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Review

Nitric oxide signaling in the retina: What have we learned in two decades?

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ABSTRACT

Two decades after its first detection in the retina, nitric oxide (NO) continues to puzzle visual neuroscientists. While its liberation by photoreceptors remains controversial, recent evidence supports three subtypes of amacrine cells as main sources of NO in the inner retina. NO synthesis was shown to depend on light stimulation, and mounting evidence suggests that NO is a regulator of visual adaptation at different signal processing levels. NO modulates light responses in all retinal neuron classes, and specific ion conductances are activated by NO in rods, cones, bipolar and ganglion cells. Light-dependent gap junction coupling in the inner and outer plexiform layers is also affected by NO. The vast majority of these effects were shown to be mediated by activation of the NO receptor soluble guanylate cyclase and resultant cGMP elevation. This review analyzes the current state of knowledge on physiological NO signaling in the retina.

Contents

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Abbreviations: 8-Br-cGMP, 8-bromo cyclic guanosine monophosphate; CNGC, cyclic nucleotide-gated channel; C-PTIO, carboxy-PTIO (NO scavenger); Cx, connexin; DAF-2DA, 4,5-diaminofluorescein diacetate (fluorescent NO indicator); DAPI, 4′,6-diamidino-2-phenylindole; DEA/NO, diethylamine NONOate (NO donor); ERG, electroretinogram; GCL, ganglion cell layer; IBMX, isobutyl methylxanthine (phosphodiesterase inhibitor); INL, inner nuclear layer; IR, immunoreactivity; IS, (photoreceptor) inner segments; l-NAME, L-NG-nitroarginine methyl ester (NOS inhibitor); l-NMMA, N5-[imino(methylamino)methyl]-L-ornithine, monoacetate (NOS inhibitor); NADPH:, nicotinamide adenine dinucleotide phosphate; NOAC, NO producing amacrine cell; NOC-12, 1-hydroxy-2-oxo-3-(N-ethyl-2-aminoethyl)-3-ethyl-1-triazene (NO donor); NOS, nitric oxide synthase; ODQ, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin1-one (sGC inhibitor); OPL, outer plexiform layer; OPs, oscillatory potentials; OS, (photoreceptor) outer segments; PIS, photoreceptor inner segments; PKG, protein kinase G (cGMP-dependent protein kinase); SEM, standard error of mean; sGC, soluble guanylate cyclase; SIN-1, 3-morpholino-sydnonimine (NO donor); SNAP, S-nitroso-N-Acetyl-D,L-penicillamine (NO donor); SNO-Cys, S-nitroso-cysteine; SNP, sodium nitroprusside (NO donor)

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1. Introduction

Nitric oxide (NO) participates in diverse physiological functions within the central nervous system (Bredt et al., 1990; Garthwaite, 2008). NO is synthesized by conversion of L-arginine to L-citrulline, a reaction that is catalyzed by the enzyme nitric oxide synthase (NOS), in the presence of oxygen and NADPH (Alderton et al., 2001; Daff, 2010). Vertebrates express three isoforms of NOS: The constitutive calcium-dependent neuronal (nNOS or NOS-I) and endothelial (eNOS or NOS II) isoforms, and the inducible, calcium independent isoform (iNOS or NOS III). Generally, the expression of NOS isoforms follows a conserved pattern: eNOS is mainly expressed in the vascular endothelium and iNOS mostly related to inflammation or pathological states (Knowles and Moncada, 1994), while nNOS dominates in neurons of the central and peripheral nervous systems. In the vertebrate retina and adjacent tissues, nNOS expression was first detected in efferent nerve fibers, and soon afterwards in a subpopulation of amacrine cells (Bredt et al., 1990; Dawson et al., 1991). During the last two decades, it has become clear that all three NOS isoforms are expressed to variable degrees in the retina, but nNOS is the main player in visual responses (Dawson et al., 1991; Kaur et al., 2006; Palamalai et al., 2006; Park et al., 1994; Park et al., 1996; Tsumamoto et al., 2002). Estimates of NO levels produced by NOS *in vivo* have been progressively lowered in recent years; with new data suggesting that even sub-nanomolar NO concentrations may exert measurable effects (Batchelor et al., 2010; Hall and Garthwaite, 2009). Under these conditions, the enzyme soluble guanylate cyclase (sGC) is the only established NO receptor, whose activation provokes an increase of intracellular cyclic GMP (cGMP) concentrations (Garthwaite, 2005). However, at higher concentrations and depending on the oxidative state of the cellular milieu, reactive oxygen species derived from NO may also modify cysteine and tyrosine residues, thereby modulating the function of a variety of target proteins (Hess et al., 2005; Knott and Bossy-Wetzel, 2009; Miyagi et al., 2002). In this review, we will focus on the nNOS isoform and discuss the current state of knowledge regarding the synthesis and function of NO in the retina.

2. Distribution of nNOS and NO synthesis in the retina

nNOS expression, detected by immunohistochemistry and *in-situ* hybridization, has been found predominantly in the inner retina, between the inner nuclear and the ganglion cell layers (Cheon et al., 2002; Dawson et al., 1991; Neufeld et al., 2000; Shin et al., 1999; Yamamoto et al., 1993b). Three main types of nNOS positive and NO synthesizing amacrine cells with distinct morphological properties have been described in rat and termed NOAC types I, II and displaced (Kim et al., 1999; Kim et al., 2000a; Lee et al., 2003; Pang et al., 2010). Type I and II NOACs are situated in the inner nuclear layer and their processes ramify principally in stratum 3 of the inner plexiform layer. They differ by the size of soma and dendritic arbors, which are considerably larger for type I compared to type II cells. The third type of NOAC corresponds to amacrine cells displaced towards the ganglion cell layer. They have large cell bodies comparable to type I cells, but their dendritic arbors ramify in strata 4 and 5 of the inner plexiform layer. All three NOAC types receive synaptic input from cone bipolar and from different amacrine cells. While their most common targets are other amacrine cells, they also make synapses with ganglion cells in both the ON and OFF sublaminae of the inner plexiform layer, and with bipolar cells in the ON sublamina. Very few mutual synaptic contacts between NOACs could be observed, and no synapses have been found with rod bipolar cells (Chun et al., 1999). A similar characterization, with minor variations in size and dendritic process distribution, has been reported in guinea pig (Oh et al., 1999). Comparable types of NOACs were described in other mammals, such as mouse and rabbit. In the cat retina only one kind of NOAC is found in the inner nuclear layer, and two types are displaced towards the ganglion cell layer (Kim et al., 1999; Kim et al., 2000a), while in chicken retina, nNOS is expressed in four, and in turtle, in five subtypes of amacrine cells (Fischer and Stell, 1999; Haverkamp et al., 2000).

