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

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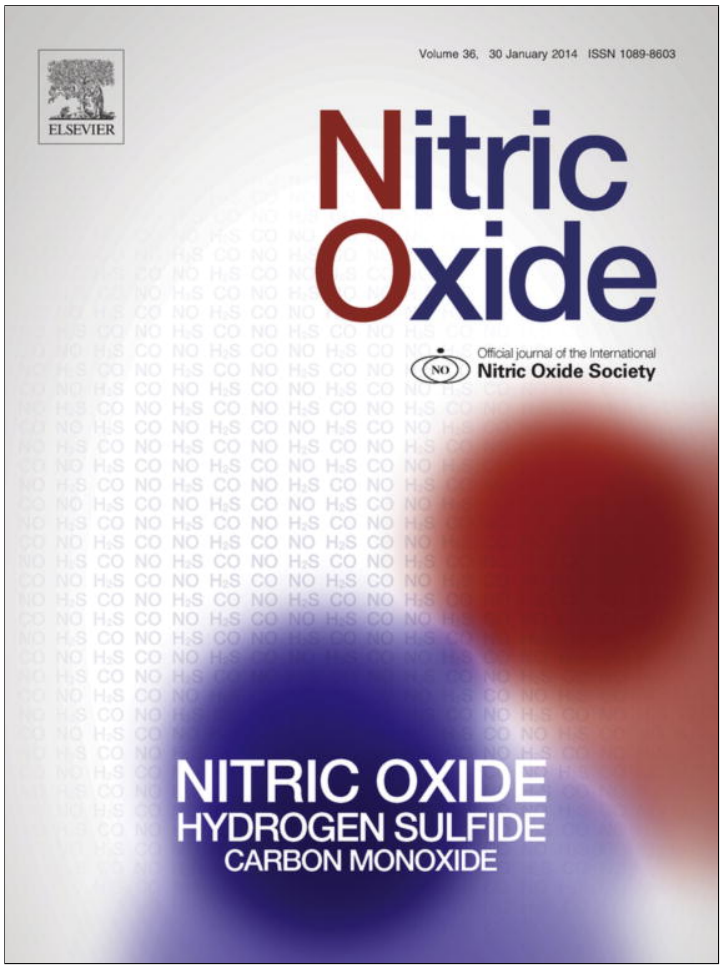

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Review

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

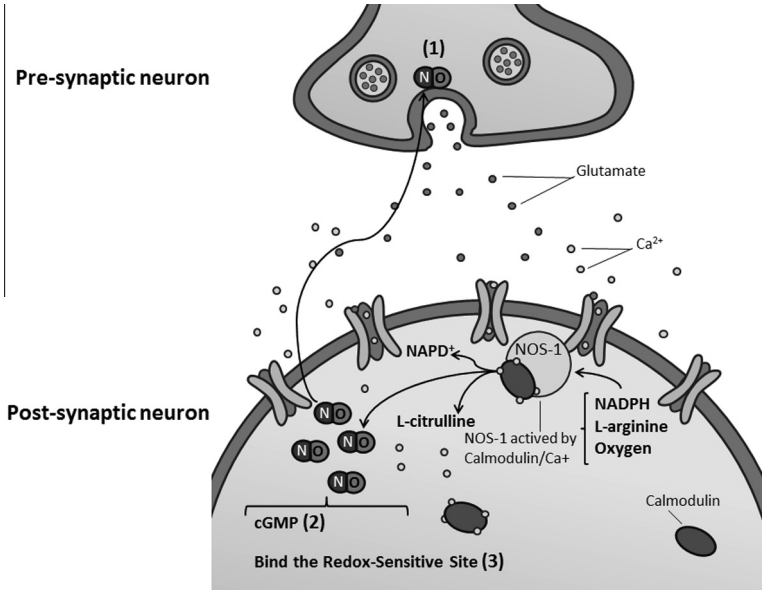

Fig. 1. Mechanism of formation andaction of NO. Glutamate activates NMDA receptors in the postsynaptic neuron, allowing the entry of Ca^{2+} that will bind to cal modul into activate NOS-1. After that, the NOS-1 is then able to catalyze the reaction that result in NO, which in turn will diffuse between 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.

