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The physiology and pathophysiology of nitric oxide in the brain

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Abstract

Nitric oxide (NO) is a molecule with pleiotropic effects in different tissues. NO is synthesized by NO synthases (NOS), a family with four major types: endothelial, neuronal, inducible and mitochondrial. They can be found in almost all the tissues and they can even co-exist in the same tissue. NO is a well-known vasorelaxant agent, but it works as a neurotransmitter when produced by neurons and is also involved in defense functions when it is produced by immune and glial cells. NO is thermodynamically unstable and tends to react with other molecules, resulting in the oxidation, nitrosylation or nitration of proteins, with the concomitant effects on many cellular mechanisms. NO intracellular signaling involves the activation of guanylate cyclase but it also interacts with MAPKs, apoptosis-related proteins, and mitochondrial respiratory chain or anti-proliferative molecules. It also plays a role in post-translational modification of proteins and protein degradation by the proteasome. However, under pathophysiological conditions NO has damaging effects. In disorders involving oxidative stress, such as Alzheimer's disease, stroke and Parkinson's disease, NO increases cell damage through the formation of highly reactive peroxynitrite. The paradox of beneficial and damaging effects of NO will be discussed in this review.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; Aβ, amyloid β-peptide; BBB, blood–brain barrier; BH4, tetrahydrobiopterin; C/EBP, CCAAT/enhancer-binding protein; cGMP, cyclic guanosine-3′,5′-monophosphate; CNS, central nervous system; CREB, Ca^{2+}/cAMP response element-binding protein; CSF, cerebrospinal fluid; DA, dopamine; EAE, encephalomyelitis; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal regulated protein kinases; FAD, flavin adenine dinucleotide; FMN, flavin adenine mononucleotide; GC, guanylate cyclase; GS, glutamine synthetase; GSH, reduced glutathione; GSNO, *S*-nitroso-L-glutathione; HAP-1, huntingtin-associated protein; Hb, hemoglobin; HD, Huntington's disease; HSP70, heat shock protein 70; 5-HT, serotonin; htt, huntingtin; INFγ, interferon gamma; iNOS, inducible nitric oxide synthase; IRF-1, interferon regulatory factor-1; Iκβ, NF-κ(inhibitor; JNK, c-jun N-terminal kinase; L-Arg, L-arginine; MAPKs, mitogen activated protein kinases; metHb, methahemoglobin; MnSOD, manganese superoxide dismutase; MS, multiple sclerosis; mtNOS, mitochondrial nitric oxide synthase; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NE, noradrenalina; NF-κ, (nuclear factor κ(; NMDA, *N*-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; $^{\bullet}NO_2$, nitrite radical; NO^+ nitrosonium ion; NO_2^-, nitrites; NO_3^-, nitrates; NOS, nitric oxide synthase; NRF-1, nuclear respiratory factor 1; $O_2^{\bullet -}$, superoxide anion; $OH^{\bullet}$, hydroxyl radical; $ONOO^-$ peroxynitrite; $ONOOCO_2^-$, nitrosoperoxycarbonate; PC12, pheochromocytoma cells; PD, Parkinson's disease; PI3K, phosphatidylinositol 3-kinase; PKA, cyclic-AMP dependent protein kinase; PKC, protein kinase C; PSD-95, postsynaptic density protein-95; ROS, reactive oxygen species; SAPK, stress-activated protein kinases; SOD, superoxide dismutase; STAT, signal transducers and activators of transcription; TNFα, tumor necrosis factor alpha; Tyr, tyrosine; VSMCs, vascular smooth muscle cells

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1. Introduction

Nitric oxide (NO) is a gas synthesized by a family of enzymes present in most of the cells of the body. The ubiquitous localization of NO demonstrates its implication in a wide range of physiological process, but it can turn harmful due to its reactivity, mainly with proteins, when involved in pathophysiological processes. The relevance of NO in brain is determined by both the neuronal, glial and vascular physiological effects and its involvement in neurodegenerative diseases, opening the possibility of pharmacological treatments directed to NO metabolic pathways. Since this review is directed toward giving an overview of the roles of NO in brain, we have examined the present knowledge of the synthesis of NO, the biological chemistry of NO and its reactivity with macromolecules, the main cellular effects of NO, the role that NO plays in brain physiology and the pathological involvement of NO in neurodegenerative processes.

2. The nitric oxide synthases

NO is produced by a group of enzymes denominated nitric oxide synthases (NOS). There are four members of the NOS family: neuronal NOS (nNOS), endothelial NOS (eNOS), inducible NOS (iNOS) and mitochondrial NOS (mtNOS). The last one is an isoform of nNOS present in the inner mitochondrial membrane (Elfering et al., 2002). All the NOSs share between 50 and 60% sequence homology (Lamas et al., 1992).

nNOS and eNOS are Ca^{2+}-calmodulin-dependent enzymes constitutively expressed in mammalian cells (Mungrue et al., 2003) that generate increments of NO lasting a few minutes. In contrast, iNOS is Ca^{2+}-calmodulin-independent and its regulation depends on de novo synthesis (Ebadi and Sharma, 2003). iNOS is expressed following immunological or inflammatory stimulation in macrophages, astrocytes, microglia and other cells producing high amounts of NO lasting hours or days (Iadecola et al., 1995) (Fig. 1).

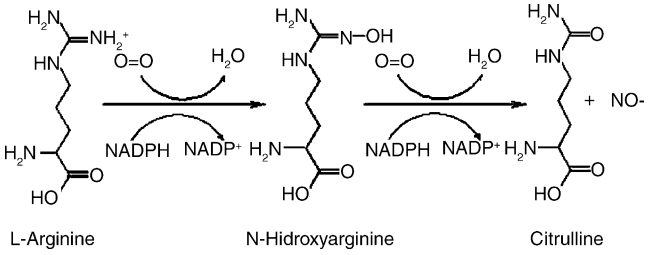

Fig. 1. Synthesis of NO by NOS. L-Arg in the presence of NADPH and O_2 is oxidized to *N*-hidroxyarginine, which is re-oxidized to citrulline producing NO.

All the NOS isoforms have four prosthetic groups: flavin adenine dinucleotide (FAD), flavin adenine mononucleotide (FMN), iron protoporphyrin IX (heme) and tetrahydrobiopterin (BH4). FAD, FMN and heme are involved in the redox reactions leading to the synthesis of NO. Heme and BH4 comprise the scaffold that maintains the substrate channel. For this reason BH4 is absolutely necessary for NOS activity (Mayer et al., 1991; Tayeh and Marletta, 1989; Wei et al., 2003).

NOS structure shows two biodomains working independently. The first one consists of a C-terminal reductase domain containing sites to bind NADPH, FAD, FMN and Ca^{2+}-calmodulin. The binding of Ca^{2+}-calmodulin triggers the activation of the enzyme opening a gate for the electron flux into the active center of the NOS (Abu-Soud and Stuehr, 1993). The N-terminal domain has oxygenase activity containing sites to bind BH4, heme and L-arginine (L-Arg) (Stuehr, 1999).

L-Arg is used by NOS to produce NO and citrulline in a process requiring NADPH and O_2. L-Arg is a semi-essential amino acid since it can be synthesized from glutamate (Wu and Morris, 1998) or produced by recycling citrulline in the citrulline-NO cycle with argininosuccinate synthetase (AS) and argininosuccinate lyase (AL) (Wiesinger, 2001). L-Arg can be taken through a cationic pH- and sodium-independent carrier (Deves and Boyd, 1998).

2.1. eNOS

Human eNOS (NOS III) is codified by a gene located in the 7q35–36 chromosome, releasing a 135 KDa protein with 1294 amino acids that is mainly expressed in the endothelium (Marsden et al., 1993). It has also been found in other cell types, such as human neuronal cells (Abe et al., 1997), human and rat astrocytes (Colasanti et al., 1998; Iwase et al., 2000), human T-cells (Reiling et al., 1996), human bone marrow cells, human osteoblasts and osteoclasts (Helfrich et al., 1997), human dermal fibroblasts (Wang et al., 1996), rat cardiac myocytes (Balligand et al., 1995), rat hepatocytes (Zimmermann et al., 1996) and rabbit colon intestinal cells (Xue et al., 1994).

This enzyme is localized to caveolae by myristolation of glycine-2 and the palmytoylation of cysteine-15/cysteine-26, allowing its binding to caveolin-1 and the inhibition of the eNOS activity (Busconi and Michel, 1993). Its activation depends on phosphorylation by phosphatidylinositol 3-kinase (PI3K)/Akt (Datta et al., 1999) and the binding of Ca^{2+}-calmodulin, which induces allosteric changes (Garcia-Cardena et al., 1997). The C-terminal reductase domain presents a 50 amino acid motif, which can block binding to Ca^{2+}-calmodulin. Ca^{2+} splits the eNOS from caveolin-1 and shifts the auto-inhibitory element from the reductase site, allowing access to calmodulin (Daff, 2003). In fact, when this motif is cut-off, eNOS is no longer regulated by Ca^{2+} and its behavior is similar to that of iNOS (Wu, 2002) (Fig. 2).