In rat, nNOS immunoreactivity (IR) of type I NOACs is detected first on postnatal day 5, whereas type II and the displaced NOACs appear labeled on postnatal days 9 and 7, respectively (Kim et al., 2000b; Perez et al., 1995). NOACs are GABAergic cells throughout and express the GABA-synthesizing enzymes GAD-65 and GAD-67, which has been confirmed in primates, rat, rabbit and turtle (Andrade da Costa and Hokoc, 2003; Haverkamp et al., 2000; Oh et al., 1998; Vardi and Auerbach, 1995). In turtle, two types of NOACs were also shown to co-express glycine (Haverkamp et al., 2000).

Apart from NOACs, nNOS-IR in the retina has been reported in cell bodies within the ganglion cell layer in most vertebrate species analyzed (human, bovine, rat, chicken, turtle, tiger salamander, catfish and goldfish) (Cao and Eldred, 2001; Fischer and Stell, 1999; Gaikwad et al., 2009; Koch et al., 1994; Lee et al., 2003; Liepe et al., 1994; Neufeld et al., 2000; Tsumamoto et al., 2002), with the exception of frogs (Soto et al., 2006). Bipolar cells were shown to express nNOS in guinea pig, mouse, rat and turtle (Cao and Eldred, 2001; Giove et al., 2009; Kim et al., 1999; Lee et al., 2003; Oh et al., 1999; Vidal et al., 2006), and in rabbit with some divergent results (Kim et al., 2000a; Perez et al., 1995).

Interestingly, two reports found mouse bipolar cells to be devoid of nNOS expression (Kim et al., 1999; Kim et al., 2000a).

The outer plexiform layer of the guinea pig retina was shown to contain nNOS-positive bipolar cell dendrites making synaptic contacts with cone pedicles (Oh et al., 1999), and in rat the synaptic contacts of rod bipolar cells and B-type horizontal cells with rod spherules were also nNOS immunoreactive (Haverkamp and Eldred, 1998). Developmentally, nNOS-IR appears later in bipolar cells than in NOACs; around postnatal day 14 in rat (Kim et al., 2000b). The retinal expression of nNOS was also localized to horizontal cells of rat, turtle and goldfish, interplexiform cells of rat, monkey and mouse, and Müller cells in cat, turtle, tiger salamander and goldfish (Andrade da Costa and Hokoc, 2003; Cao and Eldred, 2001; Kim et al., 1999; Kurenni et al., 1995; Liepe et al., 1994; Yamamoto et al., 1993a).

Photoreceptors strongly express the histochemical NOS marker NADPH diaphorase (Kurenni et al., 1995), but several immunohistochemical studies found these cells to be devoid of nNOS expression (Chun et al., 1999; Giove et al., 2009; Yamamoto et al., 1993b). However, several groups did report labeling of photoreceptors by nNOS antibodies, and this discrepancy continues to date. Specifically, nNOS-IR was reported for the inner segments of human, monkey, bovine, porcine, rat, rabbit, tiger salamander and turtle photoreceptors (Blute et al., 1997; Cao and Eldred, 2001; Chakravarthy et al., 1995; Koch et al., 1994; Liepe et al., 1994; Neufeld et al., 2000; Shin et al., 1999; Tsumamoto et al., 2002; Vidal et al., 2006). Photoreceptor external segments were reported nNOS-positive in rabbit, bovine, monkey and human retinas (Kim et al., 1999; Koch et al., 1994; Neufeld et al., 2000; Venturini et al., 1991; Zoche and Koch, 1995) (Table 1).

While direct *in situ* measurement of physiological NO levels remains a challenge for the future, a fluorescence technique to visualize NO synthesis using the cell-permeant fluorophore diaminofluorescein-2 (DAF-2) has been applied in the retina, allowing to correlate the expression of NOS enzyme with NO production (Blute et al., 2000; Kojima et al., 1998). This method, although dependent on initial oxidation of the probe by reactive oxygen or nitrogen species and not completely specific for NO (Wardman, 2007), revealed a pattern that essentially coincides with NOS expression across terrestrial vertebrates, depicting NO synthesis in photoreceptor inner segments, certain amacrine cells, the inner plexiform layer and the ganglion cell layer, but bipolar cells are only occasionally NO-positive (Blute et al., 2000; Giove et al., 2009). Photoreceptor outer segments and cell bodies are consistently devoid of NO synthesis (Fig. 1).

3. Regulation of NO synthesis and NOS expression by light and other neuromodulators

Several reports describe the regulation of retinal NO synthesis by light. Flicker stimulation provoked an increase of NO liberation from bipolar cells in rabbit and miniature pigs, while continuous illumination increased NO synthesis in amacrine cells (Donati et al., 1995; Neal et al., 1998). Furthermore, two studies demonstrated an increase of NO synthesis, as shown by NO-dependent DAF fluorescence, in the inner retina after light stimulation in a pattern that closely matched the expression of nNOS in the retina (Eldred and Blute, 2005; Giove et al., 2009). The recent description of NOAC light responses under patch clamp provides a possible explanation for these observations. Type I and II NOACs showed depolarizing inward currents upon light ON/OFF and OFF stimulation, respectively, which is expected to trigger a transient rise in intracellular calcium through activation of voltage-dependent calcium channels, leading to NO synthesis by nNOS in these cells (Pang et al., 2010).

In the outer retina, NOS expression and NO liberation are also dependent on illumination and light adaptation levels. Both continuous and flicker light stimulation induced photomechanical movements in the photoreceptor layer of carp, which were shown to be mediated by light-activated NO synthesis (Haamedi and Djamgoz, 2002; Sekaran et al., 2005). In rat, eight hours of intense illumination almost doubled the

Table 1 – nNOS distribution in the retina of different vertebrate species, determined by immunohistochemistry and *in situ* hybridization. Crosses indicate the number of relevant publications considered for this review (++++ indicate four or more articles). *Unidentified cells in GCL.