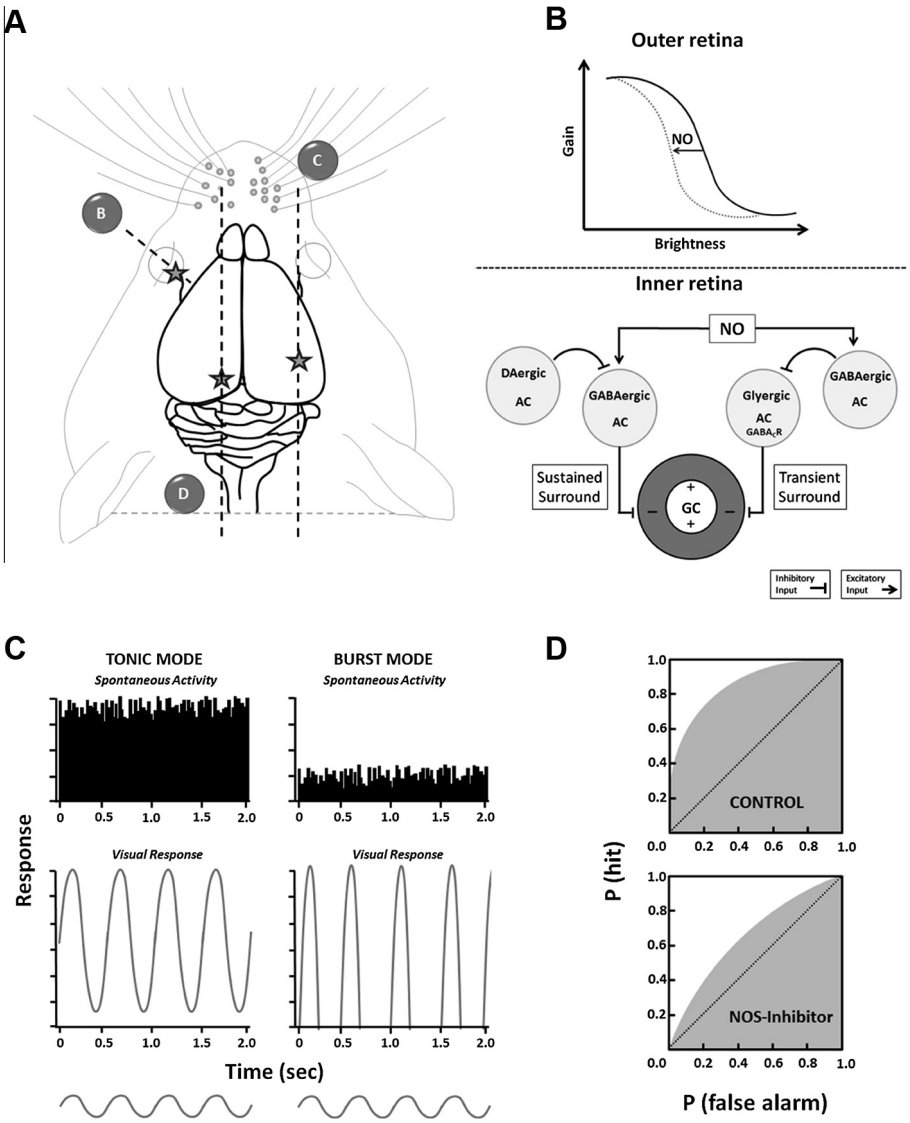

Fig. 2. Distribution of NO in retinal cells of mammals. NO is present in all cells of the retina, and it production is concentrated in the outer segments of photoreceptors (PL) and amacrine cells that haveNOS-1 (NOAC NOAC-I and -II). From its production source, NO acts locally and also diffuses a few micrometer stoneigh boring cells, creating effective levels in the PL, OPL and GCL. Bipolar and ganglion cells have sGC and NO exert its effects via activation of PKG or via cyclic nucleotide-gated channels, contributing to increased visual response. PL, photoreceptor layer; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. The grayer the cell or layer is, the higher the production or effect of NO.

the cone ERG [28,29]. Several immunohistochemical studies showed that photoreceptors are devoid of NOS-1 [30,31], others reported that inner and/or external segments present NOS-1 immunoreactivity in some species such as human, monkey, bovine, rat, rabbit, tiger salamander and turtle photoreceptors [23,32–37]. In spite of that, measures that assess the NO synthesis by fluorescence techniques using diaminofluorescein-2 (DAF-2), to correlate the expression of NOS-1 enzyme with NO production, related that photoreceptor outer segments and cell bodies are consistently devoid of NO synthesis [30,38,39].

