the brain has been highlighted by the discovery of neuroglobin, which has been proposed as an antioxidant protein [56]. Cytochrome P450 has also been shown to be a target for binding of NO resulting in functional inhibition [57, 58]; the implications of this in xenobiotic degradation have not been clearly established [59].

The metalloproteins of the mitochondrion form another principal target for NO reactivity. Cytochrome oxidase has been shown to be reversibly inhibited by NO and it has been suggested that this is an important mechanism to control cellular respiration, especially under hypoxic conditions [60–63]. There are a number of iron–sulfur proteins within the mitochondria, such as aconitase and mitochondrial electron transport chain complex I. These proteins are targets for NO reactivity [64–66]. Zinc–thiolate clusters have also been shown to be the targets for NO reactivity. Metallothionein reacts with NO to release zinc converting a redox-based signal, NO, to a redox inactive one, zinc, protecting the cell against potentially harmful reactions [67–69]. Aberrant reactions of NO and other oxidants with metalloproteins have been proposed in the mechanisms of neurodegenerative diseases such as ALS [70, 71]. Critically important in these reactions is the potential involvement of copper [70], particularly in the +1 redox state [72]. In this regard it is interesting to note that ceruloplasmin appears to react with NO to produce nitrosothiols in a copper-dependent manner [73, 74].

3.2 Oxides

As a result of the relative ease with which nitrogen can be altered in its oxidation state, NO is capable of participating in both reduction and oxidation reactions. Perhaps the best known of these reactions is its oxidation by molecular oxygen [75]. This trimolecular reaction, involving two NO molecules and one of oxygen, is slow at physiological concentrations of NO. However, under pathophysiological conditions of raised NO concentration this reaction becomes of greater relevance [76]. It is worth remembering that such reactions may become more relevant within microenvironments, such as the membrane or that surrounding NOS itself [77]. Although the autoxidation of NO is known to be bimolecular in NO and unimolecular in oxygen; there are a number of potential pathways. However, all of the potential intermediates are nitrosating agents, such as dinitrogen trioxide and dinitrogen tetroxide. Within biological systems there is a wide variety of targets for nitrosation, including reduced thiol. However, such nitrosation is by an entirely different chemical species to either that produced by transnitrosation or free radical NO. Therefore it may occur not only at different targets, such as amines, but also at different members of one class of targets, i.e. the same group of thiols may not be nitrosated.

Nitric oxide is also capable of interacting with other oxides, such as superoxide and peroxy radicals [78]. Although there is clearly a significant role for these higher oxides of nitrogen in pathological processes, it is unclear what role they play in physiological systems. Much has been made of the potentially toxic consequences of the formation of peroxynitrite, the reactive product of NO and superoxide, and certainly it is capable of a number of potentially adverse reactions such as DNA damage and the generation of 8-hydroxyguanine, lipid peroxidation, and tyrosine nitration [78]. Peroxynitrite is also capable of oxidizing thiol residues and of nitrosating a number of targets including amine and thiol residues [79]. Tyrosine nitration is often used as a hallmark of this type of chemistry [80]. Invariably the presence of tyrosine nitration is taken as a sign of pathological NO chemistry [81], however, the potential for physiological signaling does exist either through the formation of nitrosothiols or tyrosine nitration [82–85].

Recently a novel set of signaling molecules, derived from higher oxides of nitrogen, has been identified, the nitroalkenes [86]. These molecules are formed by the combined action of nitrosative and oxidative stress upon unsaturated fatty acids [87]. Among the first such molecules identified was nitro-linoleic acid [88], which was identified as having an NO-like signaling in the vasculature. Nitroalkenes have been identified within human red cells and plasma [89] and have been suggested to operate as anti-inflammatory signals by activation of targets such as peripheral peroxisome activator- γ [90], inhibiting platelet aggregation [91], and neutrophil activation [92]. There are multiple mechanisms for such molecules to act as signaling molecules including NO release [93] and post-translational modification [94] via Michael addition to nucleophilic targets like cysteine [95]. The potential for these molecules to act within the brain has not been investigated.

3.3 Thiols

There are multiple mechanisms whereby NO can modify thiol residues including nitrosation via a higher oxide intermediate, direct reaction with a thiol radical, direct reaction followed by electron abstraction, and via metal catalysis. It is also possible for NO to be involved in oxidative reactions with thiols either directly or through the decomposition of intermediates such as nitrosothiol. The chemistry of these reactions has been reviewed elsewhere [43, 96] and indeed in a recent kinetic model thiolates were predicted to form one of the principal targets for NO reactivity [97]. Although a complete discussion of the formation of nitrosothiols is beyond the scope of this submission, it is important to consider that different mechanisms may result in the synthesis of a different subset of nitrosothiols, i.e., the conditions under which NO is produced will alter which thiols are modified. These considerations have considerable importance with relevance to how higher oxides of nitrogen, such as peroxynitrite, might produce cellular signaling.