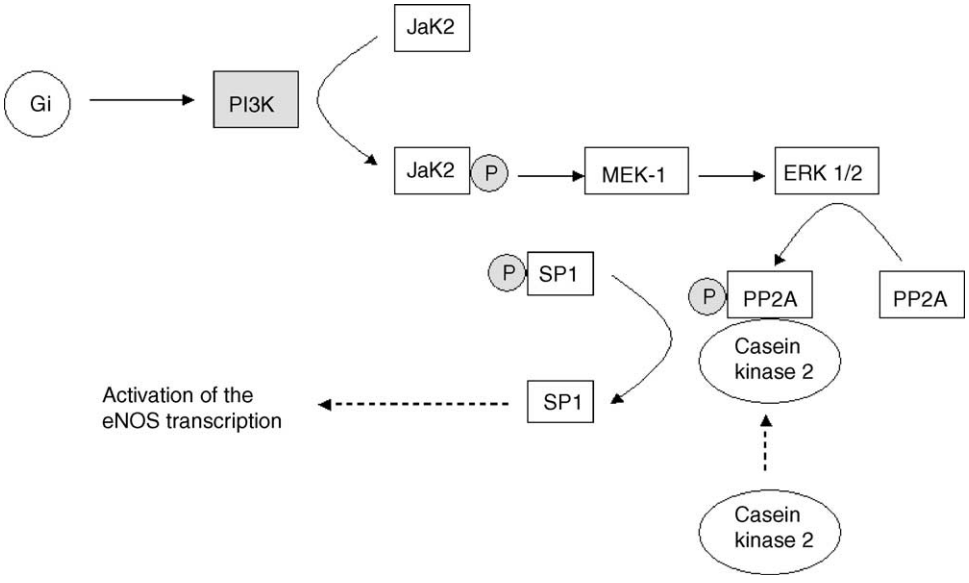

Fig. 2. Transcriptional control of eNOS. Gi proteins activate the PI3K, which phosphorylates Jak2. This protein activates MEK-1 and then ERK 1/2. ERKs phosphorylate PP2A phosphorylase, which binds the casein kinase 2, forming a dimer. This dimer dephosphorylates and induces the translocation of SP1 to the nucleus. The SP1 factor can trigger the transcription of eNOS. Through this pathway, the signals that activate eNOS are also responsible for its synthesis.

Table 1
Different stimulus that induces eNOS transcription

Agent	Effect	Mechanism	Reference
Estrogens	+	–	Weiner et al. (1994)
Glucose	+	–	Cosentino et al. (1997)
TNFα	–	May act through transcription or message stability	Nishida et al. (1992)
TGF	+	Transcriptional activation acting on promotor	Inoue et al. (1995)
IFN α/β	+	Increase expression of eNOS mRNA	Kaku et al. (1997)
LPS	±	–	Bucher et al. (1997), Liu et al. (1996)
Oxidized LDLs (low concentrations)	+	Early transcriptional inhibition and post-transcriptional mRNA destabilization	Liao et al. (1995)
Oxidized LDLs (high concentrations)	–	Early transcriptional inhibition and post-transcriptional mRNA destabilization	Liao et al. (1995)
Shear stress	+	Via a putative shear stress-responsive element (6 bp core sequence 5′-GAGACC-3′) in its promoter	Marsden et al. (1993)
Hyperthyroidism	+	–	Colin et al. (1997)
Atherosclerosis	+	–	Kanazawa et al. (1996)
Amyotrophic lateral sclerosis	+	–	Abe et al. (1997)
Hypothyreosis	–	–	Colin et al. (1997)
Hypertension	–	Local production of cytokines such as TNF-α from macrophages	Crabos et al. (1997)
Hypoxia	±	Activation of transcription by AP-1, down-regulation by decreased rate of transcription and a destabilization of the mRNA	McQuillan et al. (1994), Hoffman et al. (2001), Liao et al. (1995)
Ischemia	+	–	Zhang et al. (1994)

Rapid eNOS regulation is elicited by physiological stimuli, such as shear stress (Dimmeler et al., 1999) and 17β-estradiol actions (Chen et al., 1999). Under these conditions eNOS is phosphorylated by Akt on human serine-1177 (bovine serine-1179), enhancing calmodulin binding, which increases the activity of the enzyme three-fold (Wu, 2002).

eNOS expression can be also regulated. One example is the up-regulation of eNOS expression by shear stress acting on a putative shear stress-responsive element (6 bp core sequence 5′-GAGACC-3′) in its promoter (Marsden et al., 1993). Furthermore, some compounds, such as TNFα, down-regulate eNOS expression (Nishida et al., 1992) (Table 1).

2.2. *iNOS*

In the immune and glial cells there is an inducible isoform of NOS (iNOS or NOS II) (Galea et al., 1992; Lee et al., 1993) whose gene is located in chromosome 17 (Lowenstein et al., 1992). This isoform has been reported in other cells, such as human hepatocytes, sinusoidal and endothelial cells (Mohammed et al., 2003), rat vascular smooth muscle cells (Kanno et al., 1993) and rat liver and kidney cells (Bucher et al., 1997). It is independent of Ca^{2+} due to tight constitutive interaction with calmodulin (Cho et al., 1992), and it is also not regulated by Akt phosphorylation (Fulton et al., 1999). It is regulated transcriptionally by inflammatory stimuli, such as interferon regulatory factor-1 (IRF-1) (Kamijo et al., 1994) and nuclear factor κβ (NF-κβ) (Xie et al., 1994). As with other NOS, the activation of iNOS depends on dimerization triggered by the incorporation of the heme group into the oxygenase domain (Panda et al., 2002). The activation is enhanced by BH4 and L-Arg binding. The time observed to produce NO varies depending on the experimental procedure, i.e., this time is from 10 to 24 h after in vivo stimulation with *Fusobacterium nucleatum* in a murine model (Kato et al., 2001), whereas 3 days are required with human fetal astrocyte and microglial cells challenged with interleukine-1 (IL-1) or INFγ (Ding and Merrill, 1997) (Fig. 3).

When there is a substrate or BH_4 deficiency, superoxide anion ($O_2^{\bullet -}$) will not be added to L-Arg, resulting in a decrease of the NO production but an increase of $O_2^{\bullet -}$ (Xia and Zweier, 1997). Although all NOS isoforms can potentially produce $O_2^{\bullet -}$, iNOS is the most likely to produce $O_2^{\bullet -}$ in vivo due to L-Arg depletion during inflammation (Xia and Zweier, 1997) (Fig. 1).

Most of the studies on iNOS transcriptional control have been carried out in rodents, although similar control is suspected for human iNOS, as the human *iNOS* gene contains sequences homologous to mouse proximal and distal promoter regions (Rao, 2000). The promoter region of the mouse *iNOS* gene contains binding sites for transcription factors such as NF-κβ as well as c-Jun/c-Fos heterodimers, known as activator protein-1 (AP-1), CCAAT/enhancer-binding protein (C/EBP), Ca^{2+}/cAMP response element-binding protein (CREB) and the signal transducers and activators of transcription (STAT) family (Marks-Konczalik et al., 1998; Hecker et al., 1999).

NF-κβ is normally found in the cytoplasm bound to its inhibitor (Iκβ). Iκβ is phosphorylated under inflammatory stimuli, then NF-κβ is released and it moves to the nucleus, triggering the iNOS transcription (Rao, 2000). However, lipid peroxidation throughout its end-product 4-hydroxy-nonenal (HNE) inhibits iNOS expression by preventing Iκβ degradation (Lee et al., 2004).

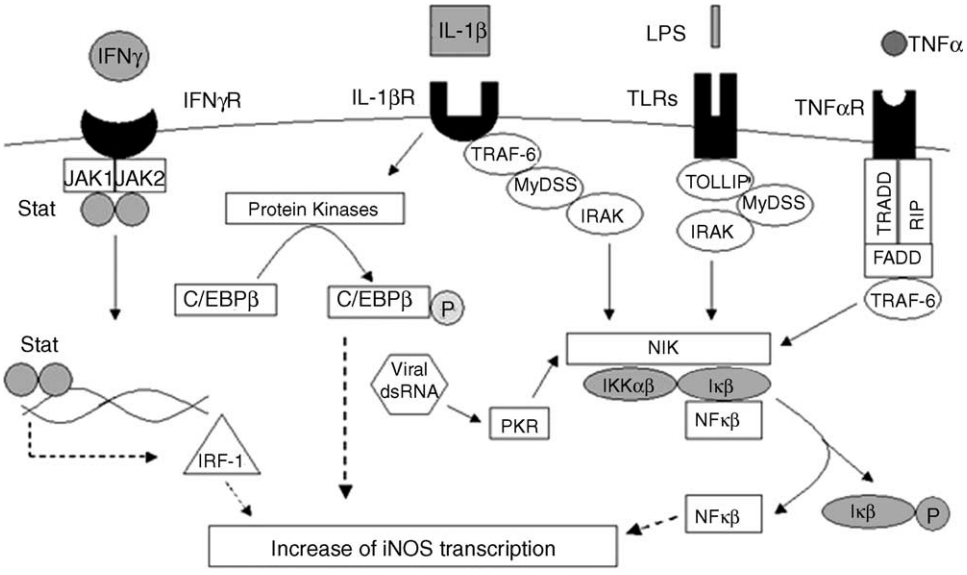

Fig. 3. Activation of iNOS transcription by inflammatory stimulation. IFNγ up-regulates the iNOS transcript through the JAK/stat pathway by IRF-1 activation. IL-1β, LPS and TNFα activate different protein–protein or kinase intracellular cascades inducing the nuclear translocation of C/EBPβ or NF-κβ. Viral challenge is also linked to the translocation of NF-κβ by PKR activation.

C/EBP can act synergistically with NF-κβ to induce iNOS expression (Hecker et al., 1997). C/EBP is phosphorylated by cyclic-AMP dependent protein kinase (PKA) (Chinery et al., 1997) and moves to the nucleus (Hecker et al., 1999). Therefore, it has also been noted that cAMP up-regulates rat iNOS gene transcription (Eberhardt et al., 1996), presumably to be mediated by the activation of PKA.

Depending on the stimuli and the cell type, other signaling pathways can induce the expression of iNOS, such as protein kinase C (PKC), tyrosine kinase, janus kinases (Jak), raf-1 protein kinase and mitogen activated protein kinases (MAPKs), or alternatively they can inhibit the expression of iNOS, such as protein tyrosine phosphatases (Lahti et al., 2002; Jeohn et al., 2002).

It has also been proposed that hypermethylation is a transcriptional inhibitory mechanism of iNOS gene promoter since in vitro methylation inhibits binding of NF-κβ to this element (Yu and Kone, 2004). iNOS can be also regulated at the post-translational level by preventing the dimerization of iNOS as occurs with the inducible NOS-associated protein (NAP 110) (Ratovitski et al., 1999), or by modifying the sub-unit heme activity by coordination of carbon monoxide with heme iron, resulting in a decrease of NO synthesis (Prabhakar, 1998) (Table 2).