	Photoreceptors		OPL	Horizontal cells	Bipolar cells	Amacrine cells	IPL	Ganglion cells	Cells in GCL*	Müller cells
	IS	OS								
Rat	++++		+++	+	++++	++++	++++	++	+	
Mouse			+		++	++	+		+	
Guinea pig					+++	++				
Rabbit	++	++				++				
Cat						+				+
Pig	+						+			
Bovine	+	+							+	
Monkey	+	+				+				
Human	+	+				+		+		
Chicken			+			+	+		+	
Turtle	++++		++	+	+	++++	+++	+++	+	+
Salamander	+++		+++			++	+++		++	++
Frog			+			+	+			
Goldfish				+	+	+			+	+
Catfish							+	+		

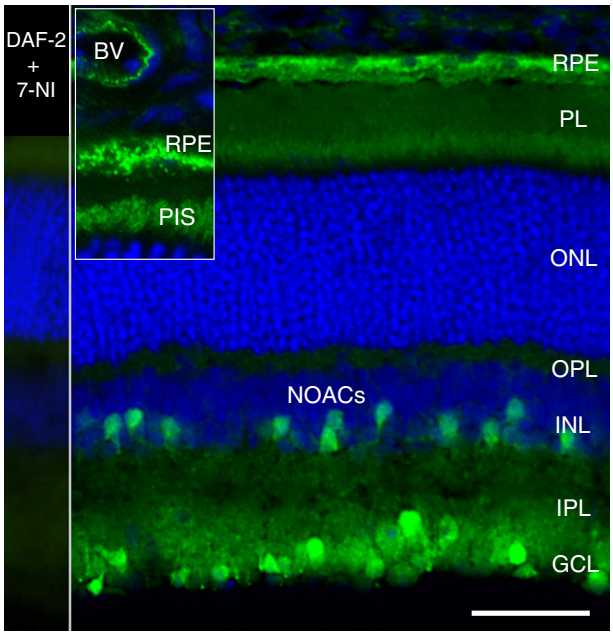

Fig. 1 – NO signaling in the adult rat retina. The distribution of NO synthesis is displayed by DAF-2 fluorescence (green). Nuclei are counterstained with DAPI (blue). DAF-2 fluorescence is strong in cell bodies of the inner nuclear layer (INL) and ganglion cell layer (GCL), presumed to be NOACs and displaced NOACs. The inner plexiform layer (IPL), photoreceptor inner segments (PIS; inset) the retinal pigment epithelium (RPE) and scleral blood vessels (BV; inset) are also labeled by DAF-2 fluorescence. Preincubation in the NOS inhibitor 7-nitroindazole (7-NI, 100 μM) abolished cellular DAF-2 fluorescence (left). OPL, outer plexiform layer; NOACs, NO-producing amacrine cells. Scale bar: 50 μm.

amount of nNOS in a preparation of rod outer segments, while iNOS expression increased even stronger, without reverting to normal levels in the subsequent hours of darkness (Palamalai et al., 2006).

The latter results suggest that high levels of illumination may also increase NO synthesis by the inducible NOS isoform as part of a pathological response. Thus, the expression level of nNOS was found unaltered while iNOS levels increased upon intense illumination of rat retina in a different study (Piehl et al., 2007). Along these lines of evidence, strong illumination was shown to promote photoreceptor apoptosis in an NO-dependent process, and to modulate the pattern of protein nitration in the outer retina (Donovan et al., 2001; Miyagi et al., 2002).

Apart from light stimulation, the synthesis of retinal NO is also regulated by acetylcholine, melatonin, dopamine and glutamate. Muscarinic acetylcholine receptor agonists like carbachol activate retinal nNOS expression and activity levels in biochemical assays (Borda et al., 2005), while melatonin inhibits NOS activity in the hamster retina (Saenz et al., 2002). The stimulation of NO synthesis in photoreceptors and the inner nuclear layer by dopamine was reported in carp, and light-induced NO synthesis in this species was inhibited by the dopamine receptor antagonist SCH-23390 (Haamedi and Djamgoz, 2002; Sekaran et al., 2005). Not surprisingly, glutamate, the main excitatory neurotransmitter in the retina, also stimulates NO synthesis. Cultured rat ganglion cells respond to glutamate by increased NO synthesis, an effect that could be suppressed by NOS inhibitors (Tsumamoto et al., 2002). In turtle, NO-dependent DAF fluorescence increased upon NMDA stimulation of the retina, mainly in the inner nuclear and ganglion cell layers, synaptic processes within the inner and outer plexiform layers, and in photoreceptor inner segments (Blute et al., 2000).

4. Distribution and stimulation of the NO receptor soluble guanylate cyclase (sGC) in the retina

The NO receptor sGC is consistently detected by immunohistochemistry in subgroups of cone bipolar and amacrine cells in the rat retina. To a lesser degree, sGC is also regularly expressed by rod bipolar and ganglion cells. Rod and cone photoreceptors, horizontal cells and specific amacrine cells like the AII subtype are generally devoid of sGC (Ding and Weinberg, 2007; Haberecht et al., 1998). However, some studies observed sGC in the internal and external segments of bovine, rat and mouse photoreceptors (Koch et al., 1994; Margulis et al., 1992; Nakazawa et al., 2005) as well as the expression of sGC activating protein (GCAP) in photoreceptors and subgroups of bipolar, amacrine and ganglion cells (Cuenca et al., 1998; Palczewski et al., 1994). sGC activity was shown to be amplified by exogenous NO donors such as sodium nitroprusside (SNP), and by the NO precursor L-arginine and the NOS cofactor NADPH, an effect that could be abolished by the addition of the NO scavenger hemoglobin in the first case, and by the NOS inhibitor l-NMMA in the latter two (Koch et al., 1994).

