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Abstract

Nitric oxide (NO) is an important signaling molecule that is widely used in the nervous system. With recognition of its roles in synaptic plasticity (long-term potentiation, LTP; long-term depression, LTD) and elucidation of calcium-dependent, NMDAR-mediated activation of neuronal nitric oxide synthase (nNOS), numerous molecular and pharmacological tools have been used to explore the physiology and pathological consequences for nitrergic signaling. In this review, the authors summarize the current understanding of this subtle signaling pathway, discuss the evidence for nitrergic modulation of ion channels and homeostatic modulation of intrinsic excitability, and speculate about the pathological consequences of spillover between different nitrergic compartments in contributing to aberrant signaling in neurodegenerative disorders. Accumulating evidence points to various ion channels and particularly voltage-gated potassium channels as signaling targets, whereby NO mediates activity-dependent control of intrinsic neuronal excitability; such changes could underlie broader mechanisms of synaptic plasticity across neuronal networks. In addition, the inability to constrain NO diffusion suggests that spillover from endothelium (eNOS) and/or immune compartments (iNOS) into the nervous system provides potential pathological sources of NO and where control failure in these other systems could have broader neurological implications. Abnormal NO signaling could therefore contribute to a variety of neurodegenerative pathologies such as stroke/excitotoxicity, Alzheimer's disease, multiple sclerosis, and Parkinson's disease.

Keywords

nitric oxide, synaptic transmission, K^+ channels, homeostatic signaling, intrinsic neuronal excitability, neurodegeneration, oxidative stress, Alzheimer's disease, Parkinson's disease

The aim of this review is to provide some background to nitrergic signaling, to illustrate some of the key atypical aspects of this ubiquitous signaling pathway and briefly highlight some of the areas in which the knowledge is most uncertain—for instance, in terms of how nitrergic signaling can influence intrinsic excitability and synaptic transmission. We develop discussion of the broader relevance to modulation of synaptic transmission, the targets of nitrergic signaling, and the involvement of nitric oxide (NO) in neurodegenerative disease.

Nitric Oxide as a Signaling Molecule

Nitric oxide is the signaling molecule originally identified as endothelium-derived relaxing factor (EDRF) mediating relaxation of blood vessels (Furchgott and Zawadzki 1980). It is a small, highly diffusible, and reactive molecule with a short lifetime that is generated by nitric oxide synthase (NOS) through enzymatic conversion of L-arginine to L-citrulline (Alderton and others 2001). The substrate, L-arginine, is supplied to cells by carriers that mediate facilitated diffusion and are specific for cationic amino acids. This transport system, referred to as system y^+ (Closs 2002; Mann and others 2003), consists of at least two membrane proteins, CAT-1 and CAT-2B (cationic amino acid transporter-1 and 2B), and y^+L, which is the result of the activity of the heteromeric amino acid transporters 4F2/y^+LAT1 and 4F2/y^+LAT2 (Rotmann and others 2007). Three NOS genes with distinct tissue localization and properties are known—namely, neuronal, inducible, and endothelial NOS (nNOS [NOS1], iNOS [NOS2], and eNOS [NOS3], respectively). Activation of eNOS and

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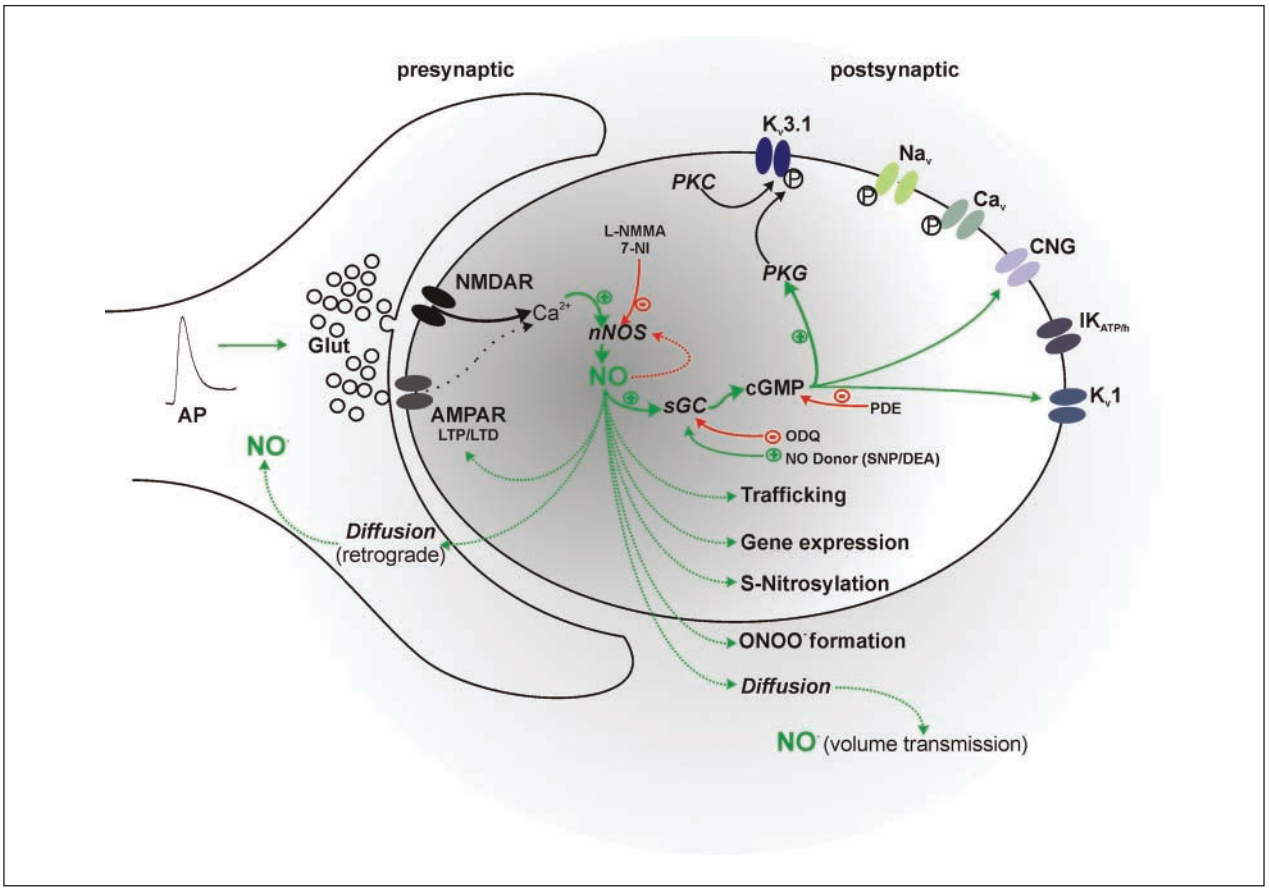