Table 2
Different stimulus that induces iNOS transcription

Agent	Effect	Mechanism	Reference
LPS	+	NF-κβ activation by IKβ phosphorylation	Huang et al. (1996)
Cytokines (such as IL-1), INFγ and TNFα	+	NF-κβ activation by IKβ phosphorylation, INFγ also acts via the Jak-STAT signaling pathway	Marks-Konczalik et al. (1998), Rao (2000)
Oxidative stress (H_2O_2 and 4-hydroxyhexenal (HHE))	+	H_2O_2 increases IKβ degradation and activation of the NF-κβ pathway; HHE inhibits IKβ degradators, activating NFkβ in endothelial cells	Han et al. (2002), Lee et al. (2004)
PKCδ	+	iNOS mRNA stabilization	Carpenter et al. (2001)
nNOS	±	nNOS has been shown to regulate iNOS translation by NF-κβ inhibition in glia; nNOS is also located in nucleus and it has been proposed that could be a mechanism to control iNOS transcription	Togashi et al. (1997), Yuan et al. (2004)
Lactacystin	−	Prevents iNOS induction by blocking IKβ degradation	Musial and Eissa (2001)
Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP)	−	Inhibition of interferon regulatory factor-1 (IRF-1) expression	Leceta et al. (2000)
Transforming growth factor beta-1 (TGFβ)	−	iNOS mRNA destabilization; it also modifies IRF-1 activation through the activation of nucleases acting on the AU rich sequence	Perrilla et al. (1994), Vodovotz (1997)
Glucocorticoids	−	Induction of IKβ synthesis	Gotoh and Mori (1999)
Hypertension	−	By the increase of TNFα	Alexander et al. (2002)

2.3. nNOS

A constitutive isoform of NOS called neuronal NOS (nNOS or NOS I) is found in neurons. It is expressed in populations of developing (Bredt and Snyder, 1994b) and mature neurons (Cork et al., 1998). nNOS has also been found in rat astrocytes (Arbones et al., 1996), the adventitia of a subset of rat brain blood vessels (Nozaki et al., 1993), rat cardiac miocytes (Xu et al., 1999), rat skeletal myocytes (Kobzik et al., 1994), human lung epithelial cells (Asano et al., 1994), rat *macula densa* (Tojo et al., 1994), human testis (Wang et al., 1997), rat *penile corpora cavernosa*, urethra and prostate (Magee et al., 1996) and human skin (Shimizu et al., 1997). nNOS is Ca^{2+}-dependent like eNOS, and is also regulated through reversible Ca^{2+}-calmodulin binding (Bredt and Snyder, 1994a). The production of $O_2^{\bullet-}$ by nNOS occurs when glutamate receptors are stimulated and the influx of Ca^{2+} is prolonged over time, releasing $O_2^{\bullet-}$, a process that stops after 10–15 min due to the depletion of L-Arg levels (Culcasi et al., 1994) (Fig. 4).

nNOS gene (chromosome 12) is the most complex human gene yet described in terms of promoter diversity. It has about 160 kbp and the open reading frame is made up of 28 exons, the translation starting in exon 2 and ending in exon 29 (Hall et al., 1994). Analysis of the DNA sequence shows that some *cis* elements might regulate its transcription, such as the activator protein-2 (AP-2), the transcriptional enhancer factor-1/MCAT binding factor (TEF-l/MCBF), cAMP response element-binding protein/activating transcription factor/c-Fos (CREB/ATF/c-Fos), nuclear respiratory factor-1 (NRF-1), Ets, nuclear factor-1 (NF-1) and NF-κβ (Hall et al., 1994; Sasaki et al., 2000). Nine different isoforms of the first exons have been identified, denominated 1a–1i (Wang et al., 1999b). Transcription can be initiated from a different first exon driven by distinct promoters producing mRNA transcripts, although all the protein products coming from the different mRNAs will be the same since the initiation codon (ATG) is found in the exon 2 (Wang et al., 1999a). This could be a regulatory mechanism of tissue and cell specificity of nNOS gene expression (Wang and Marsden, 1995).

nNOS shows four different isoforms generated by mRNA splicing (Wang et al., 1999a). nNOSα and nNOSμ are anchored to sub-cellular structures by a PDZ domain, whereas nNOSγ and nNOSβ seem to be cytoplasmatic (Martinelli et al., 2002; Riefler and Firestein, 2001). PDZ motif binds to the postsynaptic density protein-95 (PSD-95) (Brenman et al., 1996a) and/or to the related PSD-93 protein (Brenman et al., 1996b). *N*-Methyl-L-argartate (NMDA) receptors are also known to be associated with PSD-95 (Kornau et al., 1995), thereby explaining the nNOS and NMDA receptor colocalization in the central nervous system (CNS) (Bhat et al., 1995). Other molecules that have been shown to interact with nNOS in skeletal muscle and neuronal cells are some members of the dystrophin family of proteins (Brenman et al., 1995), PIN (Jaffrey and Snyder, 1996), CAPON (Jaffrey et al., 1998) and caveolin-3 (Venema et al., 1997).

nNOS can be also regulated at the post-translational level via phosphorylation by PKA, calmodulin-dependent kinases and PKC (Nakane et al., 1991; Bredt et al., 1991). Expression of nNOS is also under the control of sex hormones, such as 17β-estradiol, which increases nNOS in human neurons (Lee et al., 2003) (Table 3).

2.4. mtNOS

Associated with the inner mitochondrial membrane is a constitutive isoform of NOS called mtNOS (Tatoyan and Giulivi, 1998; Bates et al., 1995). It has been found in rat liver, kidney, lung, testis, spleen, heart, muscle and brain

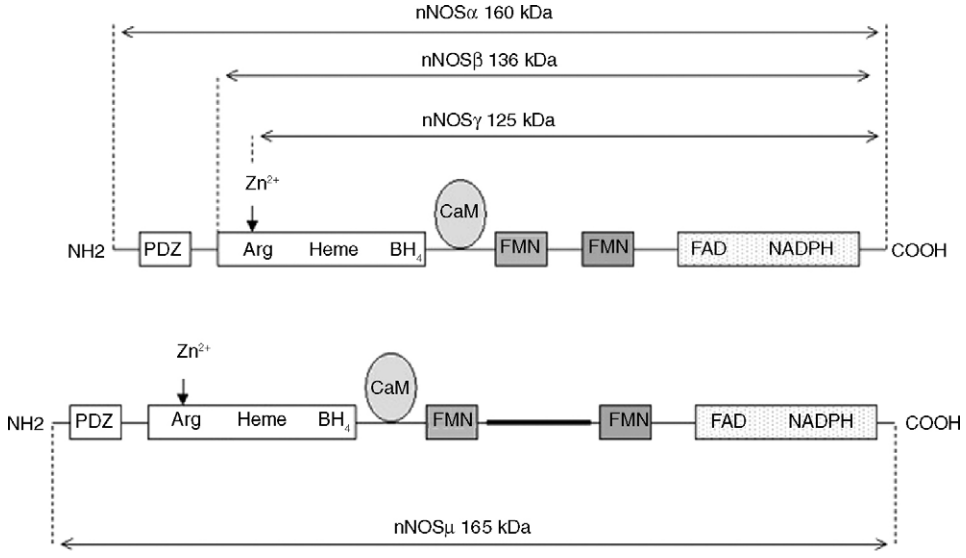

Fig. 4. Isoforms of nNOS. Four major nNOS isoforms have been described. The α, β and γ isoforms differ in the size of the N-terminus. The μ isoform is similar to nNOSα but with a larger sequence between the two FMN domains.

Table 3
Different stimulus that induces nNOS transcription

Agent	Effect	Mechanism	Reference
Hypoxia	+	Enhancement of nNOS mRNA. It could work by the action of hypoxia-induced factors (HIF) on specific *cis* elements, like for iNOS	Shaul et al. (1995), Jung et al. (2000)
High salt concentration	+	Up-regulation of nNOS mRNA in neurons that form the osmoresponsive circuit in the hypothalamo-hypophysal system	Kadowaki et al. (1994)
Estradiol	+	Enhancement of nNOS expression in various tissues of the rat	Ceccatelli et al. (1996)
Corticosterone	−	Decrease of nNOS transcription in rat brain	Weber et al. (1994)
Insulin	+	–	Yuan et al. (2004)
Epidermal growth factor receptor (EGFR) ligands	+	EGF, heparin-binding EGF, TGFα and two alternate splicing forms of the neuregulin gene seems to increase the stability of nNOS mRNA	Boissel et al. (2004)
Hypertension	−	By the increase of TNFα	Alexander et al. (2002)
Amyotrophic lateral sclerosis	+	Maybe through activation of glutamate receptors (mGluRs)	Strong (1999), Catania et al. (2001)
Angiotensin II	+	Angiotensin II is an activator of Akt which activates NOS. Another possibility is the activation of calcium-calmodulin by AT1 receptors	Moreno et al. (2002)
GABA	+	Activation of CREB	Mantelas et al. (2003)

(Elfering et al., 2002). The function of NO in the mitochondria could be related to the regulation of O_2 consumption by inhibiting the cytochrome *c* oxidase (Brown and Cooper, 1994; Cleeter et al., 1994). The modulation of O_2 consumption by mitochondrial NO is transient and reversible because NO is generated in small quantities.

mtNOS has been identified as the nNOSα isoform (Elfering et al., 2002) and it is likely coded by the same *nNOS* gene since nNOS knockout mice do not have mtNOS (Kanai et al., 2001). mtNOS has been reported as having two more post-translational modifications than nNOS, consisting of an acylation by myristic acid and a phosphorylation at the C-terminus (Elfering et al., 2002).

2.5. Alternative NO production

Although NOS is the main NO source, in some special situations this molecule can be synthesized by other mechanisms. NO can be produced by the xanthine oxidase pathway or by H_2O_2 and L-Arg in a non-enzymatic way (Nagase et al., 1997), or by the reduction of nitrites in acid and reducing conditions, as occurs in ischemic processes (Maiese and Boccone, 1995).

3. NO chemistry in biological systems

NO is a molecule with 11 valence electrons, 6 from oxygen and 5 from nitrogen, with an unpaired electron in the last orbital, making NO a free radical ($^{\bullet}NO$). NO can also exist as the nitrosonium ion (NO^+) depending on the cellular redox status (Stamler et al., 1992b). For this reason it is thermodynamically unstable and tends to react with other molecules.