As well as considering the conditions surrounding NO production as factors in determining nitrosothiol formation, it is important to consider the thiol residues themselves. The pKa of thiol side chains vary greatly depending on the surrounding environment. For instance in cysteine itself the pKa is 8.75, while in glutathione, where there are two interacting amino groups, the pKa is 8.35. But not only the pH dependency can vary, as cysteines are often buried within extremely hydrophobic areas of the protein. These differences in environment can alter the ease with which a thiol may be nitrosylated; the stability of any nitrosothiols formed; and the mechanism whereby such nitrosothiols are formed (and hence which proximal chemical species will be the nitrosylating agent). Nowhere, is this variability of thiol environment more clearly demonstrated than in hemoglobin, in which the movement between relaxed and tense structure forms the basis of nitrosothiol formation and decay, allowing for delivery of NO equivalents in areas of hypoxia [53, 54, 98]. Consideration of nitrosothiols, which have been shown to be formed, such as those on the NMDA-receptor and caspase-3, has led to the development of two potential "consensus" sequences for formation. The first is the acid/base motif, in which the presence of proton donating and accepting groups promotes the ability to nitrosate a thiolate [99]. The second is the positioning of a cysteine in a hydrophobic region, which may promote the direct interaction between NO and thiol due to the hydrophobicity of dissolved NO [100, 101]. Two groups have attempted to use a proteomic approach in order to evaluate total nitrosothiol-protein formation in vivo [102, 103]. Utilizing modified biotin-switch [104] technology coupled with mass spectrometry, these groups have identified a wide range of proteins that can be nitrosylated under stimulated conditions. Greco et al. attempted to verify the two proposed consensus motifs for nitrosothiol formation and found that all of the modified cysteine residues conformed to one or another of the motifs [102]. The development of these new technologies for assessing nitrosylation within biological systems will rapidly accelerate our understanding of the importance of this form of post-translational modification within cellular signaling.

It has been proposed that nitrosothiols form a prevalent redox-based signaling post-translational modification [105]. Central to this proposal is the ability of nitrosothiol formation to functionally regulate a wide range of proteins. Within the literature proteins ranging from regulatory kinases [106, 107] to channel proteins [10], to transcription factors [108], to metabolic enzymes [109] have been suggested to be regulated by nitrosothiol formation at key cysteine residues. As one would predict the effect of nitrosylation, in terms of function, varies from protein to protein. For instance, nitrosylation of the NMDA receptor has been shown to inhibit calcium flow [10]; however, within the ryanodine receptor it increases ion current through the channel [110]. This observation of opposite regulatory effects on proteins of similar classes is reflected in the kinases, where p21ras is activated by the reaction of NO with its key cysteine residue [106, 107] while JNK1 is inhibited [111]. The pluripotency of S-nitrosylation as a mediator of post-translational signaling is underscored by the different

mechanisms through which functional regulation is achieved. For instance, S-nitrosylation of the NMDA-receptor leads to a physical blockade of the calcium channel [10]; while nitrosothiol formation on Parkin appears to promote its association with E3 ubiquitin ligase leading to secondary enzyme activation [112]. In contrast, S-nitrosylation of GAPDH inhibits glycolytic activity while increasing its association with Siah-1 resulting in nuclear localization and initiation of a secondary signaling cascade [109].

These observations give some idea of the complexity of signaling that can be initiated by S-nitrosylation and the potential naivety of assigning nitrosothiol formation as either “good” or “bad”. This would be similar to trying to determine whether an increase in total phosphorylation would either promote or inhibit cell death. Despite this complexity it is possible to develop models of nitrosothiol-based signaling as a result of NOS activation. Largely as a result of the work of Lipton and coworkers, the NMDA-receptor system forms one such model. The NMDA-receptor possesses key regulatory cysteine residues, whose identification formed the original basis of the acid/base motif for nitrosothiol formation [10]. The receptor is also physically linked to nNOS via a PDZ domain. Upon glutamate binding the calcium channel of the receptor opens allowing calcium entry to the cell, and among other signaling events activation of the calcium-dependent nNOS. The consequent production of NO leads to inhibition of the channel function of the receptor via nitrosylation at key reactive cysteine residues [113], thus providing a feedback inhibition mechanism. Recently it has been shown that COX-2 is also physically linked to nNOS, as well as iNOS in non-neuronal tissue [114], and that stimulation of NOS function leads to nitrosothiol-mediated activation, inducing the prostaglandin signaling cascade [115]. However, nNOS also activates Dex-ras, which is not directly linked to it but rather is associated via CAPON, providing another downstream target [116]. Therefore, both COX-2 and Dex-ras are potential feedforward activators of glutamate signaling via nitrosylation; but importantly they are targeted differently as a result of their proximity to nNOS. As work continues more and more potential protein targets are being identified for nitrosylation and hence the potential consequences expand often with diametrically opposed functions. For instance nitrosylation of GAPDH [109] appears to promote apoptosis while modification of caspase-3 is inhibitory [101]. Thus it has become important to not only evaluate the potential of a particular protein to be modified but also to measure its relevant degree of nitrosylation within cellular systems.

4 Summary

The work summarized here demonstrates the huge biological diversity that is achieved by NO, a simple diatomic molecule. It is our contention that this diversity is achieved through the redox chemistry of NO and its ability to post-translationally modify proteins through a variety of mechanisms, including metal nitrosylation, amino acid side chain oxidation and/or nitration, thiol

alkylation, and/or nitrosylation. Thus it becomes a question not so much of when is NO made, but of how much, and under what conditions, and in the presence of what target molecules. In other words, physiological NO signaling requires the right amount of NO to be made at the right time and in the right place, which may explain the importance of NOS localization [117]. Disruption in quantity, time, or location is potentially an initiator of pathological processes and hence our often confused view of NO as both a “good” and a “bad” molecule.

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Oxidative Neural Injury

Veasey, S.C. (Ed.)

2009, XIV, 218 p. 16 illus., Hardcover

ISBN: 978-1-60327-341-1

A product of Humana Press