These findings were complemented by several studies showing increased cGMP synthesis in the retina, upon stimulation with exogenous or endogenous NO. Both L-arginine and the NO-donor DEA/NO provoked an increase of cGMP levels in hamster retina (Saenz et al., 2002; Saenz et al., 2007). Endogenous NO caused elevated cGMP levels in turtle inner retina, which was triggered by glutamate receptor activation (Blute et al., 1999). In this species, cGMP-IR was also increased by a combination of exogenous NO liberated by SNP and phosphodiesterase inhibition with IBMX in at least eight different classes of amacrine cells, three types of bipolar cells and several classes of ganglion cells (Blute et al., 1998), while glycinergic and GABAergic neurotransmission were shown to interact in the modulation of NO-dependent cGMP levels in the inner retina (Yu and Eldred, 2003; Yu and Eldred, 2005a). In bovine, rat and rabbit, the NO donors SNP, SIN-1 and SNAP increased cGMP-IR in cone bipolar and some amacrine and ganglion cells (Gotzes et al., 1998). The NO donor SNAP also triggered an increase of cGMP levels in horizontal, bipolar, amacrine and ganglion cells of the goldfish (Baldridge and Fischer, 2001).

Controversy persists regarding the expression of cGMP-IR in rod bipolar cells and photoreceptor inner segments. While most studies did not find NO-dependent elevation of cGMP

levels in rod bipolar cells (Gotzes et al., 1998), in rat, application of the NO donor SNP increased cGMP concentrations in both cone and rod bipolar cells (Johansson et al., 2000; Mastrodimou et al., 2006). Another study in rabbit found cGMP-IR after NO donor stimulation of both photoreceptor inner segments, ON cone bipolar cells and certain ganglion cells (Koistinaho et al., 1993). However, cGMP-IR was not detected in rat and bovine photoreceptor inner segments upon exogenous NO stimulation, although it was purportedly increased by NOS inhibition (Gotzes et al., 1998).

Retinal acetylcholine signaling through both muscarinic and nicotinic receptors was shown to modulate NO-dependent cGMP-IR in different retinal cell types. In rat, carbachol, an agonist of muscarinic acetylcholine receptors, increased retinal cGMP levels, an effect that was sensitive to the sGC inhibitor ODQ and the NOS inhibitor l-NMMA (Borda et al., 2005). In salamander, stimulation with oxotremorine, another muscarinic acetylcholine receptor agonist, provoked elevated cGMP-IR in subgroups of bipolar, amacrine and ganglion cells, which could be prevented by the addition of different NOS inhibitors (Cimini et al., 2008).

In turtle, nicotine induced strong cGMP-IR in amacrine cell bodies, their synaptic contacts in two substrata of the inner plexiform layer, as well as in photoreceptor inner segments and terminals. In the inner retina, the nicotine-induced cGMP-IR was sensitive to NOS inhibition, while photoreceptor cGMP-IR remained unaffected, suggesting that only inner retinal cGMP-IR was regulated by NO (Blute et al., 2003).

Retinal cGMP-IR was also increased by somatostatin, an effect that involves somatostatin sst_2 receptors, tyrosine phosphatase and NOS (Mastrodimou et al., 2006). On the other hand, melatonin reportedly inhibits cGMP-IR induced by L-arginine or the NO donor SNP in retinal homogenates of the Syrian hamster (Saenz et al., 2002).

sGC, apart from being activated by NO, can also be stimulated by carbon monoxide (CO), although it is less sensitive to this compound. Interestingly, the underlying mechanism may also depend on NO. In turtle, the CO producing enzyme heme oxygenase-2 is expressed in all photoreceptors and certain bipolar, amacrine and ganglion cells, while in rat, it is only detected in amacrine and ganglion cells (Cao et al., 2000). In both turtle and salamander, stimulation with CO increased cGMP-IR in the inner retina, but the effect was strongly dependent on endogenous or exogenous NO, suggesting synergistic interactions between NO and CO signaling pathways in the retina (Cao and Eldred, 2003; Pong and Eldred, 2009).

In synthesis, prominent sGC expression and NO-dependent cGMP elevation are general features of mammalian cone bipolar cells. Rod bipolar cells and ganglion cells appear to contain lower amounts of NO-dependent sGC, and its expression might vary across species. Evidence for a NO-sGC-cGMP signaling pathway in photoreceptors is still insufficient for definitive conclusions.

5. Activation of cyclic nucleotide-gated channels (CNGCs) by NO

In vertebrate phototransduction, cGMP acts as second messenger opening CNGCs in photoreceptor outer segments. In addition, CNGCs have been detected in photoreceptor terminals. While there is no evidence that NO-induced cGMP elevation is involved in the process of phototransduction, the CNGCs of salamander cone photoreceptor axon terminals were shown to be activated by exogenous NO (Rieke and Schwartz, 1994). Similar evidence was obtained in the lizard, where exogenous NO was shown to modulate synapses between cones and horizontal cells, an effect that was sensitive to the specific sGC inhibitor ODQ (Savchenko et al., 1997).

In goldfish, CNGCs homologous to those of cone photoreceptors are expressed in rod and cone ON bipolar cells, as shown by in situ hybridization and polymerase chain reaction. However, OFF bipolar cells were completely devoid of CNGCs (Henry et al., 2003). In rat, some cells of the inner nuclear and ganglion cell layers also express CNGCs, which present a high degree of homology with those of rod photoreceptors (Ahmad et al., 1994). In patch clamp recordings of ganglion cells, addition of the membrane-permeant cGMP analog 8-Br-cGMP to the intracellular solution triggered a large inward current, which could also be observed after stimulation with NO donors. This NO-induced inward current was shown to be suppressed by activation of AMPA-type glutamate receptors in ganglion cells, and proposed to operate in the modulation of retinal output by NOACs (Kawai and Sterling, 1999; Kawai and Sterling, 2002). Finally, human and bovine Müller cells were also found to express CNGCs, which could be activated by NO donors, suggesting a NO-cGMP system operating in these retinal glial cells (Kusaka et al., 1996).