3.1. Nitrite and nitrate formation

NO undergoes various reactions (Eqs. (1)–(3)) in biological fluids resulting in the formation of nitrites (NO_2^-), nitrates (NO_3^-) and peroxynitrites ($ONOO^-$):

$$2NO + O_2 \rightarrow N_2O_4 \xrightarrow{H_2O} NO_2^- + NO_3^- + 2H^+ \quad (1)$$

$$NO + NO_2^- \rightarrow N_2O_3 \xrightarrow{H_2O} 2NO_2^- + 2H^+ \quad (2)$$

$$NO + O_2^{\bullet -} \rightarrow ONOO^- \rightarrow ONOOH \rightarrow \left[\frac{^{\bullet}NO_2}{^{\bullet}OH}\right] \rightarrow NO_3^- + H^+ \quad (3)$$

During the formation of nitrates (Eq. (3)) there are intermediate products such as nitrite radical ($^{\bullet}NO_2$) and hydroxyl radical ($OH^{\bullet}$) that are highly reactive (Beckman and Koppenol, 1996).

3.2. Peroxynitrite formation

NO reacts with $O_2^{\bullet -}$ quickly enough to avoid the action of antioxidant systems, forming peroxynitrite anion ($ONOO^-$) (Eq. (3)) (Beckman et al., 1990). The affinity of $O_2^{\bullet -}$ is higher for NO than for superoxide dismutase (SOD) (Huie and Padmaja, 1993; Cudd and Fridovich, 1982); the amount of NO and its diffusion coefficient are the limiting factors in the reaction (Saran et al., 1990) due to NOs short half-life of 3–5 s (Ignarro, 1989).

Under physiological conditions $ONOO^-$ has a half-life of 1–2 s and an action radius of 100 μm, being degraded into multiple toxic products (Beckman et al., 1990) or scavenged by the reaction with bicarbonate to produce nitrosoperoxycarbonate ($ONOOCO_2^-$) (Whiteman et al., 2002).

3.3. Protein nitration

This consists of the addition of a nitro group (NO_2) to proteins, mainly with tyrosine residues (Tyr) to give 3-nitrotyrosine. The local environment of the Tyr is important in order to be nitrated, since the proximity of negatively charged residues increases the susceptibility to nitration (Souza et al., 1999), but it is not a massive process since the

nitration under inflammatory conditions affects 1–5 of every 10,000 Tyr (Brennan et al., 2002).

$ONOO^-$ is one of the main molecules to nitrate proteins (Kanai et al., 2001; Ischiropoulos et al., 1992). The $ONOO^-$-mediated nitration depends on its secondary products ($^{\bullet}NO_2$) when is protonated to the acidic ONOOH (Eqs. (3) and (4)) (Beckman and Koppenol, 1996):

$$ONOO^- + H^+ \rightarrow ONOOH + NO \rightarrow {}^{\bullet}NO_2 + NO_2 \quad (4)$$

However, there are studies reporting that the contribution of $ONOO^-$ to protein nitration is not relevant, at least under inflammatory conditions (Pfeiffer et al., 2001). This conclusion is based on the lack of temporal correlation between the production of $O_2^{\bullet -}$ (an early event) and NO (a late event) following immune stimulation. The resulting protein nitration could be due to the action of leukocyte peroxidases, such as myeloperoxidase (MPO) (Pfeiffer et al., 2001). Leukocyte peroxidases have been reported to nitrate proteins in the presence of nitrite and H_2O_2 after stimulation of immune cells (van der Vliet et al., 1997; Eiserich et al., 1998). These enzymatic systems nitrate proteins without spatial or temporal restrictions due to the progressive generation and accumulation of nitrites, but the existence of protein nitration in leukocyte peroxidase knockout mice suggests that $ONOO^-$ may also play a key role in protein nitration (Brennan et al., 2002). It also points up the contribution of other nitration processes such as proteins with heme group plus transition metals such as iron and copper (Thomas et al., 2002).

3.4. NO as an oxidant agent

ONOOH and its intermediate reaction products (Eq. (3)) act as oxidant agents. The oxidation carried out by $^{\bullet}OH$ (Eq. (3)) is not specific and affects any cell molecule, whilst certain amino acids, such as lysines, histidines, cysteines and methionines, are more susceptible oxidation by $^{\bullet}NO_2$ (Eqs. (3) and (4)) (Butterfield and Stadtman, 1997).

3.5. Protein nitrosylation

Nitrosylation, or nitrosation, is the addition of an NO group to organic molecules without producing any change in the substrate charge, resulting in *C*-nitroso, *N*-nitroso, *O*-nitroso, or *S*-nitroso derivatives. The most common nitrosating agent is ^{+}NO. *S*-Nitrosylation occurs when NO reacts with the sulphur from a cysteine thiol surrounded by specific amino acids, which favors the nitrosylation (Stamler et al., 1997).

4. NO storage and degradation

The group heme acts as a NO scavenger and it is the main physiological pathway eliminating NO (Seregelyes et al., 2004). NO diffuses very quickly throughout the membranes to the lumen of the vessels, where it reacts with hemoglobin (Hb) (Eq. (5)) forming nitrates and methehemoglin (metHb). NO can be also oxidized in the plasma, forming nitrites that will react with Hb to produce nitrates:

$$HbO_2 + NO \rightarrow metHb + NO_3^- \quad (5)$$

Furthermore, NO can form dinitrosyl complexes with ferrum and binds to proteins containing a heme group, such as Hb. Thus, erythrocytes can transport NO by *S*-nitrosation and transnitrosation to release it in other tissues (Muller et al., 2002).

Another mechanism proposed to store NO is the production of *S*-nitroso-L-glutathione (GSNO) by reduced glutathione (GSH) nitrosylation. NO will be released from GSNO by several enzymes, such as GSH peroxidase (Hou et al., 1996), thioredoxin reductase (Nikitovic and Holmgren, 1996) and γ-glutamyl transpeptidase (Hogg et al., 1997).

In situations of high NO production, NO can be scavenged, reacting with bicarbonate to produce $ONOOCO_2^-$ (Whiteman et al., 2002).

5. Cellular effects of NO

The main NO cellular signaling pathway is the guanylate cyclase (GC) activation with the subsequent production of cyclic guanosine-3′,5′-monophosphate (cGMP) (Ignarro, 1991) and protein phosphorylation, but NO also exerts other cellular effects independent of the GC activation.

5.1. Guanylate cyclase activation

NO reacts with the heme group of the GC via the iron located in the center, producing a conformational change, which activates the catalysis of guanosine-5′-triphosphate (GTP) in cGMP. cGMP is a second messenger that activates protein kinases: PKG I, which is soluble and highly expressed in cerebellar Purkinje cells and smooth muscle cells (Butt et al., 1993), and PKG II, which is a membrane-bound protein that has been described in brain, intestine and kidney (Vaandrager and de Jonge, 1996). Previous evidence suggests that one of the main roles of PKG I is the control of intracellular calcium, while PKG II controls the flux of anions, such as chloride (French et al., 1995; Lau et al., 2003).

Moreover, cGMP modulates the activity of certain phosphodiesterases of cyclic nucleotides (PDE). The cGMP-mediated PDE III inhibition increases the intracellular levels of cAMP in mammalian heart (Ono and Trautwein, 1991), and consequently activates the proteins that are in the cAMP downstream activation pathway. The cGMP-mediated PDE II stimulation in neuronal PC12 cells (Whalin et al., 1991) mediates the opposite effects.

5.2. Protein nitrotyrosination

Nitration has been proposed as a selective post-translational modification with important biological

functions (Ischiropoulos, 2003). Nitrotyrosination alters the normal activity of proteins by inducing conformational changes (Cassina et al., 2000; Amici et al., 2003) or preventing their phosphorylation (Newman et al., 2002), leading to a loss of function. Examples of such post-translational modification occur with mitochondrial MnSOD (Ischiropoulos et al., 1992; MacMillan-Crow et al., 1996), actin (Aslan et al., 2003), glutamine synthase (GS) (Berlett et al., 1996), heme oxygenases (Kinobe et al., 2004), iron regulatory protein-1 (IRP-1) (Gonzalez et al., 2004), histone deacetylase 2 (Ito et al., 2004), mammal aldolase A (Koeck et al., 2004), p53 (Cobbs et al., 2003) and prostacyclin synthase (Hink et al., 2003). In some cases, nitrotyrosination induces a gain-function, e.g., in the case of PKC (Hink et al., 2003), cytochrome *c* (Cassina et al., 2000), fibrinogen (Vadseth et al., 2004), glutathione *S*-transferase (Ji and Bennett, 2003), JNK (Go et al., 1999) and poly-ADP-ribose synthetase (Zhang et al., 1994).

5.3. Protein nitrosylation

S-Nitrosylation is a post-translational regulatory mechanism that usually decreases the activity of the target protein. The main biological targets for nitrosylation are enzymes (GAPDH, caspases, transglutaminases, aromatases), G proteins (p21, RAC1 or cdc42) and kinases (ERK, JNK, p38) (Broillet, 1999). It has also been demonstrated that NO can *S*-nitrosylate the NMDA receptor and Na/K ATPase (Choi et al., 2000; Jaffrey et al., 2001). A down-regulation of the NMDA receptor induced by nitrosylation has been reported (Lipton et al., 1996).

S-Nitrosylation inhibits NF-κβ (Marshall and Stamler, 2001; Reynaert et al., 2004), which could be an autoregulatory mechanism of NO production, since iNOS is induced by this transcription factor. Another autoregulatory mechanism is the *S*-nitrosylation of eNOS that prevents its dimerization, resulting in a decrease in its activity (Ravi et al., 2004). Furthermore, NO interacts with plasma proteins, such as hemoglobin, to regulate the gas exchange (Jia et al., 1996), or albumin forming *S*-nitrosothiols, which has been proposed as a mechanism to store NO (Stamler et al., 1992a). NO can also act as a neural protector, due to the formation of the antioxidant and NO storing molecule, *S*-nitroso-L-glutathione (GSNO) (Rauhala et al., 1998), at the same time that it is preventing the production of peroxynitrites by substrate competition (Mayer et al., 1998).