Related with horizontal cells, cGMP analogs, L-arginine or the NO donors (as sodium nitroprusside – SNP), decrease electrical and dye-tracer coupling between these neurons [40–42]. The application of L-arginine in H1 type horizontal cells (luminosity-sensitive) reduce their responses to light, increases their input resistance and their response to stimulation of their receptive field center, while at the same time decrease their response to the receptive field surround and to kainate, and [41,43] It has been demonstrated that antagonists of $GABA_A$ and $GABA_\rho$ receptors increase retinal cGMP levels through the activation of nitric oxide synthase (NOS), and that NO stimulates GABA release from horizontal cells (due to the reversal of the GABA uptake transporter) and inhibits glycine release in the retina [44,45]. During continuous background illumination, turtle horizontal cells increased visual responses after the administration of L-arginine or NO donors, an opposite effect with addition of the L-NAME (N^G-nitro-L-arginine Methyl Ester, a NOS inhibitor) [46]. NO donors increase the cGMP levels, which induce the glutamate receptors activation, and in goldfish the application of *S*-nitroso-*N*-acetyl penicillamine (SNAP), a NO donor, display an increase of cGMP levels that in horizontal, bipolar, amacrine and ganglion cells [47], possibly resulting on increase cellular activity. Horizontal cells of monkey, rat and mouse express NOS-1 [26,32,48,49], as well as in synaptic contact between this cells and rod bipolar in rat [38], but it is devoid of sGC [38,50]

In mouse and tiger salamander bipolar cells, NO modulates cGMP levels [51,52], selectively increase responses to dim, but not bright, stimuli through a purely postsynaptic mechanism that

is blocked by PKG inhibitors [53]. PKG also decreases coupling of the ON-bipolar cell with metabotropic glutamate receptors to their downstream signaling cascade, which has the effect of amplifying small decreases in photoreceptor transmitter release [52,53], and of reducing coupling between AII amacrine cells and ON-cone bipolar cells [54,55], sustaining the evidence of cGMP on light responses in bipolar cells [52]. In goldfish, SNAP administration increase of cGMP levels in bipolar, as well as horizontal, amacrine and ganglion cells [47]. Studies with flicker ERG stimulation evoked an increase of NO liberation from bipolar cells in some, but continuous illumination increased NO synthesis in amacrine cells [56,57], and application of L-NAME reduced the amplitude of ERG a-wave (photoreceptor response related) and b-waves (ON-bipolar cell response related), but this effect is reversible by L-arginine and SNAP [58]. Bipolar cells express NOS-1 in rat, rabbit, turtle [32,59–63], and guinea pig (synaptic contacts with cone pedicles) [64], but in mouse bipolar cells the results are controversial [30,32,61].

Amacrine cells are the major source of NO in the retina, and NOS-1 is present in three amacrine cell types (AI, AII and AIII), in mammalian and turtle, with stronger immunostaining [8,32,38,50,61,63], but sGC is absent in AII and glycinergic cells [50]. NOS has been reported to have NADPH-diaphorase (NADPH-d) activity [21], and both histochemical detection of NADPH-d activity and immunoreactivity to antibodies raised against NOS are used as methods for the neuroanatomical identification of NOS-1. Light stimulation of amacrine cells leads to NO production [65], which increases the cone input and decreases the rod input during the light adaptation by uncoupling AII amacrine cells from cone bipolars. Mills and Massey [54] proposed that, in amacrine cells, increased cGMP and NO release controls the network switching between rod and cone pathways associated with light adaptation. In some amacrine cells GABA receptors and NOS coexist, and $GABA_A$ and $GABA_\rho$ receptors are involved themselves in serial interactions in the regulation of NOS activity [44]. In this sense, NO can depress $GABA_A$ receptor function by action mechanism where the NO stimulates the sGC to increase the cGMP levels, which then increase phosphorylation by protein kinase G to depress GABA currents, in other hand, the increased cGMP also stimulates a cGMP-activated phosphodiesterase to decrease cAMP levels and phosphorylation through protein kinase A [66].

