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Serotonergic Regulation of the Retina in Pathology

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Abstract

The data of the literature on the structure and physiology of the retina in pathological conditions are presented. The receptory mechanism of serotonin influence on pathological development of the retina are described. Perspectives of practical use of serotonin and serotonin receptors in therapeutical correction of retinal pathologies are briefly indicated.

Keywords: *Retinal pathologies; serotoninergic correction.*

Introduction

The inner shell of the eye, adjacent to the vitreous body, which perceives light stimuli and turns them into successive nerve impulses, is the retina. It consists of two sheets - the internal photosensitive, containing photoreceptor neurosensory cells with their processes - rods and cones, and the outer - pigmentary. The front parts of the retina, covering the iris and ciliary body, belong to the accommodative apparatus.

In the structure of the sensory retina, a layer of outer segments of photoreceptors is distinguished; an outer nuclear layer with internal segments and nuclei; external plexiform layer with synaptic contacts between photoreceptors, bipolar, horizontal cells; an inner nuclear layer with nuclei of bipolar, amacrine, and horizontal cells; an inner plexiform layer with many contacts between bipolar, amacrine and ganglionic cells; layer of ganglion cell nuclei of the retina and a layer of nerve fibers formed by axons of ganglion cells forming the optic nerve [1] . Photoreceptors form synapses on bipolar horizontal neurons of the retina. Horizontal and amacrine cells of the retina provide lateral inhibition, respectively, between bipolar and ganglionic neurons, which ensures the regulation of the transfer of impulses from photoreceptors to these neurons. Ganglionic neurons give rise to optic nerve fibers.

In the vertebrate retina, all the components of the serotonergic system-indolamine itself (5-HT, 5-hydroxytryptamine), its receptors, tryptophan hydroxylase synthesis enzyme, SERT transporter and inactivation enzyme of 5-HT monoamine oxidase (MAO) are found.

Serotonin is synthesized exclusively by subpopulations of amacrine cells of the retina of many vertebrate species [2], including monkeys of the Cebus species, cats and rabbits. 5-HT is also deposited in bipolar [3] and, to a lesser extent, ganglionic and glial cells of the retina and in photoreceptors. The human photoreceptors are represented by 120 million rods and 6-7 million cones, and the rods are adapted to low illumination, the cones to the perception of colors at high illumination [4]. The effect of serotonin increases the excitability of the type-B Hermissenda photoreceptors. Serotonin modulates ion currents in type-B photoreceptors, including the correcting internal current (I (h)) activated by hyperpolarization. The introduction of serotonin leads to the predominance of the correcting internal current I (h) activated by hyperpolarization, which activates photoreceptors that transfer excitation to bipolar retinal cells [5].

Serotonin receptors. Although the absolute serotonin content in the retina is relatively small, a number

of data indicate a significant role for indolamine in regulating retinal activity. This is evidenced by the presence of all 7 types of serotonin receptors in the retina, as shown in a recent study by L Vitanova et al. (2017) on the example of the frog and tortoise retina [6]. Serotonin receptors are mediators of the effect of serotonin on the eye system in a wide physiological range from normal blood supply to the eye, regulation of intraocular pressure and dynamics of chamber moisture, upto perception, processing and storage of visual images, and trophism of neurons.

Main part

Diabetic retinopathy

Diabetic retinopathy is known to be retinal damage due to a complication of diabetes that ultimately can lead to loss of vision and is a manifestation of systemic diseases that affect up to 80% of all diabetic patients who have had diabetes for 10 or more years . At least 90% of the newly diagnosed cases of retinopathy can be reduced with proper and thorough treatment and eye monitoring.