Additionally, *S*-nitrosylation is also involved in the pathological process of activating matrix metalloproteases, e.g., in stroke and neurodegenerative diseases (Gu et al., 2002; Chung et al., 2004).

5.4. Actions on mitochondrial respiratory chain and cell metabolism

NO induces the reversible inhibition of cytochrome *c* oxidase (Brown and Cooper, 1994; Cleeter et al., 1994) a regulation that can explain the existence of mtNOS (Moncada and Erusalimsky, 2002). The NOS activation brings about a decrease in oxygen consumption and regulation of the cellular energetic metabolism (Brown and Cooper, 1994; Cleeter et al., 1994; Nisoli et al., 2003).

Furthermore, NO induces the synthesis of new mitochondria through the peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) (Nisoli et al., 2003). PGC-1 is a transcriptional coactivator that increases the expression of both NRF-1 and mitochondrial transcription factor A (mtTFA). These factors promote the expression of nuclear and mitochondrial genes, which are needed for mitochondrial biogenesis (Scarpulla, 2002). Therefore, mice lacking functional eNOS show a lower number of mitochondria (Nisoli et al., 2003), and mice overexpressing PGC-1alfa have a larger number of mitochondria in cardiac and skeletal muscles (Lin et al., 2002).

5.5. Activation of ADP-ribotransferases

NO activates ADP-ribosyltransferasa (ADP-RT), which can transfer the ADP-ribose from NAD^+ to an amino acid. ADP-ribosylation of G proteins by NO has been proposed as a mechanism to control neuronal transmission and arterial tone (Kanagy et al., 1995).

5.6. NO-mediated antiproliferative effect

NO is an inhibitor of cell proliferation (Corraliza and Moncada, 2002; Peunova et al., 2001). NOS and arginase II compete for L-Arg. When the activity of arginase II increases, a larger amount of L-ornitine will be produced. L-Ornitine is the main substrate for polyamine biogenesis in cellular proliferation. This balance can be modified by NO since it inhibits the ornitine-descarboxylase, and, therefore, shifts the L-Arg metabolism to NO production (Ignarro et al., 2002). The inhibitory effect of NO on cell proliferation is independent of GC activation (Murillo-Carretero et al., 2002; Ignarro et al., 2002). NO can also exert its anti-proliferative action via the Ras signaling pathway (Gonzalez-Zulueta et al., 2000).

Other intracellular targets that mediate the anti-proliferative effect of NO are transcription factors, which can be inactivated by *S*-nitrosylation (Vossen and Erard, 2002). An increase of the PKA has also been described, which in turn would raise the expression of P53, P21 (D'Souza et al., 2003; Luth et al., 2000; Poluha et al., 1997) and hemooxigenase-1 (HO-1) (Zamora et al., 2002).

Moreover, the anti-proliferative differentiation effect of NO has been associated with the inhibition of cyclin A and the activation of the cyclin-dependent kinase inhibitor $p21^{Cip1}$ (Ishida et al., 1997). NO-mediated neuronal differentiation also uses similar mechanisms to those described above (Poluha et al., 1997).

5.7. NO effect on MAPK intracellular signaling

NO interacts with JNK and STAT signaling pathways and the NF-κβ pathways, as well as MAPKs and some G proteins (Schindler and Bogdan, 2001).

NO activates $p21^{ras}$, a monomeric G protein that responds to many extracellular signals interacting with raf and triggers an MEK and extracellular signal-regulated kinases (ERK1/2) cascade pathway, playing a key role in proliferation, differentiation and apoptosis by the modulation of cyclins, cyclin-dependent kinases and their inhibitors (Lander et al., 1996; Luth et al., 2000). NO also exerts its function directly on the c-Jun N-terminal kinases (JNKs), stress-activated protein kinases (SAPK) and p38 MAPK (Lander et al., 1996). LPS leads to the expression of iNOS in mouse microglial cells enhancing JNK activity (Han et al., 2002). However, there is evidence that NO can also inhibit JNK and SAPK pathways by *S*-nitrosylation (Park et al., 2000). Thus, it has been demonstrated that INFγ stimulation led to increased NO production and inhibition of JNK1 (Park et al., 2000). This event was cGMP-independent, but dependent on *S*-nitrosylation of Cys 116 of JNK.

In the vascular system, endogenous NO can enhance JNK activity in endothelial cells (Go et al., 2001). Moreover, JNK activation derived from shear stress is blocked by the addition of NOS-inhibitors (Go et al., 1999). However, molecules other than NO are responsible for this activating effect since NO donors alone could not completely activate JNK (Go et al., 1999).

NO also inhibits platelet aggregation, due to the prevention of PI3K activation. Thrombin-induced platelet activation depends on PI3K. In human platelets, the addition of GSNO inhibited the p85/PI3K activation by cGMP (Pigazzi et al., 1999).

5.8. NO and apoptosis

NO has been reported as both an anti-apoptotic and a pro-apoptotic molecule. However, the latest widely held view is that NO is an anti-apoptotic molecule under physiological conditions. The pathophysiological role of NO depends on the cell type, the NO concentration and the co-existence of other noxious agents.

5.8.1. Pro-apoptotic role of NO

NO triggers apoptosis when it binds to cytochrome *c* oxidase and induces the formation of $O_2^{\bullet -}$ in the mitochondria, generating $ONOO^-$, which inhibits or damages the mitochondrial complexes I, II, IV and V, aconitasa, creatin-quinase, mitochondrial membrane, mitochondrial DNA and mitochondrial SOD, and induces Ca^{2+} release, transient permeability, cytochrome *c* release and mitochondrial swelling (Brown, 1999). Thus, in tumor cells the cytotoxic effects of NO and $ONOO^-$ are the consequence of DNA damage leading to p53 accumulation (Messmer et al., 1994) and consequently to p21 over-egulation. Moreover, NO-induced apoptosis is related to the increase in the Bax/Bcl-xL rate, the release of cytochrome *c* and caspase activation (Kolb, 2000). Protein nitration of MnSOD also triggers apoptosis due to the thiol oxidation-dependent assembly of the permeability transition pore (Radi et al., 2002).

Additionally, NOs activation of JNK/SAPK and p38 MAPK, the classical kinase pathways involved in the oxidative stress-mediated damage, has also been demonstrated in rat cortical neurons (Kang and Chae, 2003; Wang et al., 2003). These pathways yield to the activation of caspase cascades, the nuclear migration of c-jun/c-fos and the activation of the proapoptotic gene program. Moreover, NO donors increase the cellular levels of ceramide, which triggers caspase activation (Verheij et al., 1996) and inhibits Bcl-2 expression (Di Nardo et al., 2000).

However, NO and $ONOO^-$ production does not trigger apoptosis at physiological concentrations in endothelial and mononuclear cells (Lin et al., 1995), and high amounts of $ONOO^-$ or antioxidant depletion could be required to activate apoptotic processes.

5.8.2. Anti-apoptotic role of NO

One of the main protective effects of NO has been attributed to the *S*-nitrosylation of thiols from cysteines, e.g., inhibition of caspase 3 (Mannick et al., 1999), caspase 1 (Kim et al., 1998) and caspase 9, and the release of Bax (Thippeswamy et al., 2001). NO has other anti-apoptotic roles at physiological concentrations, such as inhibition of the mitochondrial permeability transition pore (MPTP) and cytochrome *c* release (Brookes et al., 2000).

NO induces the expression of cytoprotective genes such as HSP70 (Hao et al., 1999). HSP70 inhibits Apaf-1 oligomerization by binding to the Apaf-1 caspase domain (CARD), which prevents the formation of the apoptosome (Beere et al., 2000). Another possible mechanism is the direct inhibition of cytochrome *c* release by the activation of HSP70 (Mosser et al., 1997). Moreover, Bcl-2 levels can be maintained by NO (Genaro et al., 1995). This mechanism of modulation is dependent on GC activation and inhibits Bcl-2 caspase-mediated degradation (Kim et al., 1997).

In neuronal PC12 cells and U937 immune cells, the NO anti-apoptotic effects are linked to cGMP production, which suppresses cytochrome *c* release and ceramide generation (Li and Billiar, 1999; Fiscus, 2002; De Nadai et al., 2000). Moreover, both NO and cGMP protect lymphocytes from apoptosis by maintaining Bcl-2 levels and the activation of Akt/PKB. The former step induces the inactivation of the pro-apoptotic Bad and procaspase-9 by phosphorylation (Genaro et al., 1995). In endothelial cells, NO protects against apoptosis by an independent-cGMP pathway (Kwon et al., 2001). The protective role of NO in endothelial cells has been demonstrated to be effective even against TNF (Kim et al., 1997).

6. Physiological effects of NO

6.1. Vascular effects

One of the main physiological functions of NO is related to the vascular system. Endothelial cells control vessel relaxation by the production of NO; thus knockout mice for eNOS are hypertensive (Huang, 1999). The main target for NO is the vascular smooth muscle cell (VSMC). The vasorelaxant action of NO on the VSMCs involves the generation of cGMP and PKG-dependent modulation of ion channels, such as MaxiK-channel or Ca^{2+}-activated K^+-channels, inducing hyperpolarization of the membrane (Tanaka et al., 2000; Kudlacek et al., 2003) or a direct activation of Ca^{2+}-dependent K^+ channels (Bolotina et al., 1994). Moreover, NO activates sarcoplasmic–endoplasmic reticulum Ca^{2+} ATPases, depleting the Ca^{2+} levels of the cytosol (Raghavan and Dikshit, 2004). Contraction of VSMCs occurs when myosin light chain (MLC) is phosphorylated by the Ca^{2+}-calmudulin-dependent MLC kinase and is reverted by the MLC phosphatase. This latter action can be modulated by a RhoA-dependent kinase (Rho kinase), which phosphorylates and inhibits the MLC phosphatase triggering contraction (Sauzeau et al., 2000). NO activates the MLC phosphatase and causes smooth muscle cell relaxation by activation of cGMP-dependent protein kinase cGKIα. This enzyme is responsible for the inhibition of the Rho kinase, which allows the MLC phosphatase to perform its task of stopping contraction. Further, cGMP-dependent protein kinases phosphorylate and inactivate the G-protein-activated phospholipases C PLCβ2 and PLCβ3 (Xia et al., 2001). G-protein-activated phospholipase C (PLC) catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphates to generate diacylglycerol and inositol 1,4,5-triphosphate, leading to the activation of PKC and the mobilization of intracellular Ca^{2+}, which, once bound to calmodulin, can activate the MLC kinase, thereby increasing the contraction. Thus, PLCβ inactivation is another mechanism to relax VSMCs.