6. NO modulates retinal light responses

A modulation of light responses by NO has been shown to occur in different retinal cell types. In salamander photoreceptors, NO donors increased voltage-dependent calcium currents, supporting a modulation of signal transmission to second-order neurons by NO (Kurenny et al., 1994). However, a closer analysis of the effect showed that it was limited to rods and absent from cones, suggesting a differential regulation of rod and cone pathways and a role in light/dark adaptation (Kourennyi et al., 2004). In turtle, cone light responses were amplified by exogenous NO and the NO precursor L-arginine, and reduced through NOS inhibition (Levy et al., 2004). Along these lines of evidence, cone light responses were reduced by application of the NO scavenger C-PTIO during light adaptation, suggesting that NO is involved in light adaptive processes in the outer retina (Sato et al., 2011). Furthermore, in frog, rod light responses and dark currents were shown to be modulated by endogenous NO signaling, with NOS inhibition favoring rod hyperpolarization (Noll et al., 1994). In other non-mammalian vertebrates such as carp, bream and frog, exogenous NO was shown to trigger photomechanical movements of cone photoreceptors, which plays an important role in light adaptation in lower vertebrates. Conversely, cone contraction by light adaptation was diminished by NO scavengers, indicating the presence of an endogenous NO signaling pathway regulating light adaptation via photomechanical movements in these species (Angotzi et al., 2002; Djamgoz et al., 2000).

At the second level of retinal processing, turtle horizontal cells displayed increased visual responses after stimulation

with NO donors or L-arginine, while addition of the NOS inhibitor l-NAME had the opposite effect (Levy et al., 2004). In carp, a differential effect of exogenous NO on rod and cone horizontal cell light responses was reported, which could be reverted by inhibition of the NO receptor sGC (Ye et al., 1997). Furthermore, the light adaptive chromatic difference in receptive field size of carp horizontal cells was shown to be modulated by both exogenous and endogenous NO, adding to the evidence that NO functions as a regulator of retinal light adaptation in lower vertebrates (Furukawa et al., 1997; Furukawa et al., 2002). Again, the effect was mediated by cGMP and sensitive to NO scavenger application. Horizontal cell responses to glutamate and kainate were also modulated by NO-cGMP signaling, as evidenced by the effects of the NO donor SNAP, the NO precursor L-arginine or the NO scavenger hemoglobin, which reduced the receptor's affinity for glutamate but increased its maximum currents. This effect, observed in perch and hybrid bass, was further amplified by dopamine (McMahon and Ponomareva, 1996; McMahon and Schmidt, 1999).

Evidence for an amplification of light responses in bipolar cells was obtained in mouse and tiger salamander. In mouse ON bipolar cells, both exogenous NO and cGMP increased the responses to weak stimuli, but not to strong ones. Inhibitors of cGMP-dependent protein kinase (PKG) prevented the result, suggesting a NO–sGC–PKG transduction pathway operating in these cells (Snellman and Nawy, 2004). These findings support earlier evidence for a boosting effect of cGMP on light responses in bipolar cells (Nawy and Jahr, 1991).

At the next processing level, amacrine cells are the major source of NO in the retina, but few reports have addressed their putative responses to NO. In light-adapted rabbit AII amacrine cells both exogenous NO and 8-Br-cGMP eliminated ON responses and caused a slight membrane depolarization, but had no effect if the retina was dark adapted (Xin and Bloomfield, 1999a). In cultured chick embryo amacrine cells, exogenous NO altered $GABA_A$ receptor function by elevating the intracellular chloride concentration. Thus, between coupled amacrine cells, synaptic inhibition was effectively converted into excitation, as occurs *in vivo* during early development (Hoffpauir et al., 2006). In adult chick retina, GABA synthesis was shown to be sensitive to drugs affecting endogenous NO synthesis: NOS inhibition significantly reduced the number of GABA-immunoreactive amacrine cells, while the NO precursor L-arginine increased that number, suggesting that NO enhances overall signal inhibition in the inner retina (Maggesissi et al., 2009). Surprisingly, there is currently no information regarding direct effects of exogenous NO on the NO-synthesizing amacrine cells themselves.

In guinea pig ganglion cells, both NO donors and membrane-permeant cGMP analogs generate membrane depolarization and lower the excitation threshold, by a mechanism that, unlike that of bipolar cells, does not involve PKG but apparently a direct activation of CNGCs (Kawai and Sterling, 2002). In ganglion cells of the dark adapted ferret retina, L-arginine and the NO donor SNAP reduced ganglion cell ON responses and in most cells practically eliminated OFF responses (Wang et al., 2003). A modulation of light responses was also seen 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 (Nemargut and Wang, 2009). These findings are in line with the observation that nNOS knockout mice display a reduced light sensitivity at the ganglion cell level (Wang et al., 2007).

The modulation of overall light responses of the retina has been analyzed in a variety of studies by electroretinogram (ERG) recording, mostly in combination with drug application through injection into the vitreous. As the ERG represents a summation of field potentials from all retinal layers, the results are generally complex and sometimes difficult to interpret. In cats, application of the NOS inhibitor l-NAME reduced the amplitude of ERG a- and b-waves, representing photoreceptor and ON-bipolar cell responses respectively, while the NO precursor L-arginine and the NO donor SNAP reverted the effect (Ostwald et al., 1997). However, in rat, ERG a- and b-waves were reduced one day after injection of the NO donor SNP (Fawcett and Osborne, 2007). In albino rabbits, the NO donor SNAP diminished the ERG a-wave; left the b-wave unchanged and augmented the oscillatory potentials associated with amacrine cell signaling. Co-application of the NO scavenger C-PTIO abolished this effect (Oku et al., 1997). Further studies reported disparate effects depending on light versus dark adaptation of the retina, or selective recordings of rod and cone signal. In carp, the NO donor SNP diminished the scotopic and amplified the photopic ERG b-wave. Both effects could be reverted by addition of the NO scavenger hemoglobin (Ye et al., 1997). A recent study in rat showed that NO supplied with the NO donor SNAP reduced the rod a-wave, while the cone a-wave increased. Inhibition of endogenous NO by l-NAME had the opposite effect on the rod a-wave, but did not affect the cone signal (Sato and Ohtsuka, 2010).

In our laboratory, we observed a dose-dependent effect of exogenous NO on the ERG response (Fig. 2). The NO donor NOC-12 reversibly amplified all components of the scotopic ERG at a concentration of up to 200 μM, while higher doses reduced or even abolished the visual response. Similar findings were obtained with the NO donor SNP. Under photopic adaptation, the amplifying effect of NO was reduced, but still statistically significant, which suggests that the rod pathway was the main target of NO.

