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Emerging novel roles of neuropeptide Y in the retina: From neuromodulation to neuroprotection

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ABSTRACT

Neuropeptide Y (NPY) and NPY receptors are widely expressed in the central nervous system, including the retina. Retinal cells, in particular neurons, astrocytes, and Müller, microglial and endothelial cells express this peptide and its receptors (Y_1, Y_2, Y_4 and/or Y_5). Several studies have shown that NPY is expressed in the retina of various mammalian and non-mammalian species. However, studies analyzing the distribution of NPY receptors in the retina are still scarce. Although the physiological roles of NPY in the retina have not been completely elucidated, its early expression strongly suggests that NPY may be involved in the development of retinal circuitry. NPY inhibits the increase in $[Ca^{2+}]_i$ triggered by elevated KCl in retinal neurons, protects retinal neural cells against toxic insults and induces the proliferation of retinal progenitor cells. In this review, we will focus on the roles of NPY in the retina, specifically proliferation, neuromodulation and neuroprotection. Alterations in the NPY system in the retina might contribute to the pathogenesis of retinal degenerative diseases, such as diabetic retinopathy and glaucoma, and NPY and its receptors might be viewed as potentially novel therapeutic targets.

Contents

Abbreviations: BrdU, 5-bromo-2′-deoxyuridine; $[Ca^{2+}]_i$, intracellular calcium; CNS, central nervous system; DPP-IV, dipeptidyl peptidase IV; E18, embrionic day 18; ERK, extracellular signal-regulated kinases; GABA, γ-aminobutyric acid; GAD 65, glutamic acid decarboxylase 65; GAT-1, GABA transporter 1; GCL, ganglion cell layer; hESC, human embryonic stem cells; iGluRs, ionotropic glutamate receptors; INL, inner nuclear layer; IPL, inner plexiform layer; Leu, leucine; MAPK, mitogen activated protein kinase; MDMA, 3,4-methylenedioxymethamphetamine; mGLuRs, metabotropic glutamate receptors; mRNA, messenger ribonucleic acid; NO, nitric oxide; NOS–sGC, nitric oxide synthase – soluble guanylyl cyclase; NPY, neuropeptide Y; NPY–IR, neuropeptide Y immunoreactivity; NPY Y_1, NPY receptor type 1; ONL, outer nuclear layer; OPL, outer plexiform layer; P7, postnatal day 7; PKA, protein kinase A; POS, photoreceptor outer segment; Pro, proline; RPE, retinal pigmented epithelium.

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1. The retina

1.1. Visual pathways in the retina

The vertebrate retina, like other regions of the central nervous system (CNS), is nervous tissue derived embryologically from the neural tube (Yang, 2004). The retina is composed of four main groups of cells: neurons, glial cells (astrocytes, Müller and microglial cells), epithelial cells (retinal pigment epithelium) and vascular cells. There are five basic types of neurons in the retina: photoreceptors, bipolar cells, horizontal cells, amacrine cells and ganglion cells. These cells are organized into clearly distinct layers, namely three layers of nerve cell bodies: outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL), and two layers of synapses: the outer plexiform layer (OPL) and the inner plexiform layer (IPL). The ONL contains cell bodies of rods and cones, the INL contains cell bodies of bipolar, horizontal and amacrine cells, while the GCL contains cell bodies of ganglion cells and displaced amacrine cells. In the OPL there are connections between rods and cones, with vertically running bipolar, and horizontally oriented horizontal cells. The second synaptic area is the IPL. It works simultaneously as a relay station for the vertical-information-carrying nerve cells, the bipolar cells, to connect to ganglion cells, and as a station for information processing which is mainly carried out by amacrine cells. It is at the end of all this neural processing in the IPL that the message concerning the visual image is transmitted to the brain along the optic nerve (Fig. 1).