NO could play a protective role in the vascular system by inhibiting the proliferation of VSMCs in the tunica media and limiting the subsequent invasion and destruction of the intima that occur in atherogenic processes involved in ischemia or multi-infarct dementia. This inhibitory mechanism of the cellular proliferation, or even the maintenance of basal myorelaxation levels, could justify the endogenous NO availability of the VSMCs. Another important vascular effect of NO in the regulation of blood flow is mediated by cGMP-dependent inhibition of platelet aggregation (Moncada et al., 1991).

6.2. Immunological and glial role

Constitutive NOS (endothelial or neural) is activated by a transitory increase of the cytosolic Ca^{2+} and causes an increment of NO for a few minutes, whereas iNOS is expressed in glial and immunological cells after receiving an immunological or inflammatory stimulation and causes a large amount of NO even for several days.

NO is produced by different stimuli playing a relevant role in the immune response (Nathan, 1997). Its presence in oxidant environments determines the formation of $ONOO^-$, which is a powerful anti-microbial and anti-tumoral agent (Xie and Nathan, 1994). The massive NO production by iNOS is toxic per se because it inactivates the mitochondrial respiratory chain enzymes and can induce apoptosis in the target cells.

NO has been reported to activate cyclooxygenase-II (COX-2) producing the metabolism of arachidonic acid in a pro-inflammatory pathway in glial cells (Molina-Holgado et al., 1995; Minghetti et al., 1996). NO is also a well-known regulator of leukocyte adhesion in vessels (Kubes et al., 1991).

6.3. Neuronal effects of NO

NO is a neurotransmitter and/or neuromodulator in both central and peripheral nervous systems by cGMP-dependent mechanisms (Bredt and Snyder, 1994a; Prast and Philippu, 2001; Lewko and Stepinski, 2002; Trabace and Kendrick, 2000). The NO role in the brain was known even before its chemical nature was revealed. Garthwaite et al. (1988) were the first to observe that activation of brain NMDA receptors resulted in the release of NO. nNOS actions in CNS have been associated with pain perception, especially at the spinal cord level (Yamamoto et al., 1993), and of control of sleep, appetite, thermoregulation (Monti and Jantos, 2004), neural development (Cheng et al., 2003) and synaptic plasticity (Dinerman et al., 1994).

6.3.1. NO and glutamate

NMDA receptor triggers activation of nNOS with a peak at 5–15 min, returning to baseline levels after 60 min, most likely due to substrate exhaustion (Do et al., 2002). This process has been described in several brain regions such as hippocampus, striatum, hypothalamus and locus coeruleus (Fedele et al., 2001; Maura et al., 2000; Trabace et al., 2004). An inverse relationship between NO and glutamate has also been observed. In vivo and in vitro studies with NO donors, NOS inhibitors and glutamate receptor antagonists suggest that in several brain areas and the spinal cord, NO enhances glutamate release (Prast et al., 1998). This retrograde mechanism gains importance in the memory process. Long-term potentiation (LTP) has been proposed as the main mechanism to store information and it consists of the continuous synaptic activation in some part of the hippocampus. To maintain the postsynaptic activation, some retrograde communication with the presynaptic component must exist. NO has been suggested as the retrograde molecule that activates the glutamate release in a cGMP-dependent pathway (Nowicky and Bindman, 1993). Animal models have suggested that compensatory

mechanisms, involving nNOS and eNOS, are present in order to maintain LTP (O'Dell et al., 1994; Son et al., 1996).

The effect of NO on glutamate release depends on the NO level. Thus, when NO concentrations are low there is a decrease in glutamate release despite elevated cGMP levels. But when NO increases the cGMP levels, the inhibitory effect on glutamate release is reversed, suggesting that cGMP exerts a biphasic effect (Sequeira et al., 1997).

It is known that NMDA receptor activation leads to the activation of nNOS, which could play a protective role through the blocking of caspases (Khaldi et al., 2002). The *S*-nitrosylation of NMDA receptor seems to be an inhibitory mechanism by which its activity is regulated in order to prevent toxic effects. But NO has also been suggested as an activator of NMDA-dependent neurotoxicity (Dawson et al., 1991). Ammonia is detoxified in the brain by glutamine synthetase (GS). The activation of NMDA receptors enhances nNOS activity, producing NO capable of inhibiting GS by nitration or nitrosylation (Kosenko et al., 2003).

6.3.2. NO and other neurotransmitters

Cholinergic transmission in basal forebrain and ventral striatum is modulated by endogenous NO (Prast et al., 1998; Buchholzer and Klein, 2002). Endogenous NO does not produce ACh release from cholinergic neurons directly but rather by stimulating neighbouring glutamatergic neurons.

The effect of NO in both GABA and glutamate release is biphasic, depending on the NO concentration. Basal NO levels induce a depletion of GABA release but high concentrations of NO increase GABA release (Getting et al., 1996). The NO-induced GABA release is mediated by two different mechanisms: a Ca^{2+}-dependent process and a Na^{+}-dependent carrier-mediated GABA uptake (Ohkuma et al., 1996). It has also been observed that $OONO^{-}$ partially participates in NO-induced GABA release (Kuriyama and Ohkuma, 1995; Trabace and Kendrick, 2000).

NMDA receptors and NO are responsible for the modulation of noradrenaline (NE) release (Feldman and Weidenfeld, 2004). Treatments with NO donors stimulate NE release in the hippocampus both in vivo and in vitro and NOS inhibitors decrease NE levels (Lonart et al., 1992). Other studies suggest that thiol compounds, such as L-cysteine, are required to facilitate NO-mediated neurotransmitter release (Satoh et al., 1996). On the other hand, NO and $ONOO^{-}$ were found to react directly with NE, deactivating this neurotransmitter, which enhanced NOs vasodilator properties (Kolo et al., 2004; Shelkovnikov et al., 2004).

Serotonin (5-HT) release is linked to the formation of NO by NMDA receptor activation in rat striatum (Lorrain and Hull, 1993; Trabace et al., 2004). It has been observed that NO donors produce 5-HT release in a biphasic way (Kaehler et al., 1999), with low concentrations of NO donors decreasing 5-HT release in the hypothalamus and high concentrations increasing it. Both effects are mediated by cGMP (Kaehler et al., 1999). Curiously, in the locus coeruleus, endogenous NO facilitates 5-HT release while NO released under resting conditions does not modulate serotoninergic neuron activity (Sinner et al., 2001). 5-HT is expressed early during CNS development and plays an important role during this period. NO is also involved in neuronal development (Tagliaferro et al., 2003). The connections between the nitrergic and the serotonergic systems have been shown in several studies. One example is the aggressive behavior of nNOS −/− knockout mice, which was shown to be caused by reductions in 5-HT turnover and a deficiency of 5-HT1A and 5-HT1B receptor function in the brain regions regulating emotions (Tagliaferro et al., 2003). Moreover, 5-HT mediates the antidepressant-like effects of NOS inhibitors (Harkin et al., 2003).

Adenosine has been thought to act as an endogenous neuroprotectant against cerebral ischemia and neuronal damage (Saransaari and Oja, 2004). There is scarce information about adenosine release by NO. It has been suggested that endogenous NO modulates adenosine release, also due to NMDA receptor activation (Saransaari and Oja, 2004), and that it represents a neuroprotective mechanism that could help limit the detrimental effects of excitatory neurotransmission by modulating NO production triggered by NMDA receptor stimulation (Bhardwaj et al., 1995).

Regarding histamine, an increase in extracellular NO concentration decreases histamine release in the hypothalamus (Prast et al., 1996). The inhibition of histamine release is mediated by ACh released from neighbouring cholinergic neurons through the stimulation of M_1 receptors located on histaminergic neurons. But NO can also promote histamine release by M_1 receptor blockade because of glutamate action, which enhances histamine liberation in the hypothalamus (Prast et al., 1994). Histamine is able to modify NO synthesis. H_1-receptors activate NOS by G-protein-coupled pathways resulting in a cGMP-dependent increased interneuronal coupling in vasopressinergic neurons (Yang and Hatton, 2002) and higher permeability of the blood–brain barrier (BBB) and pial arterioles (Mayhan, 1996).

6.3.3. NO and neuronal survival

Neurons belonging to the dorsal root ganglion (DRG) die if they are treated with nNOS inhibitors (Thippeswamy and Morris, 1997a), showing a positive, beneficial role of NO in the nervous system. After peripheral nerve axotomy, DRG neurons express nNOS (Verge et al., 1992). When DRG neurons are deprived of NGF, they increase the expression of nNOS (Thippeswamy and Morris, 1997b), which is presumably a neuroprotective mechanism, as nNOS inhibition induces apoptosis in these neurons (Thippeswamy and Morris, 1997a).

7. NO and neurodegenerative diseases

When NO is produced in an excessive amount, NO changes from a physiological neuromodulator to a

neurotoxic factor. It has been observed that NO overproduction can be due to nNOS activation following persistent stimulation of excitatory amino acid receptors mediating glutamate toxicity and/or to iNOS induction by diverse stimuli, such as endotoxin or cytokines (Chabrier et al., 1999).

NO is especially harmful under pathological conditions involving the production of reactive oxygen species (ROS) and $ONOO^-$ formation. Nitrotyrosination inhibits tyrosine phosphorylation and hence affects the signal transduction pathways of growth factor (Jonnala and Buccafusco, 2001). All neurodegenerative diseases show a slow and gradually evolving death of selective neuronal populations that can occur sporadically or by gene mutation inheritance. Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and ischemia are all neurodegenerative processes in which the role of NO is suggested because all of them exhibit oxidative stress (Chabrier et al., 1999). Moreover, the presence of nitrotyrosination has been described in several neurodegenerative diseases linked to oxidative stress, such as AD (Good et al., 1996; Smith et al., 1997), PD (Good et al., 1998) and ALS (Cookson and Shaw, 1999).