Figure 1. The nitric oxide (NO) signaling pathways. Nitric oxide, produced from the amino acid arginine by nNOS, has various physiological effects. Synaptic glutamate release activates postsynaptic AMPA and NMDA receptors (AMPAR, NMDAR), leading to Ca^{2+}-induced nNOS activation. This NO will diffuse and subsequently activate sGC to produce cGMP (from GTP), which has several signaling roles, including activation of PKG or cyclic nucleotide-gated ion channels. NO will act locally at the source of production and in neighboring neurons through a process of volume transmission to affect postsynaptic neuronal excitability or presynaptic neurotransmitter release. In addition to short-term effects, NO is also involved in CREB-mediated gene expression (Contestabile 2008). Pharmacological studies use 7-NI and L-NMMA as nitric oxide synthase (NOS) competitive antagonists or ODQ as an GC inhibitor (red arrows), whereas there are many different NO donors (e.g., SNP or DEA-NONOate) that generate NO an independent to NOS and thereby activate sGC. Other powerful modulation is achieved by PDEs, mediating breakdown of cGMP and reducing NO/sGC signaling. Several ion channel targets for nitrergic signaling are indicated. AP = action potential; Ca_v = voltage-gated calcium channel; CNG = cyclic nucleotide-gated ion channels; $IK_{ATP/h}$ = ATP-sensitive potassium channel/hyperpolarizing potassium channel; $K_v3.1$ = voltage-gated potassium channel; L-NMMA = N^G-methyl-L-arginine; LTD = long-term depression; LTP = long-term potentiation; Na_v = sodium channel; ODQ = 1H-[1,2,4]Oxadiazolo[4,3-a] quinoxalin-1-one; $ONOO^-$ = peroxynitrite; PDE = phosphodiesterase; SNP = sodium nitroprusside; 7-NI = 7-nitroindazole.

nNOS is classically Ca^{2+}/calmodulin dependent, with nNOS being closely coupled to Ca^{2+}-permeable NMDA receptors (NMDAR) at the postsynaptic density (PSD-95), through their mutual PDZ binding motifs (Brenman and others 1996). Nanomolar concentrations of NO are generated by eNOS and nNOS, whereas iNOS can produce micromolar levels in response to proinflammatory stimuli (see Fig. 1 for different pathways of NO signaling). NO potentially acts via multiple downstream signaling mechanisms, depending on the concentration, with low concentrations being neuroprotective and mediate physiological signaling (e.g., neurotransmission or vasodilatation), whereas higher concentrations mediate immune/inflammatory actions and are neurotoxic. Because of its mobility, unconstrained by cell membranes, NO can act across a broad volume (hence the term *volume transmitter*), and its actions are limited by inactivation (e.g., scavenging or degradation). It has long been postulated that NO could also act as a retrograde messenger

at the synapse, mediating transmission from target neurons back onto the synapse and regulating synaptic plasticity, but the same properties also enable NO to signal to any local compartment and to cells that lack synaptic activity or NOS expression.

There are many comprehensive reviews concerning nitric oxide signaling and synaptic transmission in the CNS that the reader is referred to (Moncada and Bolanos 2006; Garthwaite 2008; Mustafa and others 2009).

NOS Genes and Splice Variants

nNOS. Although first identified in the brain, nNOS is expressed widely in the peripheral nervous system and skeletal muscle. Knockout (KO, $NOS^{-/-}$) mice have provided important insights into the physiological roles of the three NOS genes and their splice variants. There are four splice variants of nNOS (α, β, γ, and μ; see Fig. 2). By far the dominant splice variant is nNOSα, which possesses an amino terminal PDZ domain and associates with the NMDAR at postsynaptic densities (Brenman and others 1996; Fig. 2). The nNOSβ lacks this structure and so is less closely coupled to NMDAR-mediated synaptic activity (Gyurko and others 2002). nNOSγ has little or no enzymatic activity. nNOSμ is similar to nNOSα with an insert around the calmodulin binding motif; it is predominantly expressed in skeletal muscle but accounts for approximately 10% of total brain nNOS (Ihara and others 2006), particularly the cerebellum.

The first nNOS knockout (KN1; Huang and others 1993) was a deletion of exon 2, which encodes for the Discs large Zo-1 (PDZ) domain (and binds the postsynaptic density protein-95, PSD-95). This deletes the predominant nNOSα splice variant. nNOSβ (which does not include exon 2) is expressed and up-regulated in the striatum and cortex (Eliasson and others 1997; Langnaese and others 2007) of the KN1 mice, which probably accounts for the relatively mild phenotype. In addition, nNOSβ is prominently expressed in areas of the brainstem, including the ventral cochlear nucleus (Eliasson and others 1997). Although nNOSγ is also maintained in the KN1 knockout, it lacks a functional catalytic domain, and its functions are unclear (Huang and others 1993; Eliasson and others 1997). A more "complete" knockout was achieved by deletion of exon 6 (Gyurko and others 2002), which encodes the heme-binding catalytic domain, rendering all nNOS splice variants inactive. This homozygous KN2 mouse is viable, with lower body weight, but infertile, consistent with involvement of nNOS in hormonal regulation of reproduction. $nNOS^{-/-}$ mice exhibit hypertrophy of the pyloric sphincter, increased aggressive behavior, and protection from cerebral ischemia. Although lack of endothelial or inducible NOS is well tolerated, deficiency of nNOS enhanced neuronal competence-to-die and led to a substantial apoptotic cell death of spinal cord neurons (Keilhoff and others 2004).

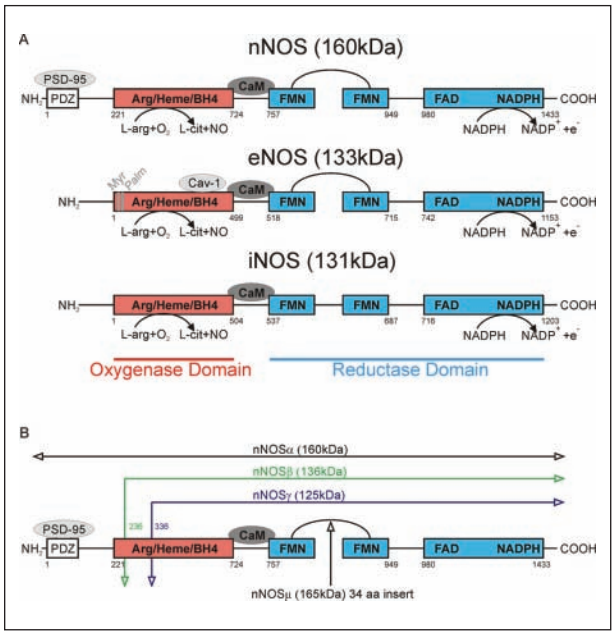

Figure 2. Structure of human nNOS, eNOS, and iNOS and main nNOS splice variants. (*A*) NOS contains an oxygenase domain (N-terminal) and a reductase domain (C-terminal) that can be separated by a calmodulin binding motif. The reductase domain, which binds NADPH, contains a binding site for FMN and FAD, and the oxygenase domain, which binds L-arginine, contains a tetrahydrobiopterin (BH4) binding site and a cytochrome P-450-type heme active site. Electrons (e^-) that transfer from the reductase domain to the oxygenase domain via FMN and FAD are donated by NADPH. The caveolin-1 (Cav-1) binding site is located at the oxidase domain. Note that only nNOS via the PDZ domain binds to PSD-95. Oxygenase, reductase, and PDZ domains are denoted by solid boxes, and the amino acid residue number at the start/end of each domain is shown. Myristoylation (Myr) and palmitoylation (Palm) sites on eNOS are shown as this is the only NOS enzyme undergoing these modifications. The autoinhibitory loop within the FMN regions of nNOS and eNOS are also shown. (*B*) Protein products of the nNOS splice variants are shown by arrowed lines as follows: black, nNOSα amino acids 1 to 1433; green, nNOSβ amino acids 236 to 1433; purple, nNOSγ amino acids 336 to 1433; and nNOSμ (black), which has an additional 34 amino acids inserted between the CaM- and flavin-binding domains. Both nNOSβ and nNOSγ lack the PDZ domain of nNOS, which is encoded by exon 2, and do not bind PSD-95 from brain postsynaptic densities or are associated with synaptic membranes. Sequences for all NOSs are numbered according to the human sequence.