These partly divergent results of different ERG studies regarding an increase or decrease of visual responses after exogenous NO application can be explained by the different time scales of the experiments, and by large differences in the applied NO donor concentrations. It is well established that NO is cytotoxic at high levels, and might therefore cause an unspecific reduction of visual responses in the retina (Takahata et al., 2003a; Takahata et al., 2003b).

7. Modulation of other neurotransmitters by retinal NO

Ample evidence suggests that retinal NO modulates GABA and glycine signaling, but the observed effects are too diverse to allow a generalization across species. In the retina, inhibitory neurotransmitters are liberated by amacrine cells, of which a subpopulation also releases NO. In cultured rat amacrine cells, NO donors and membrane-permeant cGMP analogs inhibit $GABA_A$ receptor signaling through a mechanism

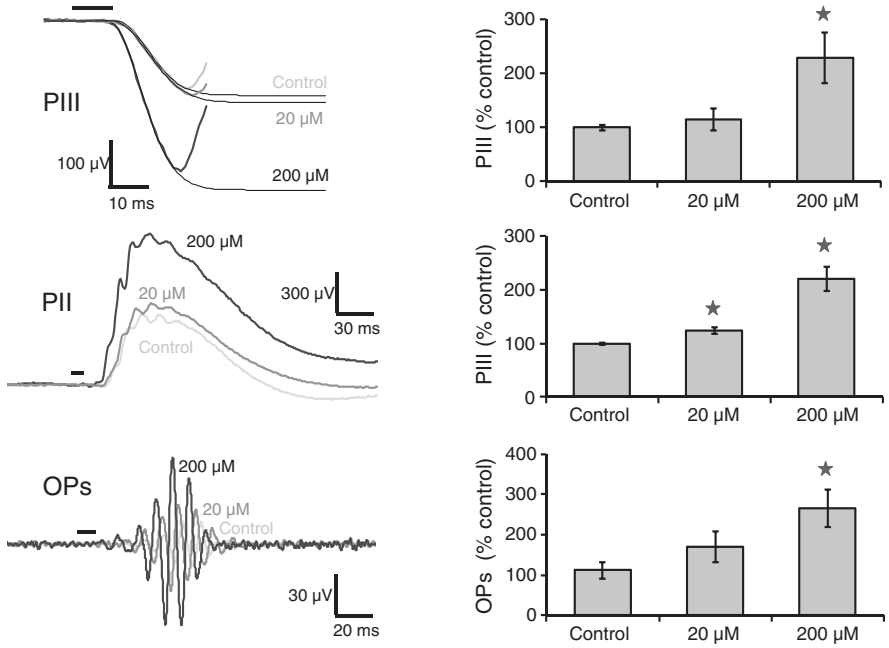

Fig. 2 – NO amplifies the visual response of photoreceptors, bipolar cells and amacrine cells in the scotopic flash ERG (Vielma et al., 2010). Left column: Representative responses after control (saline) and NO donor (NOC-12; 20 and 200 μM) injection into the vitreous before the experiments. The top traces display mathematical modeling of the ERG generators PIII and PII according to the model of Hood and Birch (Hood and Birch, 1990). Below, oscillatory potentials (OPs) were isolated by band-pass filtering the ERG signal. Light stimuli are indicated by horizontal bars. Right column: Average relative response amplitude (mean ± SEM) of the ERG generators PIII, PII and the OPs 1h after NOC-12 application. Asterisks indicate statistically significant difference compared to control (Student's paired t-test, $p < 0.05$).

dependent on PKG (Wexler et al., 1998), while basal GABA release from amacrine and ganglion cells was inhibited by endogenous NO in chicken retina (Maggesissi et al., 2009). On the other hand, an increase of $GABA_A$ receptor currents was caused by stimulation with the NO donor NOC-12 in amacrine cells of the same species (Hoffpauir and Gleason, 2005), and in turtle, exogenous NO provoked an increase of GABA release from amacrine cells, while glycine signaling was inhibited (Yu and Eldred, 2005b). Several other reports found functional links between NO and GABA signaling in the inner retina, in diverse species (Andrade da Costa et al., 2001; Ientile et al., 1997; Jung, 2002).

Apparently conflicting results were published regarding the regulation of acetylcholine signaling by NO. In rat retina, acetylcholine is synthesized and released exclusively by starburst amacrine cells, which do not produce NO. In this species, NO donors inhibited depolarization-induced acetylcholine release; an effect that was mediated by enhanced GABA signaling on cholinergic neurons (Okada et al., 2001). However, another study in rabbit found that the NO donor SNAP increased light-induced acetylcholine release, through a mechanism involving NO-dependent inhibition of glycine signaling by amacrine cells (Neal et al., 1997). Possibly, both effects could be reconciled by the observation that NO regulates retinal GABA and glycine signaling in opposite ways (Yu and Eldred, 2005b).

Further retinal neuromodulators that are affected by NO signaling are dopamine, somatostatin and melatonin. In both rat and rabbit, exogenous NO was shown to reduce the liberation of depolarization-induced dopamine release. In addition, NO might also directly degrade dopamine by oxidation (Djamgoz et al., 1995; Neal et al., 1999). In agreement with these data, NOS inhibition increased basal dopamine levels in bovine retina, through a mechanism independent from cGMP (Bugnon et al., 1994). Somatostatin release was also shown to be increased by both exogenous NO and the NO precursor L-arginine in rat (Kiagiadaki et al., 2008), while melatonin synthesis by photoreceptors was inhibited by NO donor application (Wellard and Morgan, 1996; Wellard and Morgan, 2004). Many more reports have addressed functional interactions of NO with other retinal neuromodulators, but cannot be cited here due to space restrictions.

