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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).