Why is nitric oxide important for our brain?

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Summary

The freely diffusible gaseous compound nitric oxide (NO) has been shown to be an important messenger in many organ systems throughout the body, and particularly in the central nervous system (CNS).
The importance of NO as an intermediary in cell communication in the brain is highlighted by the fact that the excitatory amino acid glutamate, the most abundant CNS neurotransmitter, is an initiator of the reaction that forms NO.
Because of its numerous physiological and pathophysiological roles, the impact of NO on clinical medicine is developing. NO can act as a "double-edged sword" and it has been demonstrated that clarification of the dual effect of NO might have implications for clinical medicine, and could lead to the emergence of therapeutic opportunities. Accordingly, NO was proclaimed "Molecule of the Year" in 1992 by the journal *Science*, while discovery of the pathways and roles of NO was acknowledged with the Nobel Prize in 1998.
Additionally, the ubiquity of NO in the CNS implies that drugs designed to modify the biological activity of NO may have distinct effects. Thus, further clinical applications of NO, of its analogs or of newly developed NOS inhibitors are forthcoming. The therapeutic challenge would be to succeed in manipulating the NO pathways selectively.

KEY WORDS: central nervous system/brain, neurology, neurotoxicity, nitric oxide

Introduction

There is a growing body of evidence that nitric oxide (NO), a ubiquitous gaseous cellular messenger, plays significant roles in a variety of neurobiological processes. Several functions of this regulatory molecule have been identified in the nervous system, in the process of endothelium-dependent vasodilatation (Michell et al., 2004; Duncan and Heales, 2005; Stojanović et al., 2003, 2004), in neurotransmission (Yamamoto et al., 2015; Yassin et al., 2014), and in host-defense mechanisms (Boje, 2004; Akyol et al., 2004). The results of various studies have shown that in the central nervous system (CNS) NO expresses not only cytoprotective but also cytotoxic effects (Boje, 2004; Akyol et al., 2004; Colasanti and Suzuki, 2000). The list of pathological conditions in which NO has been shown to be an important mediator is increasing and alterations of the NO system could be implicated in a wide variety of neurological diseases (Colasanti and Suzuki, 2000; Džoljić et al., 2005; Nakamura et al., 2010a). NO was proclaimed "Molecule of the Year" for 1992 by the journal *Science*, and six years later the Nobel Prize in Physiology or Medicine was awarded to scientists who had discovered NO pathways and shed light on the roles of NO (Zhou et al., 2009).
Under physiological conditions, the concentration of NO fluctuates within the range of low values (of the order of magnitude 10^{-8}-10^{-6}) (Tieu et al., 2003). These NO levels are regulated by two constitutive isoforms of the enzyme NO synthase (NOS): neuronal NOS (nNOS) and endothelial NOS (eNOS). In brain ischemia/reperfusion injury, as well as in degeneration processes affecting the CNS, triggered and modulated by glutamate (Glu), NO levels rise rapidly due to hyperactivity of nNOS (Tieu et al., 2003; Hsu et al., 2005). In pathological conditions such as inflammation, the levels of NO produced by inducible NO synthase (iNOS) are temporarily extremely high. Accordingly, NO can act as a "double-edged sword" (Snyder et al., 1993). It has been demonstrated that clarification of the dual effect of NO might have implications for clinical medicine, and could lead to the emergence of therapeutic opportunities (Shen and Johnson, 2010; Nakamura et al., 2010a).
Furthermore, it has been shown that although their genetic underpinnings differ, Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) are all characterized by the untimely death of brain cells (Nakamura and Lipton, 2010). The role of NO as a Janus molecule involved in both cell survival

and cell death is particularly interesting (Calabrese et al., 2009). What triggers cell death in the brain? According to recent results (Nakamura and Lipton, 2010), the answer in some cases is the untimely transfer of NO from one protein to another. It has been shown that NO and related molecules can contribute to either nerve cell death or nerve cell survival. However, these new findings reveal that NO can actually be transferred from one protein to another in molecular pathways that lead to cellular suicide. This fact can be used to better diagnose and treat diseases like Parkinson's, Huntington's or Alzheimer's disease (Džoljić et al., 2005; Nakamura and Lipton, 2010).