8. Regulation of electrical coupling in the retina by NO

It has been reported that both NO levels and the degree of light/dark adaptation regulate electrical coupling between different retinal cell types, but it remains unclear if both processes are directly related. In rabbit, a low degree of electrical coupling between horizontal cells is observed under extreme light or dark adaptation, but coupling increases dramatically under dim light stimulation. Exogenous NO, its precursor L-arginine and the membrane-permeant cGMP analog 8-Br-cGMP provoked a reduction in the coupling rate of A- and B-type horizontal cells, suggesting an involvement of NO in retinal light

adaptation (Miyachi et al., 1990; Xin and Bloomfield, 2000). Similar results were obtained in catfish, bass, carp and goldfish in which both cGMP analogs and NO donors promoted uncoupling of horizontal cells (Daniels and Baldridge, 2011; DeVries and Schwartz, 1989; Lu and McMahon, 1997; Pottek et al., 1997). In turtle, both the NO precursor L-arginine and its second messenger cGMP reduced gap junction coupling of horizontal cells (Miyachi et al., 1990), and dopamine, which stimulates NO synthesis in the retina, had a similar effect in mouse (He et al., 2000; Weiler et al., 2000). These antecedents suggest that NO participates in the regulation of horizontal cell coupling as part of the light adapting mechanisms operating in the retina, throughout a wide range of vertebrate species.

However, the localization of the endogenous NO source responsible for this effect remains unclear. According to most studies in mammals, horizontal cells and the outer plexiform layer are generally devoid of nNOS, and a diffusion of NO from photoreceptor inner segments or the inner plexiform layer seems unlikely. Yet, localized nNOS expression within subcellular compartments of certain bipolar and horizontal cell processes has been reported and might represent NO sources affecting horizontal cell coupling (Cao and Eldred, 2001; Haverkamp and Eldred, 1998; Liepe et al., 1994).

As opposed to the outer plexiform layer, electrical coupling in the inner plexiform layer could easily be modified by NO liberated from NOACs. AII amacrine cells display dramatically increased coupling after light adaptation, while coupling between AII amacrine and cone bipolar cells is only moderately affected (Bloomfield et al., 1997). The NO donor SNAP and 8-Br-cGMP blocked coupling between the latter cell types, while AII-AII coupling appears to be regulated by dopamine (Mills and Massey, 1995; Xia and Mills, 2004).

Together, these data suggest that NO is involved in the light-dependent regulation of gap junction coupling in both

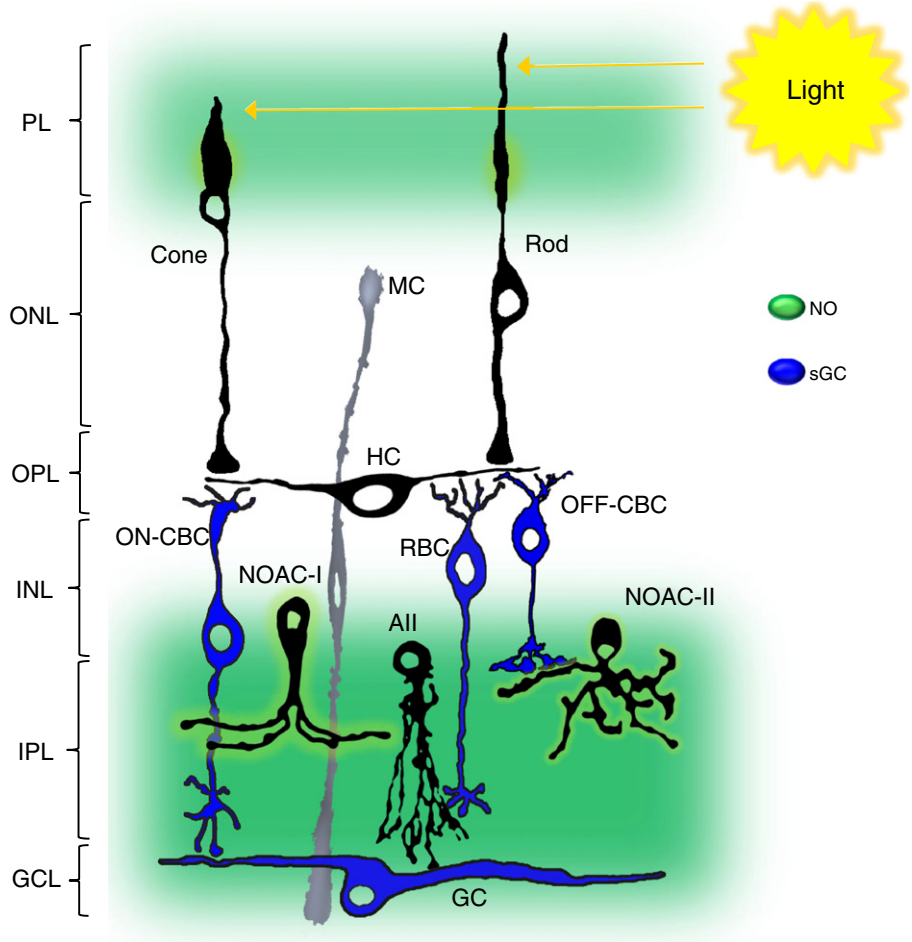

Fig. 3 – Schematic model of cellular NO signaling in the mammalian retina. Biochemical and histochemical data from several species indicate that NO is synthesized in the outer retina in photoreceptor inner segments, and in the inner retina by the NOAC subtypes of amacrine cells. DAF-2 imaging and theoretical considerations suggest that NO acts locally and diffuses only few micrometers from its source. However, the sum of many local sources might generate effective levels throughout the PL, the IPL and the GCL. NOACs receive synaptic input from amacrine as well as ON and OFF bipolar cells and form conventional synapses with on cone bipolar and other amacrine cells. Both bipolar and ganglion cells express sGC and are thus potential NO targets. In these cells, NO exerts its effects through PKG or direct CNGC activation, generally increasing visual responses. Müller cells have been proposed to be NO sources or targets in different species, but their role in NO signaling of the mammalian retina remains uncertain.

the inner and outer retina, in combination with dopamine and possibly other neuromodulators (Bloomfield and Volgyi, 2009).