7.1. NO and Alzheimer's disease

Brains from AD patients are characterized by extracellular aggregates of amyloid β-peptide (Aβ) forming the neuritic plaques and intracellular neurofibrillary tangles due to the hyperphosphorylation of tau protein (Selkoe, 2001). Aβ fibrils are toxic because they induce ROS formation (Miranda et al., 2000), which can produce $ONOO^-$ when reacting with NO. It has been reported that chronic $A\beta_{1-40}$ intracerebroventricular infusion causes $ONOO^-$ formation and subsequent tyrosine nitration of proteins (Tran et al., 2003) (Fig. 5).

The fact that $ONOO^-$ formation depends on the NO levels indicates that both neuronal and glial NOS play a relevant role in its generation in brain (Smith et al., 1997). Moreover, positive neurons for NOS are spread all around the AD brain and NO diffusion reaches NOS negative neurons (Hyman et al., 1992). Astrocyte nNOS has been implied in the pathogenesis of AD (Simic et al., 2000). nNOS-positive reactive astrocytes were found in AD patients near amyloid plaques in CA1 and subiculum and at those places where neuron loss was present, particularly in the layer II of the entorhinal cortex and CA4 of hippocampus. Evidence for the involvement of nNOS in AD is also provided by Thorns et al. (1998), who find an increased expression of nNOS in those neurons with neurofibrillary tangles in the entorhinal cortex and hippocampus of AD patients (Thorns et al., 1998).

Increased expression of iNOS and eNOS in astrocytes has been associated with the presence of neuritic plaques (Luth et al., 2000, 2001; Wallace et al., 1997; de la Monte et al., 2000a). Further, Aβ deposition in brain vessels correlates with a decrease in the expression of eNOS in endothelial cells (de la Monte et al., 2000b).

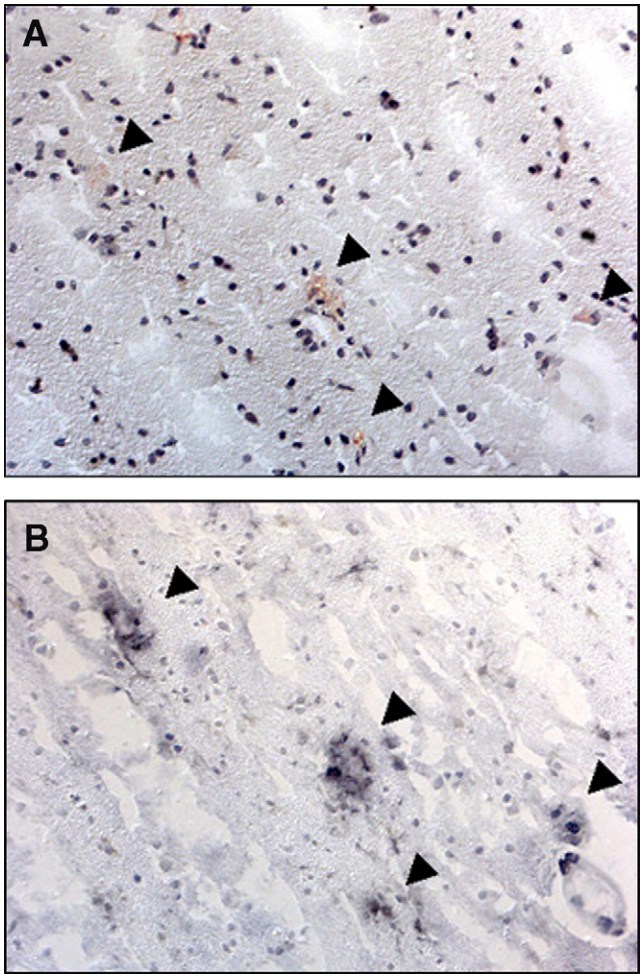

Fig. 5. Colocalization of amyloid deposits (A) with nitrotyrosination (B). Amyloid deposits were identified by Congo red staining. Nitrotyrosination was detected with an anti-nitrotyrosine antibody in consecutive sections of frontal cortex from an AD patient (stage VI). Tissues were counterstained with hematoxylin.

It has been demonstrated that specific cerebral regions of patients with AD have higher protein nitrotyrosination levels than controls, especially in the hippocampus and the cerebral cortex (Smith et al., 1997; Hensley et al., 1998), as well as in cerebrospinal fluid (CSF) proteins (Tohgi et al., 1999). However, some studies show no difference in 3-nitrotyrosine levels in the CSF of AD and ALS patients (Ryberg et al., 2004). Since one of the main targets for nitrotyrosination is synaptophysin (Tran et al., 2003), it has been suggested that the damage in synaptophysin is related to Aβ-induced impairment of ACh release. Other proteins nitrotyrosinated in AD are related to glucose metabolism (γ-enolase/α-enolase, lactate deshydrogenase and triosephosphate isomerase (TPI)) or cellular cytoskeleton (α-actin) (Castegna et al., 2003). We have found that Aβ on endothelial cells induces the nitrotyrosination of proteins involved in glucose metabolism (TPI), cytoskeletal integrity

(vinculin), antioxidant defense (non-selenium glutathione peroxidase) and protein turnover (TCP1, eukaryotic translation elongation factor 2, 26S proteasome and mtHSP75) (Muñoz et al., 2002; Coma et al., 2005). It is possible that the depletion of acetyl-CoA by the impairment of glucose metabolism, which is used by choline acetyltransferase to acetylate choline, could result in ACh deficit (Meier-Ruge and Bertoni-Freddari, 1996). Moreover, the damage in the neuron cytoskeleton contributes to the loss of neuronal network communication (Radtke-Schuller, 2001).

A key role for microglia in NO production after Aβ stimulation has been reported (Weldon et al., 1998). However, transgenic mice overexpressing a double mutation for the amyloid precursor protein (APP) and presenilin 1 (PS1) show neuritic plaques but do not express iNOS either in microglia or in astroglia (Hartlage-Rubsamen et al., 2001). These controversial results are in contrast to those demonstrating that Aβ can induce iNOS expression in microglial cells and astrocytes, which would suggest the presence of reactive glia surrounding the neuritic plaques in AD brains (Boje and Arora, 1992; Akama et al., 1998).

7.2. NO and ischemia

Oxidative stress plays a key role in ischemic-reperfusion situations (Cuzzocrea et al., 2001). The increase of NO production in a pro-oxidant environment contributes to brain damage (Moro et al., 2004), and the involvement of $ONOO^-$ in ischemia-mediated damage has been linked to $ONOO^-$ decomposition and brain damage reduction (Thiyagarajan et al., 2004).

An increase in intracellular Ca^{2+} levels is a primary response of cells to ischemia. Although the higher levels of NO in ischemia/reperfusion and stroke are due to iNOS, a sustained increase in Ca^{2+} induces a burst of NO production by the constitutive isoforms of NO (Gross and Wolin, 1995). Immediately after the first minutes of ischemic cerebral damage the activity of eNOS is elevated (Depre et al., 1997), a condition lasting from 30 min to some hours, in an attempt to improve blood supply (Wada et al., 1998a; Brevetti et al., 2003). Similarly, the activity of nNOS is also triggered under ischemic conditions aimed to improve blood supply (Gursoy-Ozdemir et al., 2000) since nNOS is widely expressed in perivascular nerves of the brain parenchyma (Tomimoto et al., 1994). Later on, the activity of these NOS falls below even the basal level for days. The local depletion of substrates such as O_2^- and mainly L-Arg could partially explain the dramatic reduction in NO production by constitutive NOS after an ischemic process, since it has been demonstrated that L-Arg administration enhances NO production (Huk et al., 1997). The expression of iNOS increased from 12 h to 7 days after injury (Iadecola et al., 1995; Wada et al., 1998b), contributing to the damage associated with the ischemic process (Iadecola et al., 1997).

The pathological role of NO in cerebral ischemia has been demonstrated in iNOS knockout mice, which show a reduction in neuronal death following cerebral ischemia (Iadecola et al., 1997). Moreover, nNOS knockout mice show decreased neuronal death after a cerebral ischemia (Eliasson et al., 1999). Interestingly, eNOS knockout mice show an increase in neuronal death after suffering a stroke (Huang et al., 1996), which suggests a protective role for this enzyme, maybe due to its key role in the control of blood flow.

The inhibition of NO production by 7-nitroindazole, a non-selective inhibitor of NOS in vitro, improves neurological outcome in some models of traumatic brain injury (TBI) (Cherian et al., 2004), and an attenuation of lesion expansion in pre- and post-injury treatment with the iNOS inhibitor aminoguanidine (AG) has been reported (Stoffel et al., 2000; Lu et al., 2003; Rinecker et al., 2003). Moreover, the inhibition of nNOS reduces the damage (Yoshida et al., 1994). Nevertheless, inhibition of NO production in cerebral damage is controversial, perhaps due to the animal model, injury procedure or the NOS inhibitor used. Thus, it has been described that pre-injury administration of L-NAME, a non-selective NOS inhibitor, significantly increases mortality, whereas post-injury L-NAME treatment has no effect on cerebral ischemia injury (Lu et al., 1997). Estrogen reduces ischemic-reperfusion damage in rat brain (Shi et al., 2001). In the former case, there is an increase in eNOS activity due to the direct effect of estrogens, as well as the beneficial effects of the estrogen's antioxidant properties and neuroprotective action.

On the other hand, a protective role for low concentrations of NO in ischemic situations has been proposed. NO interacts with GSH, producing GSNO, which has been demonstrated to be a neuroprotector (Rauhala et al., 1998). The production of nitrosoglutathione could amielorate the oxidative damage in the ischemic tissue.

7.3. NO and Parkinson's disease

PD is a neurodegenerative disorder of aging characterized by a selective and progressive loss of dopaminergic neurons within the substantia nigra, which produces a lack of dopaminergic control in the striatum (Shults, 2003). Post-mortem studies have shown oxidative damage in PD mediated by ROS (Jenner, 2003) and several studies suggest that $ONOO^-$ plays an important role in the pathogenesis of the disease (Torreilles et al., 1999).