eNOS and iNOS. There is considerable evidence that both eNOS and iNOS contribute to physiology and pathology in the nervous system. Hypertension is clearly the major phenotype in eNOS$^{-/-}$ as endothelial-derived NO is essential to maintain physiological vascular tone and peripheral resistance (Ortiz and Garvin 2003). eNOS$^{-/-}$ mice are susceptible to cerebral ischemia (Huang and others 1996). Given that iNOS induction is predominantly associated with inflammation and disease, one phenotype of iNOS$^{-/-}$ is decreased lipopolysaccharide (LPS)–induced microvascular responsiveness to vasoconstrictors (i.e., septic shock; Boyle and others 2000; Hollenberg and others 2000) and an increased susceptibility to infections (Flodstrom and others 2001), although this strongly depends on the type of infection and affected organ (Bogdan 2001). Expression of iNOS in the brain and vasculature is low under physiological conditions, and it has little role in maintaining vascular tone (Ortiz and Garvin 2003). The association with inflammation provides a significant association with pathology, and although iNOS activity is not calcium dependent, the capability to generate NO at micromolar levels provides potent pathological potential.

Double and triple KO. Several studies have shown that both eNOS and nNOS are necessary in the nitrergic mechanism of long-term potentiation (LTP) in the hippocampus, with the implication that eNOS provides an essential basal level upon which activity-dependent nNOS activation then summates; KOs of either nNOS or eNOS block NO-dependent potentiation of LTP (O'Dell and others 1994; Son and others 1996). The triple KO mouse e/i/nNOS$^{-/-}$ mouse is viable, showing a 20% survival rate at 10 months, but fertility was markedly reduced compared with wild-type, and they show a variety of cardiovascular diseases (Tsutsui and others 2006). The survival of the triple knockout suggests that although NO signaling may be near ubiquitous, it is not essential or is well compensated by other control mechanisms, perhaps consistent with a subtle physiological impact.

Contribution to Neuronal Processing

A recurring theme in nitrergic signaling in the nervous system is its role in rhythm generation and gut motility (Bartho and others 2008). In the pond snail *Lymnaea* (Korneev and others 2005; Ribeiro and others 2008), it is associated with feeding and memory. And in the mammalian enteric nervous system, it contributes to the inhibitory nonadrenergic-noncholinergic (NANC) neurotransmitter mechanism (Toda and Herman 2005), with NO causing smooth muscle relaxation mediated by both sGC/cGMP-dependent mechanisms (acting to reduce intracellular $[Ca^{2+}]_i$ and the sensitivity of smooth muscle contraction) and cGMP-independent mechanisms generating membrane potential hyperpolarization, through activation of calcium-dependent potassium channels. Cotransmission of many NANC myenteric neurons further increases the subtlety and spectrum of nitrergic signaling (Toda and Herman 2005).

Metabolism of cGMP by phosphodiesterase (PDE) suppresses or terminates NO/sGC signaling. There are 11 PDE genes identified with specific differential expression in nervous tissue. Signaling activity will then reflect the equilibrium between cGMP synthesis and degradation (e.g., Sildenafil/Viagra is an antagonist of phosphodiesterase-5 [PDE5], reducing cGMP degradation so that lower activity of sGC will maintain erection; Kleppisch 2009). Another route of action that is particularly relevant with high NO concentrations is the direct S-nitrosylation of thiol groups or nitrotyrosination in proteins, and there is considerable debate as to whether this constitutes a physiological or pathological signaling pathway. S-nitrosylation is the reaction of NO with cysteine to form nitrosothiols (Stamler and others 2001), and nitrotyrosination is the reaction of tyrosine with peroxynitrite ($ONOO^-$) to form 3-nitrotyrosine residues. This protein modification is distinguishable from that mediated by sGC because the latter is blocked by specific sGC antagonists such as 1H-[1,2,4] oxadiazolo [4.3-a] quinoxalin-1-one (ODQ).

Nitrergic signaling has a well-established role in reproductive physiology, contributing to gonadotrophin and oxytocin release, ovulation, and penile erection. Enhancement of NO signaling in the treatment of male impotence with antagonists of PDE5 (Viagra) is well documented. The physiology requires both eNOS in the corpus cavernosum vasculature smooth muscle and nNOSβ in the presynaptic nerve (Hurt and others 2002), with nNOS initiating erection and eNOS contributing to maintenance (Burnett and others 1992; Hurt and others 2002). Central aspects of gonadotrophin release and modulation of oxytocin release are also regulated by NO signaling via modulation of presynaptic calcium-dependent potassium channels (Ahern and others 1999; Zhang and others 2007) and control of cGMP by PDE5.

Hippocampus and cerebellum. Nitric oxide signaling in the brain modulates various forms of plasticity (LTP and long-term depression [LTD]); rhythmic activity, including respiratory and circadian rhythms; and locomotor and thalamocortical oscillation. It is involved in learning and memory in the cerebellum (Jacoby and others 2001; Qiu and Knopfel 2007), hippocampus (Garthwaite 2008; Phillips and others 2008; Taqatqeh and others 2009), and neocortex (Hardingham and others 2003; Hardingham and Fox 2006) and LTD in the cerebellum (Shin and Linden 2005; Ogasawara and others 2007). LTD in the cerebellum is generated on stimulation of parallel fibers, acts postsynaptically in Purkinje cells, and requires the NO/PKG

pathway (Shibuki and Okada 1991; Hartell 1994; Boxall and Garthwaite 1996; Jacoby and others 2001). An interesting link between NO signaling and LTD is given by the actions of G-substrate, a potent inhibitor of protein phosphatase 1 (PP1) and 2A (PP2A), activated as a result of PKG stimulation (Endo and others 2003; Chung and others 2007). The effects of G-substrate on LTD formation are age dependent, where LTD is only diminished in G-substrate-deficient mice during postnatal weeks five to six (Endo and others 2009).

The targets of nitrergic signaling pathways are diverse and often unresolved; there is some evidence for modulation of presynaptic transmitter release at excitatory glutamatergic and inhibitory GABAergic synapses, postsynaptic AMPAR phosphorylation and trafficking, calcium channels, potassium channels, and interactions with other signaling pathways (such as mGluR, endocannabinoid, and catecholamine).

The retrograde messenger hypothesis at glutamatergic synapses has been a powerful influence in stimulating research, and there is clear evidence for the involvement of NO in LTP in both the hippocampus and cerebellum. The tight coupling between NMDAR-mediated calcium influx and nNOS activation (through their mutual PDZ-binding) provides a clear synaptic, activity, and plasticity-associated trigger to postsynaptic NO generation. However, the balance of arguments favors postsynaptic rather than presynaptic mechanisms of LTP (Malenka and Bear 2004; Kerchner and Nicoll 2008), and so the idea that NO is a retrograde messenger for this form of plasticity is not proven (Regehr and others 2009), although LTP in the cerebellum is suggested to be of presynaptic origin (Jacoby and others 2001; Qiu and Knopfel 2007).