1.2. Neurotransmitters in the retina

Chemical transmission mediated by neurotransmitters is predominant in the neural circuitry of the retina. Although the retina contains a variety of neurotransmitters, glutamate and γ-aminobutyric acid (GABA) are the major excitatory and inhibitory neurotransmitters, respectively. Glutamate is responsible for the radial flow of the visual signal in the retina, and both photoreceptors (rods and cones) and bipolar cells release glutamate, which induces and/or alters the activity of the post-synaptic neurons (horizontal and bipolar cells for photoreceptors in the outer retina; amacrine and ganglion cells for bipolar cells in the inner retina) by directly changing membrane permeability to ions or by activating intracellular systems through ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs) (Yang, 2004). There is also a lateral or indirect pathway in the retina. This pathway is mainly mediated by GABA, which is used by numerous horizontal and amacrine cells, modulating synaptic transmission in both synaptic layers. In the OPL, horizontal cells receive direct input from photoreceptors and reply with a negative feedback to cone photoreceptors. Horizontal cells mediate the responses of the surrounding receptive field of bipolar cells. The inputs to bipolar cells are from both photoreceptors and horizontal cells. In the IPL, reciprocal synapses connect bipolar and amacrine cells, and both types of cells send input to ganglion cells. Amacrine cells are involved in spatial and temporal integration of visual signals in the IPL (Yang, 2004).

Although glutamate and GABA are the main neurotransmitters in the retina, other neurotransmitters are present, such as glycine, acetylcholine (Lindeman, 1947), dopamine (Haeggendal and Malmfors, 1963), serotonin (Kojima et al., 1961), ATP and adenosine (De Berardinis and Auricchio, 1951). Retina has also several neuropeptides, which we describe below.

1.3. Neuropeptides in the retina

Neuropeptides are widely distributed, both in the central and peripheral nervous systems. Functionally, neuropeptides act as

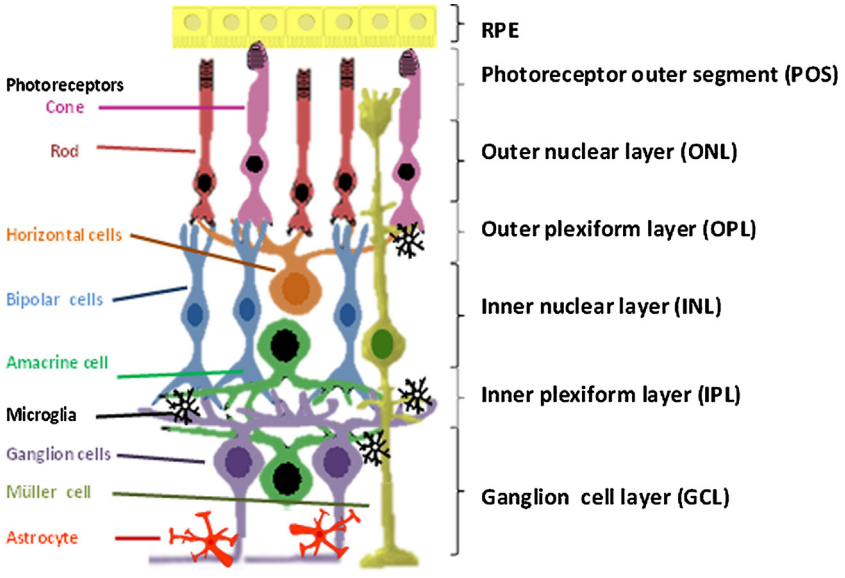

Fig. 1. The structural organization of the retina. Diagram illustrating the distribution of retinal neurons (photoreceptors, bipolar cells, ganglion cells, horizontal and amacrine cells), macroglia and microglial cells in organized layers in the retina. Retinal cells are well organized in several layers: retinal pigment epithelium (RPE); photoreceptor outer segment (POS); outer nuclear layer (ONL); outer plexiform layer (OPL); inner nuclear layer (INL); inner plexiform layer (IPL) and ganglion cell layer (GCL). The astrocytes are in the GCL, while the Müller cells extend through the entire thickness of the retina, extending processes from the outer until the inner limiting membrane. Microglial cells are mainly in OPL, IPL and GCL.

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