Striatal release of dopamine (DA) is modulated by NMDA receptor stimulation both in vivo and in vitro (Kegeles et al., 2002; Castro and Zigmond, 2001). Endogenous NO enhances DA efflux in the striatum through the elevation of glutamatergic tone (West and Galloway, 1997). However, high concentrations of NO decrease NMDA-induced DA levels. This may be due to the activation of a negative feedback mechanism, which modulates NMDA receptor function, or to increased GABA release (Ujihara et al., 1993). Other authors have proposed that NO produces DA release in a Ca^{2+}-independent mechanism (Stewart et al., 1996).

Tyrosine hydroxilase is the initial and rate-limiting enzyme in the biosynthesis of DA and this enzyme can be inhibited by nitrotyrosination (Kuhn and Geddes, 2002). Further, MAO B, whose activity increases with aging (Bhaskaran and Radha, 1983), is located in the external mitochondrial membrane and generates H_2O_2 during the catecholamine metabolism (Tipton, 1967), possibly acting as a source of $O_2^{\bullet -}$, and subsequent $ONOO^-$ production. Then dopaminergic neurons would be highly exposed to $ONOO^-$ damage (LaVoie and Hastings, 1999).

Parkin is a protein that adds ubiquitin on specific substrates; its mutation is related with familial PD (Kitada et al., 1998). Recently, it has been demonstrated in vitro that *S*-nitrosylation of parkin inhibits the protective function of this key protein (Chung et al., 2004).

A loss of intracellular GSH from substantia nigra as an early event in PD has been observed (Sian et al., 1994). Furthermore, GSH reductase, the enzyme that regenerates GSH from its oxidized form, is susceptible to the action of $ONOO^-$ (Barker et al., 1996). These data suggest that $ONOO^-$ could contribute to the depletion of major cellular antioxidant defense, making the nigrostriatal pathway especially susceptible to toxic insult (Barker et al., 1996). Moreover, $ONOO^-$ has been implicated in the apoptosis of dopaminergic neurons in PD (Naoi and Maruyama, 2001).

The contribution of NO to PD was reinforced by the studies carried out with nNOS knockout mice. The knockout animals are more resistant to neurotoxicity induced by MPTP (Przedborski et al., 1996), a PD inducer. Moreover, polymorphonuclear cells from PD patients exhibit an increase of NO production that is accompanied by accumulation of nitrotyrosine-containing proteins together with a neuronal over-expression of nNOS (Gatto et al., 2000). Finally, glial derived neural factor (GDNF), which exerts a protective effect in PD (Toledo-Aral et al., 2003), inhibits nNOS activity and apoptosis in neurons (Wang et al., 2002).

7.4. NO and Huntington's disease

HD is a neurodegenerative disease producing dementia and involuntary movements characterized by neuronal loss in some brain regions, mainly in the striatum (Vonsattel et al., 1985). HD is an autosomal dominant disease caused by an expansion of a CAG trinucleotide repeat on the huntingtin (htt) gene located on the short arm of chromosome 4 (The Huntington's Disease Collaborative Research Group, 1993). Most HD patients have CAG repeat sequences that vary from 40 to 49 repeats; they develop symptoms between the third and the fifth decades of life (Lucotte et al., 1995). In HD, htt has an expanded polyglutamine tract at the extreme N-terminus, which triggers neurotoxicity through a number of proposed mechanisms involving excitotoxicity by NMDA receptors (Zeron et al., 2004), impairment in vesicle trafficking, lack of neurotrophines and transcriptional effects (Ross, 2004).

There are at least two putative pathways that link HD with NO production: htt/HAP-1 (htt-associated protein)/calmodulin/NOS and CREB binding protein (CBP)/htt/NOS. HAP-1 forms a complex with htt (Li et al., 1995), which could bind to calmodulin, the main regulator of nNOS and eNOS (Bao et al., 1996). When htt/HAP-1 complex is mutated, its affinity for calmodulin increases, preventing nNOS activation (Bao et al., 1996). On the other hand, it has recently been found that Ca^{2+} regulates nNOS expression through a promoter located on exon 2 of the *nNOS* gene (Sasaki et al., 2000). This promoter responds to CBP (Sasaki et al., 2000), which binds to two critical cAMP/Ca^{2+} response elements, which are immediately upstream of the nNOS transcription start site. It has been found that htt interacts with CBP and represses nNOS transcription (Steffan et al., 2000). Moreover, CREB/CBP complex is under the control of the calmodulin kinases (Chawla et al., 1998; Matthews et al., 1994), which could be inactive due to the interaction of htt/HAP-1 with calmodulin.

An excessive production of NO might contribute to the development of HD by destroying neighbouring neurons (Butterfield et al., 2001). This observation is in accordance with the increased iNOS expression seen in glial, neuronal and vascular cells from brains of HD patients and HD mouse models (Chen et al., 2000). In fact, increased production of oxidative stress products in HD patients and HD transgenic mice has been reported (Tabrizi et al., 1999).

7.5. NO and amyotrophic lateral sclerosis

ALS is a neurodegenerative disease characterized by selective death of motor neurons in the cerebral cortex, brain stem and spinal cord (Rosen et al., 1993). Motor neurons die due to apoptotic processes (Martin, 1999) triggered by the activation of caspases 1 and 3 (Li et al., 2000). There is evidence that glutamate-induced neurotoxicity is involved in sporadic ALS (Patten et al., 1978; Rothstein et al., 1990; Lin et al., 1998) and NO was found to contribute to glutamate-induced neuronal death (Beckman et al., 1993). It has been demonstrated that nitrotyrosination induces motor neuron death (Peluffo et al., 2004) and the irreversible inhibition of the mitochondrial respiratory chain in these cells (Radi et al., 1994). On the other hand, treatment with a non-selective NOS inhibitor decreases motor neuron degeneration in an ALS mouse model (Hyun et al., 2003). Accordingly, increased levels of NO metabolites in the CSF from ALS patients have been found (Boll et al., 2003), although other authors have not found such increase (Pirttila et al., 2004; Taskiran et al., 2000).

Another line of evidence suggests that astrocytes could be the major NO source in ALS and might also contribute to ALS development by the production of pro-apoptotic molecules, such as NGF (Pehar et al., 2004) and Fas-ligand, which result in the activation of p38 MAPK, nNOS and caspases 3 and 8 (Wengenack et al., 2004; Raoul et al., 2002). Interestingly, there are reactive astrocytes that

surround the upper and lower motor neurons affected by ALS (Schiffer and Fiano, 2004).

Twenty percent of familial ALS is associated with gain-of-function mutations in the copper/zinc SOD (SOD-1) (Reaume et al., 1996). It has been reported that nNOS, cGMP and SOD1 co-localized in the swollen axons of the anterior horn cells in ALS patients (Chou et al., 1996). The $O_2^{\bullet -}$ binding site of mutant SOD-1 is, abnormally, more accessible to other oxidants including H_2O_2 and $ONOO^-$ (Beckman et al., 1993), which could be related to a loss of affinity for zinc in the mutated SOD-1 (Crow et al., 1997; Estevez et al., 1999). The reaction of $ONOO^-$ with mutant SOD1 allows the formation of reactive intermediates with the capacity to nitrotyrosinate proteins (Beckman et al., 1993), which correlates with the high nitrotyrosination found in ALS patients (Abe et al., 1995). Moreover, it has been proposed that the high breakdown of the protective *S*-nitrosothioles by mutated SOD-1 could contribute to the triggering of apoptosis (Johnson et al., 2001) since there is a decrease in the levels of GSNO, a possible activation of caspases and an increase in Ca^{2+} input through more active NMDA receptors.

7.6. NO and multiple sclerosis

MS is an inflammatory disease of the CNS characterized by demyelinization, gliosis and axonal damage resulting in neurological impairment with limb weakness, sensory loss and many other complications. Microglia, macrophages and T lymphocytes play key roles in the development of MS in humans (Prineas and Wright, 1978; Woodroofe et al., 1986) and experimental allergic encephalomyelitis (EAE), the MS model in rodents (Vass et al., 1986).

In both MS and EAE, there is evidence of oxidative stress (Griot et al., 1990; Mehindate et al., 2001), and $ONOO^-$ is believed to contribute to the cell damage (Liu et al., 2001; Scott et al., 2002). In fact, an increased expression of iNOS has been reported in peripheral mononuclear cells, macrophages, microglia and astrocytes from MS patients (Sarchielli et al., 1997; Broholm et al., 2004; Bagasra et al., 1995; Hill et al., 2004). However, when inflammation is reduced, iNOS expression decreases in demyelinated plaques from MS patients (Liu et al., 2001). There are some controversial results inhibiting iNOS in EAE animals, since both a reduction in the inflammatory response and demyelination (Cross et al., 1994), and an increase in the inflammatory response, has been reported (Kahl et al., 2003).

NO produces the disruption of the BBB, oligodendrocyte injury and demyelination, and axonal degeneration, and it contributes to the loss of function through impairment of axonal conduction. Elevated levels of nitrate and nitrite have been described in CSF, urine and serum of MS patients (Giovannoni et al., 1997, 1999; Yamashita et al., 1997). Particularly, nitrate and nitrite levels are significantly higher in CSF compared to serum (Yuceyar et al., 2001), which could be the consequence of a BBB dysfunction mediated by NO (Mayhan, 1996). Although nitrate and nitrite are elevated in CSF, there is no significant correlation between their levels and clinical disease activity (Yuceyar et al., 2001).

8. Conclusions

NO is a pleiotropic molecule that is needed for physiological functions, especially in the brain. NO induces vasodilatation, inhibits apoptosis and plays an important role in memory processes, making it a putatively valuable therapeutic agent in ageing-associated diseases. However, NO can be harmful, mainly under oxidative stress conditions, due to the oxidation and nitrotyrosination of functional proteins. Therefore, the pharmacological modification of the NO metabolism should be carefully reviewed. Thus, the use of NO donors to improve the blood supply in the brain should be avoided, since the production of $ONOO^-$ will be triggered, and the use of NOS inhibitors has shown controversial effects, or even an increase of the damage in animal models. Probably the best possible scenario would be the prevention of peroxynitrite formation with antioxidant therapy without modifying the activity of NOS, an enzyme widely distributed and involved in a plethora of necessary physiological responses outside the brain.

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