NO Receptors

The remarkably low nanomolar concentrations of NO required for physiological activity and the short tissue half-life suggest that various inactivation mechanisms could be physiologically relevant (i.e., rapid diffusion, scavenging of NO by hemoglobin in red blood cells, buffering by carrier molecules or receptor proteins; Keynes and others 2005). The major physiological receptor for NO is soluble guanylyl cyclase (sGC; see Fig. 1), which mediates the production of cGMP from GTP. sGC is a hemoprotein with formation of a NO-heme complex inducing a conformational change and enzyme activation (Roy and Garthwaite 2006). Three subunits have been identified—$\alpha1$, $\alpha2$, and $\beta1$—which function as heterodimers composed of one α and one β subunit (Friebe and Koesling 2009), generating two isoforms ($\alpha1\beta1$ and $\alpha2\beta1$) with differential expression even between cell types in the same tissue (Friebe and Koesling 2009). The $\alpha2\beta1$ isoform has highest expression in the brain, and distinct subcellular localization to the synapse is achieved through association of the $\alpha2$ subunit with PSD95.

Ion Channels as Targets of NO Signaling

One limitation in understanding the roles of nitrergic signaling in the nervous system is knowledge of its sources and means of induction; we know considerably more about generation of cGMP and the physiology in terms of changes in synaptic transmission. We have much less understanding of the pathways linking cGMP production to protein targets mediating the physiological response. Modulation or induction of LTP/LTD does not constitute a "target" but a physiological response that is itself triggered and modulated by synaptic activity in either presynaptic or postsynaptic compartments. A concept receiving increased recognition is the idea that synaptic plasticity can be achieved by modulation of postsynaptic voltage-gated ion channels, so that neuronal excitability changes independently of synaptic strength and contributes to changes in information transmission.

Nitrergic signaling in the CNS modulates multiple suites of different ion channels, triggering alteration of postsynaptic glutamate receptor currents and changes in intrinsic neuronal excitability via phosphorylation or S-nitrosylation of voltage-gated ion channels (see Fig. 1), including sodium, voltage-gated calcium, Ca^{2+}-activated and ATP-sensitive potassium, and cyclic nucleotide-gated and I_H channels (see reviews by Biel and others 1998; Ahern and others 2002; Sanders and Koh 2006; Kawano and others 2009) and including leak channels (K2P and Kir; Gonzalez-Forero and others 2007; Kang and others 2007).

The targeting of potassium channels to modulate intrinsic excitability is part of the nitrergic mechanisms in smooth muscle (Ahern and others 2002) and in neurohypophysis/oxytocin regulation (Zhang and others 2007), and most recently, it has been observed in the auditory brainstem (Steinert and others 2008). At this site, although there was no evidence for presynaptic retrograde action of NO, NO generation on synaptic activity at the calyx of Held synapse was followed by increased postsynaptic cGMP, together with suppression of Kv3 potassium channels. This suppression increased action potential (AP) duration and reduced the fidelity of synaptic transmission during high-frequency synaptic stimulation. This action was mediated by cGMP-dependent protein kinases and was blocked by NMDAR, nNOS, and sGC antagonists and was absent in nNOS knockout mice. Although the major site of action was voltage-gated potassium channels, modulation of postsynaptic voltage-gated sodium channels, AMPAR, and NMDAR was also observed. From a physiological viewpoint, this signaling pathway would act as a

gain control, reducing AP transmission during periods of high activity, but it remains to be established whether this constitutes a form of homeostatic feedback regulating neuronal intrinsic excitability. On a broader level, we would speculate that the modulation of voltage-gated potassium channels could be a general role of nitrergic signaling elsewhere in the brain. For instance, there is coexpression of Kv3 channels and nNOS in hippocampal inhibitory interneurons (Tansey and others 2002). And there is the potential for this phenomenon to have a broad role in controlling excitability in the CNS.

Kv3 channels, which affect transmitter release by shaping the presynaptic action potentials, are suppressed by the NO-cGMP pathway, not through direct phosphorylation by PKG but through the intermediate step of a phosphatase, which dephosphorylates recombinant channel protein in Chinese hamster ovary (CHO) cells (Moreno and others 2001). Should this mechanism occur in nerve terminals, spike broadening would lead to increased transmitter release, but this has yet to be demonstrated in an intact *native* neuron.

Other examples of NO-mediated K^+ channel modulation include inhibition of Kv4 currents in CHO cells and a transient outward current (predominantly carried by Kv4.3 subunits) in human atrial and mouse ventricular myocytes as a consequence of the activation of adenylyl cyclase and the subsequent activation of the cAMP-dependent protein kinase and the serine-threonine phosphatase 2A (Gomez and others 2008). This prolongs the plateau phase of the atrial AP and lengthens AP duration. Neuronal excitability is predominantly set by the activities of Kv1 channels, which are inhibited by cGMP-dependent actions of NO or direct S-nitrosylation in CHO cells and mouse myocytes (Nunez and others 2006). Neurons in the paraventricular nucleus of the hypothalamus respond with an increased frequency of GABAergic miniature inhibitory postsynaptic currents (IPSCs) on NO donor application (Yang and others 2007), and this is thought to be mediated by Kv1 channels.

Neuronal excitability of B5 neurons of the mollusk *Helisoma trivolvis* is modulated in a NO-dependent manner by inhibition of an apamin-sensitive potassium channel (BK- and SK-like potassium conductances), resulting in temporary increased firing followed by a neuronal silencing (Artinian and others 2010). This change in excitability was achieved in synaptically inactive neurons that were exposed to NO generated by a neighboring active neuron.

Synaptic strength is also regulated by NO modulation of AMPARs. Delivery of AMPARs to the postsynaptic membrane leads to LTP, whereas removal of these receptors leads to LTD (Malinow and Malenka 2002; Song and Huganir 2002). In particular, GluR1 phosphorylation of serine-845 by cGMP-dependent kinase type II leads to enhanced membrane expression of this receptor (Serulle and others 2008). Further direct action by NO via S-nitrosylation of AMPAR regulatory proteins (Stargazing [GluR1] and N-ethylmaleimide sensitive factor [GluR2]) results in increased receptor surface expression (Huang and others 2005; Selvakumar and others 2009). In contrast, phosphorylation-independent inhibition of AMPAR occurs in CA1 hippocampal neurons in response to cGMP (Lei and others 2000).

Together these data show that NO can not only modulate synaptic strength but also affect postsynaptic neuronal intrinsic excitability and action potential waveform generation in various cell types by predominately regulating voltage-gated potassium channels.

Regulation of NOS Activity

Interacting proteins CAPON and protein inhibitor of nNOS. The competitive binding for nNOS by CAPON and PSD-95 suggests a model for regulating the translocation of nNOS between synaptic and nonsynaptic structures. Although CAPON does not inhibit nNOS catalytic activity directly, CAPON would reduce the accessibility of nNOS to a NMDAR-mediated calcium influx, thus diminishing the capacity of nNOS to exert its physiologic or pathologic effects (Jaffrey and others 1998).