9. Protein S-nitrosylation and nitration

Apart from binding to the heme group of sGC, activating the enzyme and elevating intracellular cGMP levels, NO may also be converted into reactive nitrogen species that affect cellular physiology through covalent reactions with target proteins (Martinez-Ruiz et al., 2011). Cysteine residues have a thiol group that can be oxidized by these compounds under certain conditions, producing protein S-nitrosylation. Although the precise reaction mechanism remains somewhat uncertain, it appears to involve NO_2 or S-nitrosoglutathione as intermediates (Gaston et al., 2003; Gow et al., 1997; Hess et al., 2005; Jaffrey et al., 2001; Pacher et al., 2007). Several types of ion channels, such as TRP channels (Yoshida et al., 2006), different families of potassium channels (Asada et al., 2009; Kawano et al., 2009; Nunez et al., 2006), ryanodine and G-protein-coupled-receptors (Aracena-Parks et al., 2006; Estrada et al., 1997), cyclic nucleotide-gated ion channels (Broillet, 2000), and certain connexins, like Cx43 among others (Retamal et al., 2006) are subject to S-nitrosylation. In the retina, the physiological role of protein S-nitrosylation has not been studied in detail. However, it has been suggested that retinal cell proliferation, dendritic growth, and neuroprotection are in part controlled through this covalent modification (Cheung et al., 2000; Koriyama et al., 2010; Magalhaes et al., 2006). Olfactory CNGCs are activated through S-nitrosylation (Broillet, 2000), and since homologous channels are expressed in photoreceptors and bipolar cells, a similar mechanism might take place in the retina. We recently showed that exogenous NO, applied through different NO donors, strongly amplifies the ERG PII, PIII and oscillatory potentials (Fig. 2). Since these effects were not sensitive to the potent sGC inhibitors ODQ and NS-2028, they are unlikely to involve cGMP as second messenger (Vielma et al., 2010). Instead, protein S-nitrosylation appears as a possible mechanism of action of NO-donors on photoreceptors. However, further studies are necessary in order to clarify which proteins can be S-nitrosylated under appropriate conditions and how this post-translational modification affects their properties. Channels formed by connexins (Cx) are fundamental for retinal development and function in the adult (Bloomfield and Volgyi, 2009). All retinal cells express at least one type of connexin, which form specific contacts between different cell types. One of the connexins that is readily S-nitrosylated is Cx43 (Retamal et al., 2006). In the retina, Cx43 is expressed in the ganglion cell layer and optic nerve, apart from some Müller and pigment epithelial cells (Kerr et al., 2010). This raises the possibility that NO may be converted into reactive nitrogen species which affect retinal signal processing through S-nitrosylation of Cx43. Recent works support the idea that additional connexins are also modified by S-nitrosylation (Retamal et al., 2009). It will be interesting to examine if Cx 36, 45, 59 and 62, which are expressed in the retina (Sohl et al., 2010), are also subject to protein S-nitrosylation, and if this occurs *in vivo* triggered by endogenous NO.

Another posttranslational protein modification is nitration, which is the oxidation of tyrosine residues through reactive nitrogen oxides like $ONOO^-$ or NO_2 (Pacher et al., 2007). Contrary to S-nitrosylation, tyrosine nitration is irreversible and is likely to be limited to highly oxidative environments. In general, it is therefore correlated with pathological conditions. Retinal tyrosine nitration is observed after prolonged exposure to intense light, and is associated with light-induced photoreceptor cell death (Palamalai et al., 2006). Interestingly, formation of nitro-tyrosine was detected in photoreceptor outer segments of rats adapted to darkness, but after light adaptation, nitration decreased in the outer segments and increased in the inner segments and pigmented epithelia (Miyagi et al., 2002). Early studies already showed that retinal light-dependent cell damage is correlated with rhodopsin activity (Noell et al., 1966). Thus, cell death in the retina after light exposure is attenuated in rhodopsin knockout mice (Grimm et al., 2000), and significantly reduced in animals treated with antioxidants such as ascorbate, dimethylthiourea (Organisciak et al., 1985; Organisciak et al., 1999), and phenyl-N-tert-butylnitrone (Ranchon et al., 2001). These results suggest that cell death induced by intense light is mediated by reactive oxygen and nitrogen species, which together promote retinal tyrosine nitration.

10. Conclusions

In the vertebrate retina, nNOS is principally expressed in three types of amacrine cells, termed type I, II and displaced NOACs, which display ON/OFF and OFF responses to light (Pang et al., 2010). The canonical NO receptor sGC is highly expressed in certain ON cone bipolar cells and to a lesser degree also in OFF and rod bipolar cells as well as some ganglion cells (Ahmad and Barnstable, 1993; Ding and Weinberg, 2007). Accordingly, stimulation of cGMP synthesis by NO has been established for ON cone bipolar cells and for some rod bipolar cells (Johansson et al., 2000). cGMP either directly opens CNGCs, or acts though activation of PKG on downstream targets (Snellman and Nawy, 2004).

Recent data on NO signaling in general suggest that physiological NO concentrations are in the low nanomolar range, and that the mean diffusion distance is highly limited by abundant NO sinks in tissue, such as the heme groups of hemoglobin and sGC (Hall and Garthwaite, 2009). This implies that NO synthesis by NOACs would influence only cells in the inner retina, and NO from photoreceptor inner segments will most likely affect the photoreceptors themselves (Fig. 3).

At the systems level, retinal NO synthesis is regulated by light stimulation and the degree of visual adaptation (Giove et al., 2009; Levy et al., 2004; Piehl et al., 2007). Conversely, NO appears to modulate light/dark adaptation through the amplification of visual responses in photoreceptors, bipolar, horizontal and amacrine cells (Kourennyi et al., 2004; Vielma et al., 2010), and through the regulation of gap junction coupling between horizontal cells and AII-amacrine and bipolar cells (Mills and Massey, 1995; Xin and Bloomfield, 1999b). Its effects are also evident in ganglion cell output, where NO affects ON and OFF responses (Wang et al., 2003). Consequently, nNOS knockout mice displayed decreased visual responses of ganglion cells (Wang et al., 2007).

Protein S-nitrosylation and nitration, covalent posttranslational modifications caused by nitrosative species derived from NO, have been proposed as alternative NO signaling mechanisms in the retina, but their physiological relevance remains to be demonstrated.

In summary, while NO may not be the highly diffusible global modulator once thought to be, it exerts a series of specific local effects between identified cells in the inner retina, whose concerted actions might generate a significant and synchronized modulation of light/dark adaptation, contributing to the combination of extreme sensitivity and wide response range that is one of the hallmarks of the retina.

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