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Review

Nitric oxide as a regulatory molecule in the processing of the visual stimulus

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ABSTRACT

Nitric oxide (NO) is a highly reactive gas with considerable diffusion power that is produced pre- and post synaptically in the central nervous system (CNS). In the visual system, it is involved in the processing of the visual information from the retina to superior visual centers. In this review we discuss the main mechanisms through which nitric oxide acts, in physiological levels, on the retina, lateral geniculate nucleus (LGN) and primary visual cortex. In the retina, the cGMP-dependent nitric oxide activity initially amplifies the signal, subsequently increasing the inhibitory activity, suggesting that the signal is "filtered". In the thalamus, on dLGN, neuronal activity is amplified by NO derived from brainstem cholinergic cells, in a cGMP-independent mechanism; the result is the amplification of the signal arriving from retina. Finally, on the visual cortex (V1), NO acts through changes on the cGMP levels, increasing signal detection. These observations suggest that NO works like a filter, modulating the signal along the visual pathways.

Contents

Introduction

Vision corresponds to a process dependent on sensation (detection of stimulus in environment) and perception (interpretation, by subject, of the informations obtained and process by sense) produced by the brain initiated right after the detection of environmental light by the eyes [1,2]. Visual processing starts in the retina, where the image is initially decoded by receptor fields of visual cells, the visual information follows to the thalamic dorsal lateral geniculate nucleus (dLGN), a structure which presents retino-recipient laminar organization that segregates inputs from retinal ganglion cells according to the visual hemifield, the type of ganglion cell which originates the input, and other species-specific characteristics [3]. In the LGN, axons from ganglion cells make synapse with other neurons that project to the primary visual cortex (V1). From V1, the information could be send to other visual areas in cortex and to sub-cortical structures where the visual information is processed and stored [4].

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Analyses performed in different species have demonstrated that visual stimulus involves the activation of many receptors of the excitatory and inhibitory amino acids as glutamate and GABA respectively, although is well documented that others molecules, such as dopamine, norepinephrine, and acetylcholine also exert a significant role in retinal physiology. Added to this, several studies reveal that neuromodulatory molecules as nitric oxide (NO) are able to modulate the visual activity [5,6].

As ample described, NO is a gas generated as a product of the enzymatic conversion of L-arginine to L-citruline by different isoforms of nitric oxide synthase (NOS). NOS enzyme is expressed as Ca^{+}-dependent constitutive isoform (NOS-1 e NOS-3) and as Ca^{+}-independent inducible isoform (NOS-2). In the central nervous system (CNS) the constitutive isoforms of NOS are closely associated with physiological control of homeostasis. Ca^{+}-dependent NOS isoform are activated by calcium/calmodulin (CaM) and signal pathways that induces increase of intracellular calcium concentrations facilitates the complexification of CaM with NOS, which, in the presence of oxygen and NADPH, is activated [7]. Classical studies have demonstrated that the main signaling mechanism associated with NO signalization is the activation of soluble *guanylatecyclase* (sGC) which catalyzes the synthesis of cyclic guanosine monophosphate (cGMP) [8].

In the CNS, including brain and retina, many different regions present significant production of NO, suggesting its involvement in many aspects of CNS function [9]. After NO production there is an intense diffusion between cells, presenting three possible actions: (1) NO can nitrosylate proteins, including SNARE complex proteins which control exocytosis; (2) NO can activate sGC, inducing an increase in intracellular concentrations of cGMP; and (3) NO can bind the redox-sensitive site of specific receptors, such as NMDA, altering its conductive state [7,8,10–13]. In fact, nitric oxide has or presents a dual effect in the CNS, since in excessive glutamatergic activation or in response to inflammatory stimuli a neurotoxicity overproduction of NO is detectable. [14]. However, neuroprotective properties have been attributed to NO (the oxidized form), since this species downregulate NMDA receptor activity by reaction with thiol group(s) in the redox modulatory site of the receptor (Fig. 1) [15–17].