The main roles of nitric oxide in the brain

Nitric oxide binds to guanylyl cyclase, the cyclic guanosine-monophosphate (cGMP)-producing enzyme which is a soluble NO receptor, and through cGMP-mediated signaling cascades it expresses its modulating effects either as a post- or a pre-synaptic retrograde messenger (Wang et al., 2005). As a retrograde neurotransmitter, NO activates the cGMP-dependent protein kinase G (PKG) pathway which phosphorylates synaptophysin, essential for fusion of Glu-containing granules with the membrane of presynaptic nerve endings. This potentiates and facilitates Glu-ergic neurotransmission, thus making NO the neuromodulator of excitatory neurotransmission (Wang et al., 2005). NO also acts on inhibitory gamma-aminobutyric acid (GABA)-ergic synaptic transmission. Recent studies have demonstrated its actions, through cGMP-dependent pathways, on ion channels and ion exchangers with directly modulating effects on membrane excitability (Yamamoto et al., 2015). Furthermore, Yassin at al. (2014) have shown that NO signaling modulates synaptic inhibition in the superior paraolivary nucleus via cGMP-dependent suppression of a potassium/chloride co-transporter. Although, through this effect at post-synaptic level, NO acts as a reducer of strength of inhibition, this in turn enables fine tuning of information processing (Yassin et al., 2014).
Soon after its identification as an endothelium-derived relaxing factor and neuromodulator, NO emerged as a possible mediator of neurovascular coupling. Neurovascular coupling is an active mechanism through which vessel diameter is enlarged in response to increasing metabolic demands imposed by neuronal activity; it is of vital importance in preserving the structural and functional integrity of the brain. NO, due to its peculiar properties – it is a potent vasodilator, released during enhanced neuronal activity resulting from Glu-ergic activation – is well suited to mediate the coupling between neuronal activity and cerebral blood flow (Girouard and Iadecola, 2006).

Neurological disorders and nitric oxide

Brain ischemia

In brain ischemia-reperfusion injury, the role of NO is more complex than in other parts of the body. NO formation is initially increased and has a protective function, inducing collateral perfusion as a result of the powerful stimulatory effect of NO on vasodilatation and angiogenesis (Su et al., 2014).
As well as NOS inhibitors, NO donors also induce neuroprotective effects. Indeed, researchers have demonstrated that the neuroprotective cerebrovascular activity induced by several NO donors in models of experimental stroke is in part due to their vasodilator activity and hemodynamic effects (Greco et al., 2007; Khan et al., 2006).

Seizures

Cytotoxicity in experimental models of seizure seems to be due to release of Glu, causing an overstimulation of NMDA receptors, leading to prolonged release of NO. It is likely that excessive NMDA receptor activation, with the consequent increase in intraneuronal Ca^{2+} through Ca^{2+}/calmodulin-regulated NOS, enhances the neurotoxicity of Glu through the further release of NO (Hofmann et al., 2006).

Memory disorders

Since NO is the retrograde messenger responsible for increasing the synaptic efficiency of presynaptic Glu-ergic neurons in the induction of long-term potentiation (LTP), a reduction of NO could explain the impaired ability of patients with AD to learn new information. This actually applies not only to AD, but to all neurodegenerative diseases, in which LTP is usually impaired (Puzzo et al., 2005). Amyloid-beta peptides impair synaptic transmission in the hippocampus in an NO-dependent manner (Puzzo et al., 2005).

Neurodegeneration

It has been proposed that overproduction of NO could contribute to cell death in the nervous system, while inhibition of NOS could be protective against neurotoxicity. Consistent with the primary role of NMDA receptors in driving NO synthesis in the CNS, NMDA receptor overactivity has been reported in numerous neurodegenerative conditions, including HD, AD, PD amyotrophic lateral sclerosis (ALS), as well as in stroke (Džoljić et al., 2005).
Recent evidence suggests that neurotoxic mechanisms may play a role in the etiology of PD predominantly. Likewise, selective nNOS inhibitors exert protection, which suggests that they might be used as novel therapeutic strategies for neuroprotection in PD (Džoljić et al., 2005).

Neurotoxicity

Recent results have shown that NO, through nitrosylation mechanisms, can have anti-apoptotic effects,

given that it can inhibit the activity of caspase-3. However, in some conditions, caspase-3 can transfer NO to the protein XIAP (which is normally anti-apoptotic), and consequently change its function. In particular, it has been reported that the protein XIAP is altered in the brains of patients with neurodegenerative diseases compared with the brains of healthy subjects (Nakamura et al., 2010a).