Using the N-terminal domain of NOS in a yeast 2-hybrid system, Jaffery and Snyder (1996) identified a 10-kDa protein that interacted with and inhibited nNOS, which they termed protein inhibitor of nitric oxide synthase (PIN; Jaffrey and Snyder 1996). In vitro experiments suggest that the PIN might act to inhibit nNOS by preventing its dimerization. In addition, because the PIN's structure is homologous to the light chain of myosin and dynein, it has been proposed that PIN could be involved with nNOS association with the neuronal cytoskeleton during axonal transport (Gillardon and others 1998; Jeong and others 1998; Chang and others 2000).

Phosphorylation. Several putative phosphorylation sites have been identified, allowing modulation of nNOS by cAMP and cGMP-dependent kinases (PKA and PKG, respectively). Protein kinase C and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) also modulate nNOS (Nakane and others 1991; Bredt and others 1992; Dinerman and others 1994). In rat brain and hippocampus, serine-847 phosphorylation is affected by glutamate stimulation in a biphasic manner: low concentrations (low μM range) increased and high concentrations (100 μM) decreased activity (Hayashi and others 1999) via a CaMKII-dependent pathway, causing a 50% reduction in NO generation (Hayashi and others 1999; Komeima and others 2000).

Protein kinase B (PKB), also known as Akt, rapidly phosphorylates nNOS at serine-1412 (Rameau and others 2007),

Table 1. Different Phosphorylation Sites at nNOS and eNOS Proteins

Phosphorylation Site	Effect on NOS	Kinase	Reported in	Reference
nNOS				
Ser-741	Inhibition	CamKI	nNOS transfected HEK cells	Song and others (2004)
Ser-847	Inhibition	CamKII	Cultured cortical neurons, NG108-15	Komeima and others (2000); Mount and others (2006); Rameau and others (2007)
Thr-1296	Inhibition	PP1/PP2A inhibition	Neuroblastoma cells (NG108-15)	Song and others (2005)
Ser-1412	Activation	Akt/PKB	Cultured cortical neurons	Rameau and others (2007)
	Activation	ERβ-mediated Src kinase activation	Primary hypothalamic neurons	Gingerich and Krukoff (2008)
eNOS				
Tyr-81	Activation	Src kinase	BAEC	Fulton and others (2008)
Ser-114	Inhibition	Enhanced association with Cav-1	BAEC	Mount and others (2007)
Thr-495	Inhibition	PKC	HCMVEC	Mount and others (2007)
Ser-615	Activation, modulatory action	PKA, Akt/PKB	BAEC	Michell and others (2002); Bauer and others (2003)
Ser-633	Activation	PKA	BAEC	Michell and others (2002)
Ser-1177	Activation	Akt/PKB, PKA, AMPK, PKG, PKC, CamKII	HUVEC, HCMVEC, human platelets	Dimmeler and others (1998); Fleming and others (2001); Fleming and others (2003); Sessa (2004); Joy and others (2006); Queen and others (2006)

AMPK = AMP-activated protein kinase; BAEC = bovine aortic endothelial cells; Cav-1 = caveolin-1; ERb = estrogen receptor b; HCMVEC = human cardiac microvascular endothelial cells; HUVEC = human umbilical vein endothelial cells; NOS = nitric oxide synthase; PKB = protein kinase B; HEK = human embryonic kidney. Sites are numbered for eNOS according to the human eNOS sequence and for nNOS according to the rat sequence.

and this glutamate-induced event is followed by a sustained CaMKII-dependent phosphorylation at serine-847, generating a fast pulse of nNOS activity followed by a sustained reduction. Protein phosphatase 1 (PP1) removes phosphorylation on serine-847, thereby increasing nNOS activity (Rameau and others 2004). Further phosphorylation sites regulating nNOS and eNOS are summarized in Table 1.

The analogous phosphorylation site to nNOS serine-1412 also up-regulates eNOS activity (serine-1177) again by Akt/PKB signaling (Dimmeler and others 1998; Fleming and others 2001; Fleming and others 2003). eNOS is also modified by N-myristolation and palmitolation (Michel 1999) at cysteine-15 and cysteine-26, mediating colocalization with caveolin-1 in endothelial cells (Liu and others 1995; Shaul and others 1996). Agonist-induced depalmitolation causes translocation of eNOS into the cytosol (Michel and others 1997). Similarly, palmitolation of PSD-95 is required for nNOS activity because depalmitolation causes dislocation of nNOSα and PSD-95 and inhibits NO production (Chaudhury and others 2009).

iNOS is transcriptionally regulated in response to various inflammatory cytokines. Protein phosphorylation has not been investigated thoroughly, but there is no evidence for serine/threonine phosphorylation. Tyrosine kinase phosphorylation enhances activity, although the specific residues are unknown. In activated macrophages, tyrosine phosphatase inhibition enhanced tyrosine phosphorylation, indicating a dynamic regulatory process (Pan and others 1996). Additional evidence for negative regulation of iNOS expression by mitogen-activated protein kinase phosphatase-1 (MKP-1) has recently been published linking this signaling cascade with microRNA-155 expression (Wang and others 2009).

Regulation of NOS by NO derivates. In resting endothelial cells, eNOS is tonically inhibited by S-nitrosylation at cysteine-94 and cysteine-99 of the zinc tetrathiolate cluster, which comprises the eNOS dimer interface (Erwin and others 2005); conformational changes affecting dimer interaction and the efficiency changes of electron transfer are postulated (Erwin and others 2005; Dudzinski and others 2006). S-nitrosylation of iNOS at cysteine-104 and cysteine-109 similarly inactivates the enzyme (Mitchell and others 2005). NO also exerts a direct negative feedback control by binding to the heme moiety of the enzyme

(Rogers and Ignarro 1992). NOS can undergo concurrent NO synthesis and ferrous-nitrosyl complex formation during steady-state activity, with the NO (formed during the oxidation of L-arginine) competing with oxygen for binding to the ferrous iron. Because the electron transfer requires iron in ferric state, the ferrous-nitrosyl complex renders NOS catalytically inactive (Abu-Soud and others 1995).

Inter- versus Intraneuronal Signaling

Given the ease with which NO passes between cellular compartments, spill-over of NO *between* the vasculature and neurons (and glial cells) and involvement of microglia and the immune system in nitrergic signaling will have a major impact on nervous system disease and neurodegeneration.

Our recent work in the auditory brainstem has highlighted the role of NO in regulating postsynaptic excitability via Kv3 voltage-gated potassium channels in activity-dependent auditory processing. Synaptic activity at the calyx of Held synapse onto principal cells of the medial nucleus of the trapezoid body (MNTB) causes NMDAR-mediated activation of postsynaptic nNOS. NO acts in the target neuron and surrounding neurons as a result of volume transmission through a slow time course (15- to 30-minute) mechanism that has a homeostatic-like function in matching postsynaptic excitability to the synaptic traffic (Steinert and others 2008). The idea that NO acts as a volume transmitter has also recently been supported in neurons of the mollusk *Helisoma trivolvis* where synaptically inactive neurons are modulated over a time course of 10 to 30 minutes in a NO-dependent manner by neighboring cells generating NO (Artinian and others 2010), suggesting a very strong involvement of NO and its ability to act as volume messenger in different physiological scenarios of homeostatic control of voltage-gated potassium channels.