The presence of NO in the major divisions of the visual system (retina, lateral geniculate nucleus and visual cortex) suggests that this gas has an important role in the processing of visual information, the subject of this review. Although, several studies revels that NO is produced in all segment of visual pathway, few reports discuss about the role of NO in the regulation of visual transduction. Thus, in the present work, we performed an ample review of literature about the role of NO in the modulation of visual information initiated in the retinal tissue until superior areas of the CNS.

NO and retina

NO is present in different types of retinal cells, including the pigment epithelium [18,19], photoreceptors [20], Müller cells, horizontal, bipolar, amacrine and ganglion cells [20,21]. NOS-1 expression has been found, by immunohistochemistry and "*in situ*" hybridization, predominantly in the inner retina, between the inner nuclear and the ganglion cell layers [21–23], which shows a remarkable expression in amacrine and bipolar cells [24] (Fig. 2).

In general, the majority of studies analyzed the modulation of membrane conductance in dissociated retinal cells. NO has been shown to increase the gain and extend the voltage range of exocytosis in cone photoreceptors and to modulate voltage-gated ion channels in rods and cyclic nucleotide-gated channels in both rods and cones [25–27]. In the same cell type, activation of protein kinase G by sGC phosphorylates exocytotic proteins, facilitating vesicle fusion and resulting in greater amplitude of glutamate release [25,27]. NO modulate the light-evoked activity of rod and cone photoreceptors on evaluation by electroretinogram (ERG): while NO-donor decreased the amplitude of the rod single-flash ERG, it increased the amplitude of the isolated, intense paired-flash cone ERG (light-adaptation causes release of nitric oxide), and NO-synthase inhibitor increased the amplitude of the rod ERG, but no on

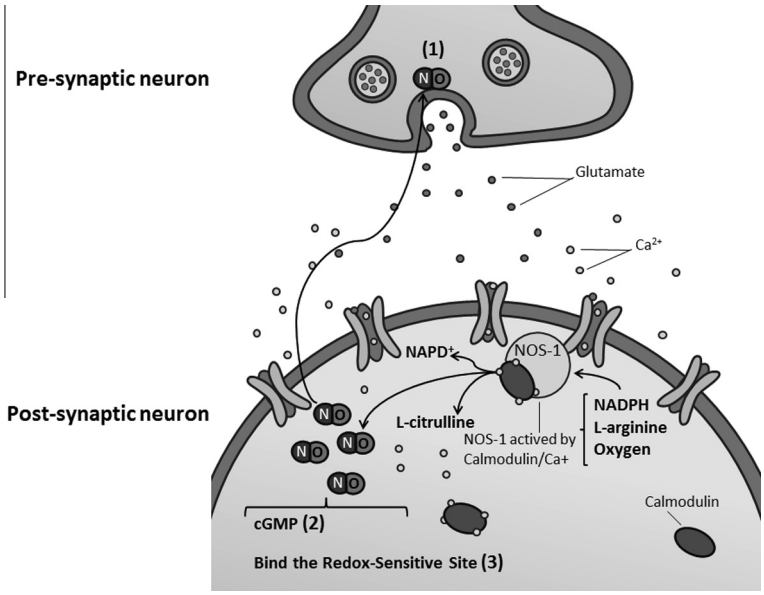

Fig. 1. Mechanism of formation andaction of NO. Glutamate activates NMDA receptors in the postsynaptic neuron, allowing the entry of Ca^{2+} that will bind to cal modul into activate NOS-1. After that, the NOS-1 is then able to catalyze the reaction that result in NO, which in turn will diffuse between the cells and can act: (1) the presynaptic neuron, promoting the exocytosis of vesicle with glutamate and consequent increasing the concentration of glutamate at the synapse, (2) increasing the concentration of cGMP, or (3) bind to sites redox-sensitive.