Nitric oxide synthase immunoreactive neurons in the mammalian retina

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Nitric oxide (NO), a free radical gas with a half-life of a few seconds, has been shown to play various physiological and pathophysiological roles in the nervous system. NO is generated by the oxidation of arginine, a reaction catalyzed by the enzyme nitric oxide synthase (NOS), which is present in three isoforms, endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). The NO thus generated acts on cells by activating soluble guanylate cyclase (sGC), thereby increasing the levels of cyclic GMP (cGMP), which then mediates the effects of NO on the cell.

Here, I focused on the morphology, synaptic connectivity and development of NO synthesizing neurons in the normal mammalian retina and the role of NO in the pathologic conditions.

1. Localization of neuronal NOS

In the rat, mouse, guinea pig and rabbit retinae, two types of amacrine cells and a class of displaced amacrine cells were consistently NOS-labeled. In the cat retina, unlike other mammals, one type of amacrine cells and two types of displaced amacrine cells showed NOS immunoreactivity. NOS immunoreactivity was further found in some bipolar cells of the rat and guine pig, some interplexiform cells of the mouse, some photoreceptor cells of the rabbit and some Müller cells of the cat.

2. Colocalization of NOS and GABA

Two types of NOS labelled amacrine cells were identified; type 1 cells with larger somata were intensely stained, and type 2 cells with smaller somata were weakly stained. A few displaced amacrine cells also showed NOS-like immunoreactivity. All of these NOS-like immunoreactive neurons

also expressed GABA-like immunoreactivity. Thus, NO-containing neurons might constitute a subpopulation of GABAergic neurons in rabbit and rat retinae.

3. Ultrastructure of nNOS-labeled neurons

Synaptic connectivity of nNOS-labeled amacrine cell processes has been observed in the IPL of rat and guinea pig. In both species in all strata of the IPL, processes of NOS-labeled amacrine cells received synaptic input from other amacrine cell processes and from bipolar cell axon terminals. The most frequent postsynaptic targets of NOS-immunoreactive amacrine cells were other amacrine cell processes. Synaptic outputs onto bipolar cells were observed in sublamina b of the IPL. In addition, a few synaptic contacts between labeled cell processes were observed. Therefore, it was suggested that NOS immunoreactive cells might be modulated by other amacrine cells and cone on-bipolar cells, and thereby act preferentially on specific amacrine cells in the IPL of the rat and guinea pig retinae.

4. Development of nNOS-labeled neurons

NOS-labeled cells were first detected at postnatal day 5 (P5) in the inner row of the neuroblastic layer. These cells were considered to correspond to the type 1 cell of the adult rat retina. Type 2 cells, characterized by a small soma and weak immunoreactivity and a class of displaced amacrine cells were detected at P9 and P7, respectively. By P14 or P15, the time of eye opening, NOS immunoreactivity appeared in some bipolar cells. NOS was first expressed at the protein level at P9. Thereafter, quantitative evaluation by immunoblotting confirmed that the intensity of the immunoreactive bands increased abruptly, reaching the same value as is found in the adult retina at P21. Our results demonstrate that differentiation of NOS-labeled cells follows a discrete developmental pattern and is most active during the second postnatal period in the rat retina.

5. The role of NO in the ischemic retina

The role of nitric oxide in the rat retina following ischemic injury induced by transient increase of intraocular pressure. The thickness of both

the inner plexiform layer and inner nuclear layer decreased during early postischemic stages (up to one week). In late postischemic stages (two to four weeks), the thickness of the outer nuclear layer (ONL) decreased markedly. Thus, mechanisms other than excitotoxic ones may contribute to postischemic retinal cell death. Treatment of rats with NG-nitro-L-arginine methyl ester, a nitric oxide synthase inhibitor, significantly reduced ischemic damage. Our findings suggest that nitric oxide is involved in the mechanism of ischemic injury, and plays a key role in the delayed and sustained cell death in the ONL following transient retinal ischemia.