In cultured chick embryo amacrine cells, NO donor promote increase of of $GABA_A$ receptor currents, and an enhance GABA release, while glycine signaling was inhibited in it [45,67]. NO is able transiently converts synaptic inhibition to excitation in retinal amacrine cells by shift in Cl^- reversal potential occurs at synaptic sites and is sufficient to promote excitation at GABAergic synapses [68]. After light adaptation, AII amacrine cells present increased coupling and AII amacrine and cone bipolar cells had the coupling littlely affected [69], but the NO donors, SNAP and 8-Br-cGMP, blocked coupling between the latter cell types, while AII-AII coupling appears to be regulated by dopamine [54,70]. NO and 8-Br-cGMP, yet, eliminated ON responses and caused a slight membrane depolarization, without effect on the retina dark adapted [71]. In adult chick, NOS inhibition reduced the number of GABA-immunoreactive amacrine cells, while the L-arginine increased this, suggesting that NO enhances overall signal inhibition in the inner retina [72], and in rat NO donors amplified ERG a- and b-waves, scotopic threshold response, and principally the oscillatory potentials (related with amacrine cells) in rats [73] suggesting that NO enhances overall signal inhibition in the inner retina.

The ganglion cells in the retina are the output from retina to LGN, and NO also influences its responses, mainly by modulating cGMP-gated conductances [74,75]. NOS-1 immunoreative was found in cell bodies within the ganglion cell layer in many vertebrates (human, bovine, rat, chicken, turtle, tiger salamander, catfish and goldfish) [23,26,33,59,63]. L-Arginine and SNP have direct influence in ganglion cells dark adapted, decreasing part of ON-responses, and decreasing or blocking OFF-responses in different types of ganglion cells; these responses are mediated by the APB-sensitive rod-OFF pathway [13,76]. NO inhibits glycine release, a mechanism that is related to the blockade of *OFF*-responses in ganglion cells [13], and also modulate light responses in light adapted ganglion cells of the mouse retina, in which NOS inhibition reduced light sensitivity, suggesting that under scotopic and photopic conditions NO plays opposite roles in the modulation of retinal light–dark adaptation [77]. The sensitivity of retinal ganglion cells to light is smaller in the retina of NOS-1 knockout mice, reinforcing the hypothesis that increasing NO dampens visual responses of ganglion cells, while a lack of NOS-1 activity decreases the sensitivity of ganglion cells to light [78]. This is a direct evidence that NO has a selective influence in inner retina, modulating the information that ganglion cells convey to the visual centers of brain.

NO in the LGN

The lateral geniculate nucleus (LGN) is the thalamic relay of retinal inputs to the visual cortex, and contains a rich array of brain terminals which modulate the visual inputs to the cortex. There is evidence that beside cholinergic, GABAergic, histaminergic, serotoninergic, and glutamatergic synapses, the LGN contains fibers and interneurons expressing NOS-1 [79–81]. The NO is involved in physiological and pathological processes of the LGN. In particular, it has been observed that this gas facilitates visual transmission from the retina to the cortex [10,82].

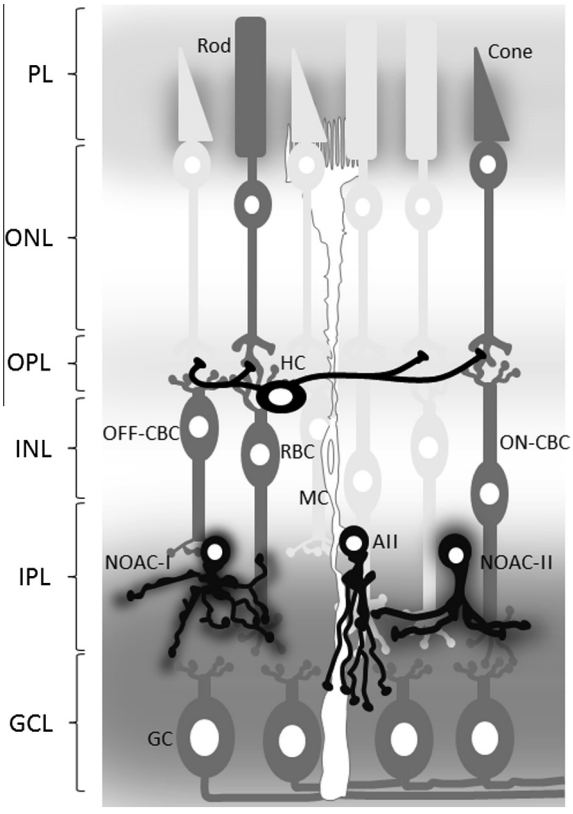

Fig. 3. Some mammals superiors not exhibit fibers of the first NOS-positive dLGN, but projections NOS-1 positive from the parabrachium, in brainsteim (dotted area). The activity in the dLGN, mediated by activation of NMDA receptors is in dependent of cGMP and has an important role in the development of this region as well as in the modulation common mechanisms of activation of NMDA receptors.