Calculating, through a new version of the Nernst equation, the redox potential of the two proteins, it is possible to predict, *in vivo*, the probability that the transnitrosylation reaction occurs from caspase-3 to XIAP. In practice, if there is a greater transfer of NO from caspase-3 to XIAP, then the latter loses its functionality (Nakamura et al., 2010b). This power of prediction might allow doctors to diagnose neurodegenerative disorders like PD or AD earlier (Džoljić et al., 2005). In addition, other data have shown the potential role of GABAergic striatal interneurons expressing somatostatin, neuropeptide Y, NADPH diaphorase and NOS in compensation for dopamine loss in experimental or idiopathic PD (Ibáñez-Sandoval et al., 2010). Recent results have demonstrated that nNOS inhibition attenuates the development of L-DOPA-induced dyskinesia in hemi-parkinsonian rats (Takuma et al., 2012), thus confirming the pathogenic effects of nNOS.

Moreover, new findings have provided further evidence of an anti-dyskinetic effect of NOS inhibitors. This effect was seen under both acute and chronic L-DOPA treatment. L-DOPA treatment also revealed an overexpression of nNOS in the frontal cortex and striatum (Padovan-Neto et al., 2011). These results are in agreement with findings that L-DOPA-induced rotation differs between acute and chronic treatment. The authors concluded that the "effect of the NOS inhibitor conceivably relied on the L-DOPA structural modifications in the Parkinsonian brain" and that "these data provided a rationale for further evaluation of NOS inhibitors in the treatment of L-DOPA-induced dyskinesia" (Padovan-Neto et al., 2011).

As mentioned, there is substantial evidence that NO is involved in the pathogenesis of neurodegenerative conditions such as AD and PD. The mitochondrion (in particular the electron transport chain) seems to play an important role in the deleterious effects of NO. Cellular and mitochondrial antioxidants, such as glutathione and ubiquinone, are involved as well (Duncan and Heales, 2005). Precisely, damage to the mitochondrial electron transport chain has been suggested to be an important factor in the pathogenesis of a range of neurological disorders, such as PD, AD, MS, stroke and ALS (Džoljić et al., 2005). According to the officially-accepted hypothesis regarding the role of oxidative stress in the etiology of neurodegeneration, particularly in PD, reactive oxygen species (ROS), in particular superoxide anion (O^{2-}), NO, peroxynitrite anion ($ONOO^{-}$) and hydroxyl radical ($OH^{\cdot}$), are involved in cell death. They damage the basic structures of the neuron, including the mitochondria (by reacting with their various transporters), by activating cascades of caspases, and by reacting with caspase substrates and cell membrane fragments and DNA, leading to permanent and irreversible cell damage and death (Mazzio and Soliman, 2004; Dehmer et al., 2004; Wang et al., 2003).

In addition, increased levels of 3-nitrotyrosine are found in Lewy body formations in PD, indicating NO-induced neuronal injury (Džoljić et al., 2005). Analyses of NOS mRNA expression in humans revealed a correlation between NO system fluctuations in basal ganglia and dopaminergic system changes (Džoljić et al., 2005; Carreras et al., 2004). In addition, basal ganglia damage has been linked to oxidative stress (Carreras et al., 2004).

Activated nNOS and iNOS both cause tissue damage by increased production of NO accompanied by an increase in the concentration of peroxynitrite, the most destructive ROS. More precisely, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes neurotoxicity mediated by nNOS-derived NO, primarily damaging dopaminergic neurons located strictly in the striatum, while iNOS-derived NO predominantly affects nigrostriatal pathway neurons. Injury induced by nNOS-derived NO might increase iNOS activity and gliosis-related deleterious effects (Przedborski et al., 2000).

It has also been suggested that neutrophils express nNOS and confer nitrosative stress on neurons involved in PD neurodegeneration (Gatto et al., 2000). Additional studies have shown that blood levels of mitochondrial complex I and sometimes complex IV in PD are slightly and constantly reduced due to oxidative stress, and have also shown compensatory increases in antioxidant enzymes (e.g. SOD, catalase). Lower activity of complex I could be detected in peripheral blood thrombocytes, which are potential PD biomarkers (Džoljić et al., 2005).

Accordingly, there is growing body of evidence for an involvement of NO in various pathophysiological mechanisms underlying neurological disorders in humans. All of these conditions have a multifactorial etiology in which different interactions and overlapping biochemical events are the factors determining disease outcome. The fact that, among the myriad processes and factors involved, oxidative stress and NO have a key role in neurodegenerative processes suggests that they could be potential targets of novel therapeutic strategies (Foley and Riederer, 2000; Džoljić et al., 2005)