NO has been long suggested to act as such a volume transmitter, thereby integrating neuronal activity over a diffusion-limited space, allowing interactions between excitability and synaptic transmission across the neuronal population, which would complement cell-autonomous mechanisms of synaptic plasticity. Differences in activity rates (including spontaneous firing) across a small volume of active neurons could adjust the functional tonotopic gradients of intrinsic conductances. This idea was suggested almost two decades ago (Gally and others 1990). It is predicted that the physiological volume of influence of a single source of NO that emits for 1 to 10 seconds has a diameter of about 200 μm, corresponding to a volume of brain enclosing 2 million synapses (Wood and Garthwaite 1994). Inactivation of NO (imposed as a half-life of 0.5–5 seconds) has to be considered and will have profound effects on effective local NO concentrations (Keynes and others 2005; Garthwaite and others 2006).

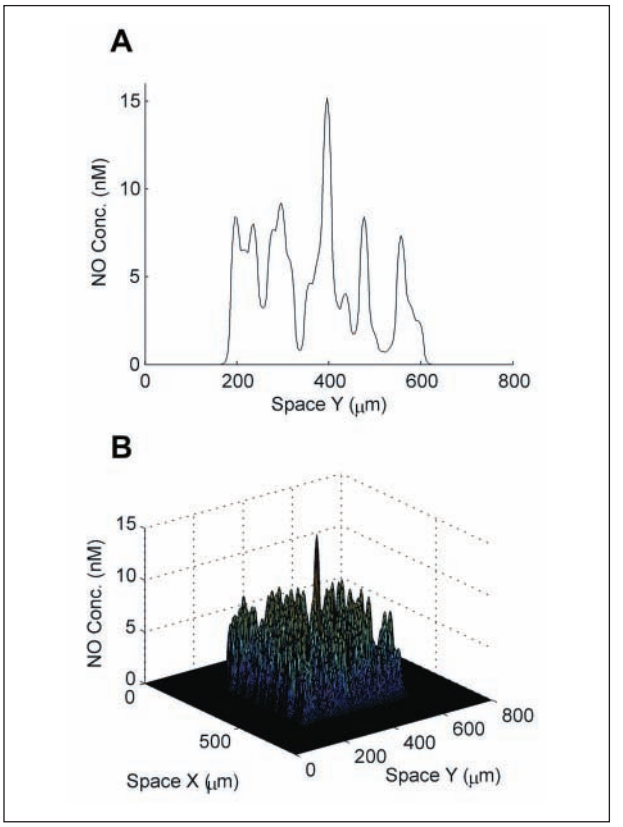

Figure 3. Nitric oxide (NO) diffusion model. (*A*) Model of NO concentration gradients produced by a 21-by-21 tightly packed planar array of 20-μm diameter spherical sources embedded in a block of neural tissue. Each source is assigned a production rate drawn randomly from a range of 0 to 1600 nM/s. The central source is assigned an elevated rate of 2400 nM/s to simulate a single activity-driven input. Simulations run for 100 ms, which is sufficient to achieve a steady (NO) profile. (*B*) Three-dimensional representation of the same data. (Adapted from Steinert and others 2008)

Assuming multiple simultaneously active NO sources within a tissue volume, the concentration of NO simply rises linearly with time, indicating the importance of negative feedback by NO on NO synthesis (Abu-Soud and others 1995). This is of particular importance in densely packed neuronal nuclei such as the MNTB of the auditory pathway, where volume diffusion by NO affects neurons across a population of active and inactive cells (Fig. 3; Steinert and others 2008), but has also been suggested in the cerebellar cortex where diffusion of NO was indicated (Jacoby and others 2001).

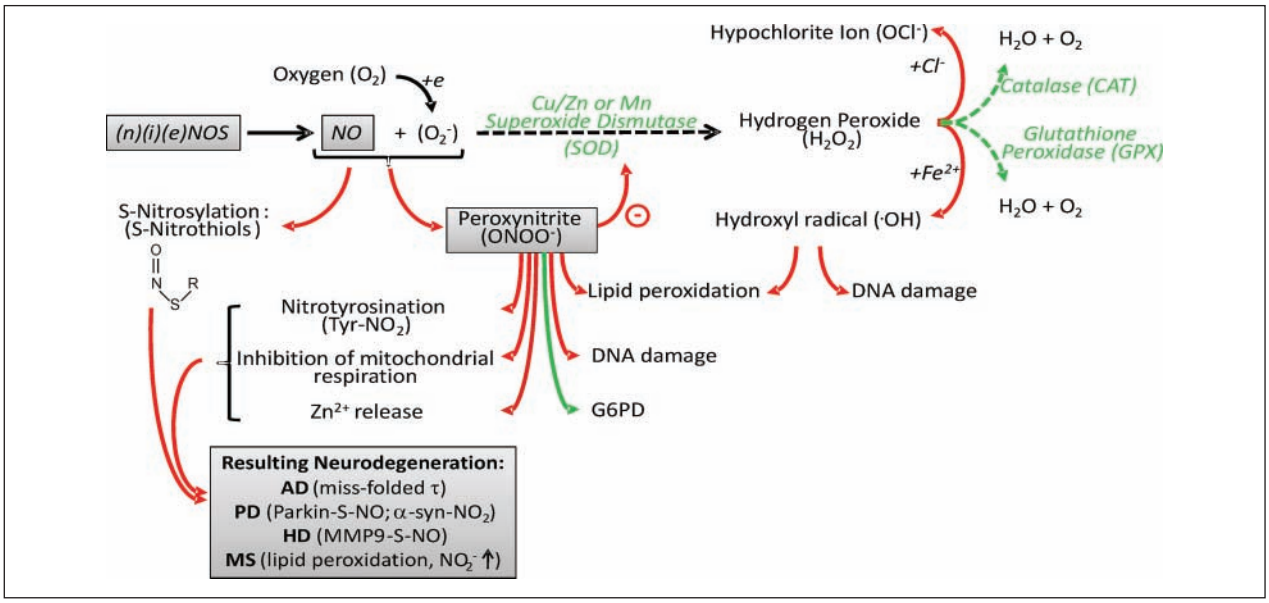

Figure 4. Oxidative and nitrosative stress: pathological consequences of nitric oxide (NO) generation. NO will react with superoxide anions (O_2^-) to form the highly reactive peroxynitrite ion ($ONOO^-$). $ONOO^-$ is responsible for protein nitrotyrosination and inhibits mitochondrial respiration. NO itself nitrosylates protein residues, leading to the formation of S-nitrothiols. All of the above effects of NO have been implicated in Alzheimer's, Parkinson's, and Huntington's diseases as well as in multiple sclerosis. Peroxynitrite rapidly and transiently activates glucose-6-phosphate dehydrogenase (G6PD), the enzyme that catalyzes the rate-limiting step of the pentose-phosphate pathway. G6PD activation by peroxynitrite regenerates the necessary NADPH for the recovery of GSH from GSSG. Thus, peroxynitrite-induced up-regulation of glutathione may be a neuroprotective factor. Several cellular antioxidant enzymes (green) break down reactive oxygen species—namely, Cu/Zn or Mn superoxide dismutase, which converts O_2^- into hydrogen peroxide (H_2O_2). H_2O_2 itself can form hypochloride ions or the highly reactive hydroxyl radical (·OH) responsible for lipid peroxidation and DNA damage. Further antioxidant actions (indicated by the dotted arrows) of either glutathione peroxidase or catalase lead to the formation of H_2O from H_2O_2.