The dorsal LGN (dLGN) has an essential role in the transmission of visual information to the cortex. NO can enhance the relay of visual responses, due specifically and selectively to NMDA-receptor-mediated excitation in dLGN [80,83]. In the rodent dLGN, NADPH diaphorase reactivity is co-localized with GABA in a sub-population of local inhibitory interneurons [84]. In that region, the action of NO does not seem to involve cGMP [83].

Rodents, primates and felines do not seem to express NOS-1 in neurons of dLGN [85,86], but NOS-1-positive fibers which originate in the parabrachium (on brainstem) terminate in this region, and not within retinal afferents, which show a exclusively presynaptic location for NOS-1 [81,87,88] (Fig. 3). These differences occur possibly because NO can exist indistinct oxidation–reduction states that have different biological actions, it can have opposite effects depending on the local redox [89], and also the NO enhances the visual responses from the retina through the LGN to the visual cortex: NO affects NMDA-mediated activity independently of cGMP and the NMDA-associated redox site [90], suggesting that NO might modulate NMDA currents by stimulating the release of glycine, the co-factor for NMDA activation [10,12,81].

For neuronal responses in LGN, different sources of NO contribute to the formation of neuronal response, with the participation of NOS-1-positive fibers of parabrachium and NOS-3 originated of the blood vessels, modulating the oxygen stores necessary for it responses [91]. NO derives from the NOS-3 present in astrocytes acting in response the retinal glutamatergic input to LGN cells [92]. Light at low intensity stimulation (low contrast) an initial increase in blood flow is obtained by a mechanism that requires small increments in basal NO concentrations, while high intensity (high contrast) the brainstem system is activated, in this last case NOS-1 is intimately related with conservation of higher amounts of oxyhemoglobin, thus the activity by NO release acts not only on neurons but also on blood vessels, modulating the oxygen stores necessary for neural responses [91].

In ferret retinogeniculate projections, NO have an important role in development it, so that NO acts with NMDA receptors in activity-dependent refinement of it connections [93]. Thus in the visual thalamus, NO may act wherever parabrachial terminals arborize, with its production controlated by activity levels in these cells in a Ca^{2+}-dependent, facilitating the visual transmission from the retina through the dLGN to the cortex, mainly by activation NMDA receptors voltage-dependent [82].

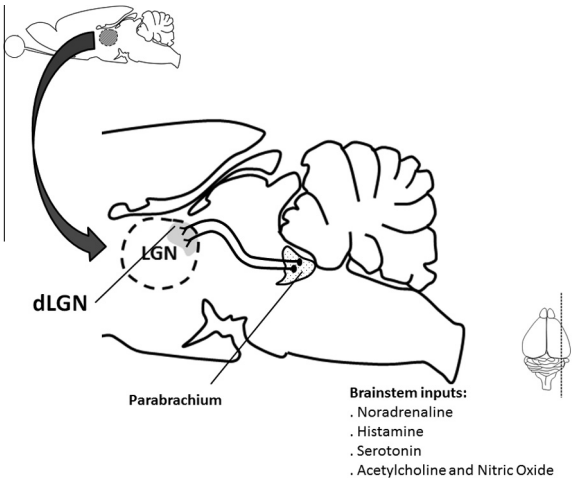

Fig. 4. Transference of nitrergic information of dLGN to V1. V1(highlighted area) receive visual inputs from the dLGN, but the production of NO is intrinsically non-cortical spiny neurons of the cortex which contain NOS-1, extending from layer II to white-matter (WM). In NO modulates visual responses via cGMP and is involved in the regulation of presynaptic neurotransmitter release.