New results, more precisely, show signaling pathways underpinning synapse loss in PD. Paracrine/retrograde NO action activates the soluble guanylyl cyclase/PKG pathway and RhoA/Rho kinase (ROCK) signaling resulting in loss of synapses (Kanao et al., 2012). In addition, NO, through the cGMP pathway, regulates the activity of transcriptional factor FoxO and alters dopaminergic neuron survival, potentiating its neurotoxicity (Kanao et al., 2012). Moehle et al. (2012) revealed the role of iNOS-derived NO in PD neurodegeneration, showing effects of microglial secretion of iNOS-derived NO on leucine-rich repeat kinase 2 (Moehle et al., 2012). Another neuroprotective antioxidant protein, peroxiredoxin 2, is also S-nitrosylated by NO-induced nitrosative stress in a similar manner, which leads to loss of the important defensive cell mechanism neces-

sary for maintaining structure, functionality and survival of the neuron (Fang et al., 2007). Thus, redox reactions triggered by excessive levels of NO can contribute to protein misfolding, the hallmark of a number of neurodegenerative disorders, including PD and AD. Similarly, S-nitrosylation of parkin disrupts its E3 ubiquitin ligase activity, and thereby affects Lewy body formation and induces neuronal cell death (Nakamura et al., 2010a; Nakamura et al., 2011; Meng et al., 2011). Additionally, Gao et al. have found nitrated α-synuclein as a component in Lewy bodies in PD mice. These results point to NO-induced nitrosative stress as an important if not the main factor in the initiation, maintenance and progression of the neuroinflammation-induced more common sporadic form of PD (Gao et al., 2008). Moreover, defects in the mitochondrial respiratory chain and extensive S-nitrosylation of mitochondrial complex I were detected prior to the dopaminergic neuronal loss. The mitochondrial injury was prevented by treatment with L-N6-(I-iminoethyl)-lysine, an iNOS inhibitor, suggesting that iNOS-derived NO is associated with the mitochondrial impairment (Choi et al., 2009). S-nitrosylation of dynamin-related protein 1, proven in AD, remains disputable in PD (Nakamura et al., 2010a; Bossy et al., 2010).

Later genetic studies mapped single nucleotide polymorphisms of NOS genes (*NOS1*, *NOS2A* and *NOS3*) associated with higher production of NO found in PD (Hancock et al., 2008). The results of the study by Durrenberger et al. (2012) highlighted the roles of eNOS confirming the genetic findings. Thus, increased levels of eNOS-positive cells were found in the substantia nigra of an MPTP mouse model of PD (Durrenberger et al., 2012).

Given the dual role of NO, neuroprotective and neurotoxic, it has been pointed out that the interrelation between constitutive forms of NOS and iNOS in cells containing both types of this enzyme (e.g. astrocytes and endothelial cells) is achieved by the NO itself through modulation of NOS activity (Colasanti and Suzuki, 2000). This further underlines the need for caution in manipulating the NO system, bearing in mind the fact that iNOS activators regulate intracellular NO levels by direct and rapid modulation of nNOS and eNOS activities, while iNOS inhibitors increase the activity of constitutive NOS forms.

The designation “nitric oxide” actually refers to the reduced, negatively charged form of the molecule, while the opposite, oxidized, positively charged form is the nitrosonium ion. Accordingly, oxidized NO, in the form of the nitrosonium ion, reacts with NMDA receptors to block neurotransmission (Snyder et al., 1993). Indeed, the oxidized, positively charged form can bind to the NMDA receptor complex (Snyder et al., 1993), resulting in changes in sensitivity of this complex to the actions of Glu. Thus, NO exerts negative feedback to the NMDA receptor, reducing intracellular Ca^{2+} with a consequent decrease in NOS activity (Snyder et al., 1993; Colasanti and Suzuki, 2000). This would be the good side of the “double-edged sword”.

In addition, some novel studies have shown that hydrogen sulfide and carbon monoxide are involved in an interactive interplay with NO in producing neuromodulatory and other effects in the brain. This puts them together with NO on the list of potential novel therapeutic targets (Zhang and Bian, 2014).

Concluding remarks

Nitric oxide can be conceived as a double-edged sword. On the one hand, in the low, constitutive mode, it has beneficial effects, mediating and protecting neuronal activity. On the other, in the high, unregulated mode, it is an indiscriminately damaging molecule. The possibility that NO can exist in distinct oxidation/reduction states with different biological actions provides further elucidation of mechanisms underlying the neuroprotective and neurotoxic effects of NO.

For neurologists, there is tremendous interest in the involvement of NO in the mediation of neurotoxicity and its role in cerebrovascular diseases, seizures, neurodegenerative disorders and pain. It is suggested that modulations of the NO pathway may become useful and important in the development of new therapeutic strategies for various neuropsychiatric diseases.

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