Contributions to Neurodegenerative Disease

Production of Reactive Nitrogen Species

The term *nitrosative stress* describes the ability of NO and its derivatives (reactive nitrogen species [RNS]) to damage proteins, lipids, and DNA. A primary reaction is for NO and O_2^- (superoxide) to form peroxynitrite ($ONOO^-$; Fig. 4), which also decreases the bioavailability of NO (Beckman and Koppenol 1996). S-nitrosylation and nitrotyrosination of proteins are important probable mediators of physiological and pathological signaling.

NOS directly contributes to O_2^- production because cells with a deficiency in the NOS cofactor tetrahydrobiopterin (BH4) or substrate (L-arginine) inefficiently catalyze the five-electron oxidation of L-arginine into L-citrulline, increasing O_2 reduction to O_2^- (Xia and others 1996) and enhancing free radical and peroxynitrite production. BH4 deficiency (NOS cofactor) is associated with both Alzheimer's disease (AD) and Parkinson's disease (PD; Kuiper and others 1994; Foxton and others 2007), implying a contribution of RNS to these neurodegenerative diseases.

Mitochondria and Oxidative Stress

Generation of reactive oxygen species (ROS) occurs in every eukaryotic cell; electron "leakage" from the mitochondrial electron transfer chain reacts with molecular oxygen to make superoxide (O_2^-; Fig. 4). Normally, this is metabolized by superoxide dismutase (SOD) to H_2O_2, which is further degraded by the antioxidant enzymes, catalase or glutathione peroxidase. NO and $ONOO^-$ both inhibit the mitochondrial respiratory chain, reducing ATP production (Heales and others 1999; Erusalimsky and Moncada 2007), so that susceptibility to neurodegeneration shows complex dependence on local metabolic rates, oxygen availability, antioxidant activity (reduced glutathione), and cell stress resistance signaling (Sims and others 2004). Other effects of $NO/ONOO^-$ include release of Zn^{2+} from internal stores (such as metallothionein) with concomitant formation of S-nitrosothiol and neurotoxicity

(Kroncke and others 1994; Knoch and others 2008). A rise in free Zn^{2+} increases respiratory block, opening of the mitochondrial permeability transition pore (mPTP), cytochrome c release, generation of ROS, and p38 MAP kinase activation, leading to caspase-independent K^+ efflux, cell volume loss, and apoptotic-like cell death (Bossy-Wetzel and others 2004). Cell energetics may be further compromised by mitochondrial fragmentation, which can occur rapidly after NMDAR activation or NO exposure and is considered a prelude to neurodegeneration and cell death (Yuan and others 2007). Increased mitochondrial fission in response to NO has been reported in AD, PD, amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD; Bossy-Wetzel and others 2008; Knott and Bossy-Wetzel 2008, 2009; Knott and others 2008). Fragmentation of other organelles, such as the Golgi apparatus, is known to occur during apoptosis in several neurodegenerative disorders. NO-mediated Golgi fragmentation is downstream of NMDAR activation and precedes neuronal cell death (Nakagomi and others 2008).

Roles of Nitrosative and Oxidative Species in Neurodegenerative Disease

Is there evidence that these processes contribute to neurodegeneration?

Neuronal NOS is tightly coupled to NMDAR activation, and hence excitotoxicity-related neuronal injury could have a nitrergic component. High-affinity Zn^{2+} inhibition, redox modulation, and S-nitrosylation of the NMDAR are mediated by at least seven cysteine residues, of which redox reactions with cysteine-744 and -798 sensitize other sites to S-nitrosylation and subsequent receptor inhibition (their own nitrosylation has little effect on NMDAR activity; Lipton and others 2002; Takahashi and others 2007).

NO production from inflammation and resulting oxidative stress is a significant factor in AD, PD, ALS, multiple sclerosis (MS), and HD, as well as in the brain damage following ischemia and reperfusion (Bennett and others 2009; see also Fig. 4). Enhanced nitrotyrosine immunoreactivity and oxidative protein damage are evident in brains from AD patients (Sultana and others 2006; Danielson and Andersen 2008; Sultana and others 2009), whereas inhibition of mitochondrial cytochrome c oxidase and enhanced H_2O_2 production in amyloid β (Aβ) mutant mice suggest mitochondrial involvement in ROS generation (Manczak and others 2006). The cerebral cortex of patients with AD has high levels of protein nitrotyrosination (Hensley and others 1998), and nitrated proteins are associated with Aβ deposition (Sultana and others 2006) along with nitrotyrosination of Tau protein (Reynolds and others 2005) and synaptophysin in AD, consistent with a dysfunction in cholinergic synaptic transmission (Tran and others 2003). Recently, S-nitrosylation of Drp1 has been shown to mediate mitochondrial fission and neuronal damage caused by nNOS activation (Cho and others 2009). Although the authors clearly showed that nNOS activation (by a Ca^{2+} ionophore, rather than physiological stimulation) leads to Drp1 S-nitrosylation, it remains to be investigated how NMDAR-mediated Drp1 S-nitrosylation exclusively occurs in AD brains, as suggested by Cho and others (2009).

iNOS is strongly implicated in neurodegenerative disease pathogenesis. Experimental inflammation models, raising NO, cause axonal degeneration, especially when accompanied by propagating electrical activity. Changes in NO release from neutrophils obtained from PD patients and increased expression of iNOS were reported in 6-OHDA and LPS-induced experimental models of PD (Gatto and others 2000; Barthwal and others 2001; Singh and others 2005). iNOS expression in humans appears to be in astrocytes rather than microglia, and raised astroglial iNOS immunoreactivity is reported in postmortem brain tissue from patients with MS (Bo and others 1994), AD (Wallace and others 1997), and PD (Hunot and others 1996).

Multiple pathogenic mechanisms are likely. In PD, S-nitrosylation of Parkin (Chung and others 2004; Yao and others 2004) initially increases but later decreases Parkin activity. Alpha-synuclein (α-syn), a protein associated with synaptic terminals and synaptic transmission, is heavily nitrated at four tyrosine residues, and this contributes to aggregation (Takahashi 2002), with nitrated α-syn being more resistant to proteolysis and with reduced lipid binding and solubility (Hodara and others 2004). Metabolic compromise by RNS in substantia nigra (Schapira and others 1989) following 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment in this PD model was slowed by competitive nNOS antagonists (Hantraye and others 1996), and nNOS inhibition also blocked MPTP-mediated decrease in striatal dopamine in mice (Yokoyama and others 2008).

These data strongly suggest an important general role of NO in neurodegenerative diseases, but because NO is an essential signaling molecule, the following question arises: what additional changes facilitate the cytotoxic pathways of NO seen in many pathological conditions? Presumably, NO generation has to be malfunctioning, or compensatory cellular responses are suppressed. Vascular dysfunction is an underlying condition contributing to various diseases, which could account for some of the pathological downstream signaling of NO.