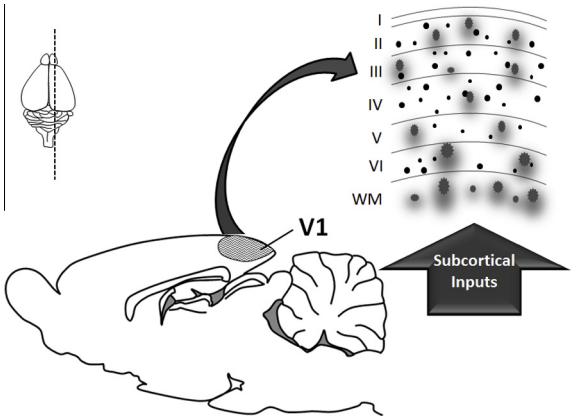

Fig. 5. Transference of nitrergic information of dLGN to V1. V1 (highlighted area) receive visual inputs from the dLGN, but the production of NO is intrinsically non-cortical spiny neurons of the cortex which contain NOS-1, extending from layer II to white-matter (WM). In NO modulates visual responses via cGMP and is involved in the regulation of presynaptic neurotransmitter release.

NO in the primary visual cortex

The primary visual cortex receive visual inputs from the dLGN, and the production of NO in this region occurs intrinsically non-spiny cortical neurons of the cortex which contain NOS-1 (Fig. 4) [18,21,94–99], also present NO derived cholinergic fibers of brainstem, and from blood vessels (with participation of NOS-3). Is possible to observe NOS-1 in neurons on layers II–VI also the subcortical white matter in mammalian [85,94–96,98,100], and it present NADPH diaphorase activity intimately related with staining to cytochrome oxidase blobs, suggesting the participation of NOS-1 on parvocellular visual processing [98]. In the primary visual cortex, NO acts through cGMP, as in the retina [11].

NO acts equally in NMDA-, AMPA- and acetylcholine-mediated currents through a cGMP-dependent pathway [11]. The majority of direction-sensitive V1 neurons are inhibited by NOS inhibitors, such as N^G-nitro-L-arginine (L-NARG). This effect is not observed in spontaneous activity, but in the cell firing rate after stimulation by NMDA, AMPA and ACh as well as in the presence of visual stimuli, but it can be blocked by co-application of L-arginine, while NO-donors synergistically increase the firing rate in the stimulated cells [11]. Kara and Friendlander [9] suggested that nitric oxide activity increases signal (by NO donors) detection by V1 cells, facilitating evoked responses, consistent with the hypothesis that, in the visual brain, nitric oxide amplifies signals which were previously filtered in the retina; but NOS inhibition significantly altered the visual response in most 83% neurons. A small population (5% of registered neurons) responded with an opposite pattern, with increased firing rate with NOS inhibitors, and decreased firing rate with NO donors. These different effects of NO might be attributable to the pharmacological substances accessing different sources of NO present in the neocortex: intrinsic intracortical neurons, that can be excitatory or inhibitory; subplate cells (below layer 6 in the white matter); dorsal raphe serotonergic neurons; and from extrinsic cholinergic brainstem inputs [87,101–103]. (See Fig. 5).

Concluding comments

In the present report we performed for the first time a literature review about the role of NO in the processing of visual information. In retinal tissue occurs the first step of this processing and is well documented that NO production plays amplifying signal by glutamatergic activation evoked from photoreceptors. After that, several phenomenons of cellular activation and inhibition are trigger in

retinal tissue started in photoreceptors and conduced to ganglion cells. In this pathway the NO produced in different cellular types (horizontal and bipolar cells) modulate the amplitude of action potentials and regulate the visual information that out from retinal tissue. In this context, is evident that NO production exerts a fundamental role for the adequate process visual transduction since retinal tissue represents the interface between physical stimulus and biological processing. The role of NO is extended to thalamic regions where studies demonstrated an intense expression of NOS isoforms in the regions that control ipsi and contra lateral determinations of retinal stimulus. Studies also reported that as well as occur on the retina in the visual cortex NO acts through changes on the cGMP levels mediated by activation of NMDA-, AMPA- and acetylcholine-mediated currents through a cGMP-dependent pathway. These phenomenons promotes increases in signal detection by V1 cells, facilitating evoked responses, which will be processed on superior visual centers. In summary, the studies reported in the present work suggest that NO represent an important regulatory molecules during visual processing and that nitrergic system contributes actively for the control of visual physiology.

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