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PHYSIOLOGICAL REVIEW

Nitric oxide and sleep

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Summary Nitric oxide (NO) is a biological messenger synthesized by three main isoforms of NO synthase (NOS): neuronal (nNOS, constitutive calcium dependent), endothelial (eNOS, constitutive, calcium dependent) and inducible (iNOS, calcium independent). NOS is distributed in the brain either in circumscribed neuronal sets or in sparse interneurons. Within the laterodorsal tegmentum (LDT), pedunculopontine tegmentum and dorsal raphe nucleus, NOS-containing neurons overlap neurons grouped according to their contribution to sleep mechanisms. The main target for NO is the soluble guanylate cyclase that triggers an overproduction of cyclic guanosine monophosphate. NO in neurons of the pontine tegmentum facilitates sleep (particularly rapid-eye-movement sleep), and NO contained within the LDT intervenes in modulating the discharge of the neurons through an auto-inhibitory process involving the co-synthesized neurotransmitters. Moreover, NO synthesized within cholinergic neurons of the basal forebrain, while under control of the LDT, may modulate the spectral components of the EEG instead of the amounts of different sleep states. Finally, impairment of NO production (e.g. neurodegeneration, iNOS induction) has identifiable effects, including ageing, neuropathologies and parasitaemia.

Introduction

The discovery of endothelium-derived relaxing factor in the late 1980s[1] initiated studies that ultimately led to the discovery of the biological paracrine messenger identified as nitric oxide (NO).[2] Although this messenger is now recognized as regulating transmission and metabolism in various cells and tissues, it might also be a potent cytotoxic agent when synthesized in excess. NO is present in periphery and in the central nervous system and regulates a great variety of physiological functions including memory processes, the sleep–wake cycle, synaptic plasticity, blood flow and gastrointestinal motility.[3] NO also exerts detrimental effects: its involvement in acute inflammatory processes,[4] ageing and associated neurodegenerative pathologies[5,6] is now recognized.

The present review first recalls the essential data related to the regulatory processes associated with NO synthesis, brain anatomical distribution of NO

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synthases (NOSs), and brain targets for NO, and then focuses on the relationships between NO and sleep in physiological and pathophysiological conditions.

NO synthesis

NO is a labile gas synthesized in mammalian cells from L-arginine through enzymatic reactions catalyzed by a family of NOSs. This family currently includes three NOS isoforms identified as neuronal (nNOS), endothelial (eNOS) and inducible (iNOS) by reference to the tissue from which they were originally purified. The above isoforms are much more widely distributed in mammalian tissues than originally suspected.[7] Moreover, a widespread nomenclature based on the earliest observations classifies the nNOS and eNOS as constitutive isoforms, whereas an induction-step is assigned for iNOS expression. This nomenclature remains questionable since under physiological conditions iNOS may function as a constitutive isoform in some cells, while the genes coding for nNOS or eNOS may also be expressed under physiological conditions.[8]

All the NOS isoforms are homodimeric proteins in their active forms. Each monomer consists of four discrete domains (reductase, calmodulin binding, oxygenase and an N-terminal sequence specific to the isoform). Following binding with calmodulin, the NOS catalytic processes require two co-substrates (the reduced form of nicotinamide adenine dinucleotide phosphate, and oxygen) and four enzyme-bound co-factors (flavin adenine dinucleotide, flavin mononucleotide, thiolate-bound haem and tetrahydrobiopterin).[7,9–12] In addition, while calcium is needed for nNOS and eNOS activities, its presence is not essential for that of iNOS since calmodulin spontaneously binds sufficiently tightly to it.[11] In aerobic conditions, the NOSs catalyze the oxidation of L-arginine in two steps, the end products being L-citrulline and NO (Fig. 1).

NOS regulation

NO cannot be stored in specialized vesicles owing to its strong reactivity in vivo (a half-life of a few seconds), and hence regulating its level of production lies in the control of biogenesis.[13] Consequently, the regulatory mechanisms attached to NOS expression and activity are of paramount importance but also complex since they include transcriptional, post-transcriptional, translational and post-translational processes.[14] Various processes regulate the constitutive isoforms of the NOS at the post-translational level. The first process relies on the control of enzyme activity by the intracellular concentration of calcium. In this respect, the triggering of NMDA (*N*-methyl-D-aspartate) receptors (NMDAR) by glutamate may result in the entry of calcium which, after binding with calmodulin, activates the nNOS isoform (Fig. 2). In blood vessels, acetylcholine, after binding to muscarinic receptors located on endothelial cells, may activate phospholipase C which in turn stimulates calcium entry, leading to eNOS activation. NO produced through the above processes then diffuses freely—irrespective of the presence of membranes—into adjacent cells. Phosphorylation/dephosphorylation processes involving protein kinases dependent on cyclic adenosine monophosphate, cyclic guanosine monophosphate (cGMP) and calcium/calmodulin, and disparate phosphatases[14] also control the constitutive isoforms of NOS. The influence of phosphorylation on the enzyme activity still remains unclear, since it has been reported as being decreased, increased or unaffected.[10] However, it has been recently reported that glutamate can dose-dependently reverse nNOS phosphorylation induced by NMDAR.[15] Thus, it is possible that phosphorylation/dephosphorylation processes contribute—through the intensity of the glutamatergic stimulus—to the maintenance of either a normal concentration (physiological situation) or

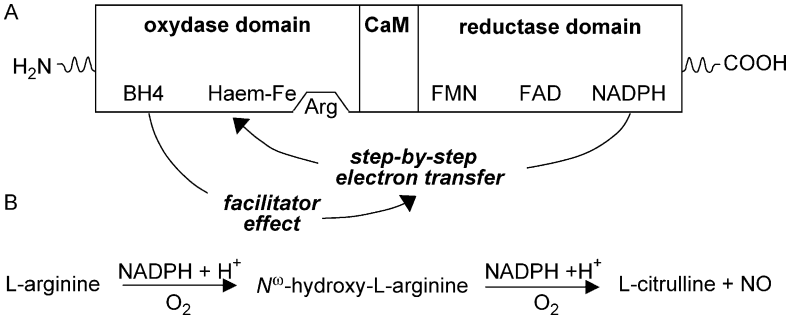

Figure 1 Schemas of the structural domains of NOS homodimer (A) and of the overall biochemical reactions related to NO production (B). Abbreviations: Arg, L-arginine; BH4, tetrahydrobiopterin; CaM, calmodulin; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form.