Cerebrovascular Dysfunction and Neurodegeneration

Generation of RNS, involvement in oxidative stress, and the propensity for spill-over between endothelium (vasculature) and immune signaling into the neuronal

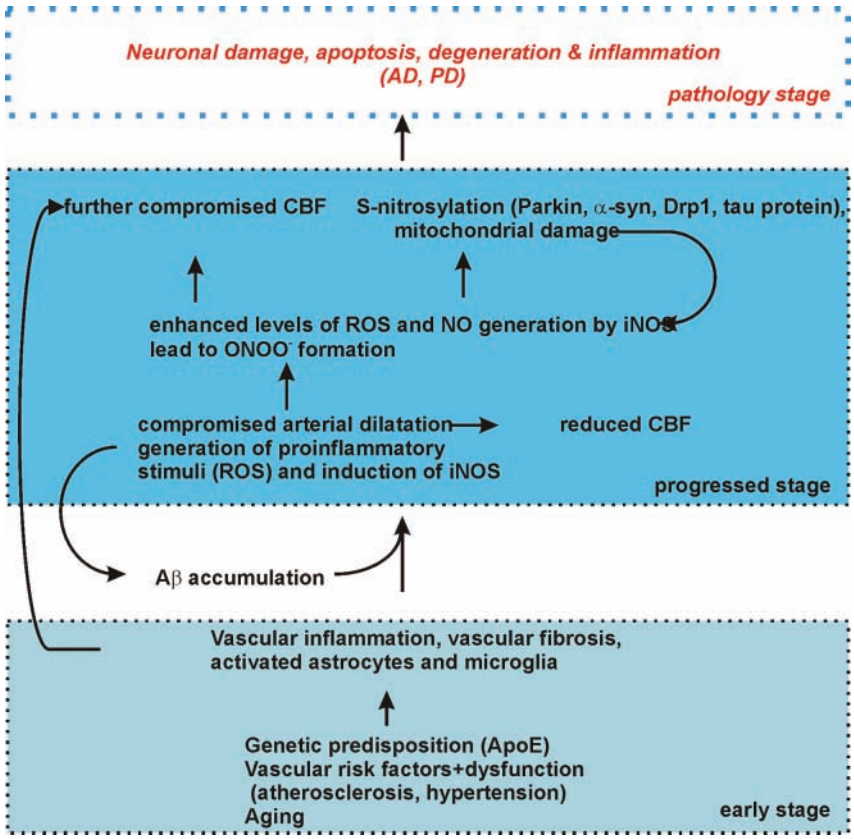

Figure 5. Cerebrovascular dysfunction and nitric oxide (NO) actions in neurodegeneration. There is evidence that NO may act as a secondary response to a cerebrovascular dysfunction. Underlying risk factors such as a genetic predisposition (apolipoprotein E genotype, ApoE) or vascular dysfunctions (hypertension, atherosclerosis) together with aging are believed to cause a vascular inflammation with vascular fibrosis and activation of glial and astrocytes. This, together with an enhanced Aβ deposition in the vascular bed, leads to reduction of cerebral blood flow (cerebral amyloid angiopathy, CAA) to cause further generation of proinflammatory stimuli, including reactive oxygen species (ROS) and iNOS-induced reactive nitrogen species (RNS). This enhanced oxidative and nitrosative stress-induced nitration and nitrosylation of various proteins known to be involved in neurodegenerative diseases ultimately cause pathologies such as Alzheimer's disease or Parkinson's disease.

environment suggest that we might expect dysfunctional nitrergic signaling to have broad involvement in neurodegenerative disease.

There is increasing evidence that chronic cerebral hypoperfusion (as a result of a cerebrovascular dysfunction) and microvascular abnormalities within the brain could contribute to Alzheimer's disease (Marlatt and others 2008; Aliev and others 2009; de la Torre 2009). Hypoperfusion leads to increased oxidative stress associated with atherosclerosis, ischemia/reperfusion conditions, and other hypertensive disorders (Lee and Griendling 2008; Higashi and others 2009; Kurauchi and others 2009; Steinert and others 2009).

Common risk factors for the sporadic prevalent form of AD are hypertension, hypercholesterolemia, ischemic stroke, or diabetes (Hamel and others 2008). Hypoperfusion and enhanced ROS generation in AD (Sultana and others 2009; Sultana and others 2010) could therefore facilitate inflammation and iNOS expression. For instance, in AD, Aβ causes a profound vasoconstriction of human cerebral arteries, generating a proinflammatory stimulus that is accompanied by generation of vasoconstrictors such as PGE_2 and $PGF_{2\alpha}$ (Townsend and others 2002). The vascular cell adhesion molecule–1 (VCAM-1), a marker molecule indicating endothelial activation, has increased plasma levels in late-onset AD, further suggesting involvement of an endothelial dysfunction (Zuliani and others 2008). Figure 5 depicts the potential mechanisms by which a vascular dysfunction might be involved in the pathology of neurodegenerative diseases. In mouse cerebral circulation, $A\beta_{1\text{-}40}$ produced a significant vasoconstriction that was reversed by application of the antioxidant enzyme SOD, implying the direct involvement of free radical production (Niwa and others 2001).

The proangiogenic vascular factor VEGF is increased in brain and cerebrospinal fluid of AD patients (Tarkowski and others 2002; Yang and others 2004); it is proinflammatory, activates microglial cells via the Flt-1 receptor subtype (Ryu and others 2009), and interacts with β-amyloidogenesis (Burger and others 2009), contributing to the pathology of AD. Activated microglial generates excessive amounts of reactive oxygen species via NADPH oxidase (Cheret and others 2008), as well as NO via iNOS expression (Moncada & Bolanos 2006; Kurauchi and others 2009). Similar inflammatory pathways and cerebrovascular dysfunction contribute to the neurodegeneration of dopaminergic neurons in PD (Miller and others 2009; Nanhoe-Mahabier and others 2009).

However, it is still unclear whether the described vascular changes are early or downstream pathological events and how the detected systemic microvascular alterations relate to cerebrovascular and neuronal pathologies in the AD brain. In this context, blood markers of microvascular pathology (i.e., Flt-1, VEGF, PGE_2, and $PGF_{2\alpha}$) measured in plasma or serum may provide a clinically easily accessible tool for screening, detection, or prediction of neurodegenerative pathologies.

Conclusion

Nitric oxide plays multiple roles in the nervous system. Under physiological conditions, it contributes to regulating proliferation, survival, and differentiation of neurons. NO is involved in synaptic activity, neural plasticity, and memory function; it exerts long-lasting effects through regulation of transcription factors and modulation of gene expression. Physiological signaling such as regulation of neuronal excitability can be mediated via the classical cGMP/PKG pathway, and voltage-dependent potassium channels seem to be the major target to be regulated in a homeostatic fashion, but generation of RNS also carries out modifications of critical cysteine residues in proteins, including S-nitrosylation or nitrotyrosination. When physiological control of this signaling fails, pathological effects of NO and other RNS undoubtedly lead to or are involved in neuroinflammation and neurodegeneration, such as in AD, ALS, PD, MS, and HD. Neurons appear particularly vulnerable to the effects of nitrosative stress. Susceptibility to NO and peroxynitrite exposure may depend on factors such as the intracellular antioxidants and stress resistance signaling pathways. Thus, the significance of NO and its redox signaling and modulation of the adaptive cellular stress responses, including cerebrovascular dysfunction in neurodegenerative diseases, requires further research to develop predictive means to deal with the increasing numbers of age-related neuropathological conditions.

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