Reduction of tissue hypoxia under the action of serotonin indicates the possibility of using serotonin in the prevention and treatment of diabetic and age-related angiopathy [7-75]. Given the genesis of smooth muscle dysfunction, and the fact that retinopathy also occurs in patients with diabetic angiopathy, the addition of intravenous serotonin adipinate to the standard therapy of diabetic retinopathy in patients on the fundus accelerated resorption of hemorrhages and decreased retinal edema compared with control ,

Proliferative diabetic retinopathy leads to an increase in serotonin concentration in plasma, trombocytopathy, increased erythrocyte stiffness and is accompanied by tissue serotonin deficiency. In patients with a pre-proliferative stage of diabetic retinopathy and central chorioretinal dystrophy, serotonin deficiency was accompanied by a progressive decrease in the level of serotonin [9].

Myopia

Myopia (myopia) is a disease associated with excessive growth of the eyeball in the axial direction. The one of the main regulators of eye growth is the retina [10], the neurons of which are involved in the regulation of trophic processes controlling the growth of the eye. Retinal mediators regulate the excessive elongation of the anterior-posterior axis of the eye, observed in myopia. It is believed that defocusing disrupts the activity of the amacrine cells of the retina, stimulating the release of mediators that influence growth [11]. One of these mediators is serotonin.

Serotonin causes a reduction in the blood vessels of the eye and has a mitogenic effect, and also acts as a neurotransmitter in regulating the length of the anterior-posterior axis of the eye in the development of myopia. However, serotonin is not a direct pathogenic factor in the onset of myopia. The lens form of myopia does not arise from a simple increase (decrease) in the level or release of serotonin in the retina, but due to the fact that serotonin stimulates the development of lens myopia, although in large doses blocks myopia, for example, 7-day-old chickens. Serotonin-containing amacrine cells are located on the inner nuclear layer of the retina. Eyes with lens myopia differ by 12.5% level of serotonin-containing amacrine cells in the central region of the retina [12].

Receptors. Another possible mechanism for the development of myopia is the serotonergic modulation of intraocular pressure, when indolamine favors both growth of intraocular pressure [13] and its decrease [14], depending on which type of receptor was activated. Excess serotonin can disrupt the development of retinal amacrine cells by activating 5-HT2A-, 5-HT2C- and 5-HT7 receptors, which increases intraocular pressure.

The absence of the effect of serotonin blockators on the development of the deprivation form of myopia [12] makes it possible to explain the contradictory data of F.Schaeffel et al. (1994) that reduced serotonin levels both suppress and stimulate excessive growth of the visual organ associated with a violation of its shape [15]. Since both forms of myopia - formdeprivatory and lens - are realized by different mechanisms, which lead, however, to the same result (sclera growth), it can be concluded that the action of serotonin is more noticeable at an early stage of myopia development, affecting more the lens form of the disease.

Consequently, serotonin plays one of the key roles in the normal form-forming processes of the eye and the realization of photo-optical functions; the excess or deficiency of serotonin and the associated neurotransmitters leads to the development of this pathology.

Ischemia

Acute ischemic disorders of the retinal vessels and the optic disc are one of the main causes of visual loss in mature and elderly patients with hypercholesterolemia, atherosclerosis and hypertension [16].

Ischemia of the retina is the main link in the pathogenesis of vascular diseases of the eye. In a number of cases, serotonin released by platelet aggregation on atherosclerotic plaques can initiate contraction of the vessels of the optic nerve and / or retina disc, which can lead to their ischemic damage. Serotonin is one of the pathogenic factors in the development of increased intima permeability for the degradation products of elastic and collagen fibers in ischemia. Spasm of the arteries can lead to temporary or permanent occlusion of blood vessels and worsening of blood flow. This is confirmed by the results of experiments on monkeys that revealed the absence of ischemic disturbances in the norm and transient occlusion or delayed filling of the central retinal artery and / or posterior ciliary artery in animals with the model of atherosclerosis, created using a special diet. The abolition of the atherogenic diet returned for a few months the serotonin-induced vascular response to normal [17]. The 5-HT2 receptor blockator MCI-9042 prevents the development of retinal ischemia of the Wistar rats [18]. Serotonin can also have a protective effect in the development of cerebral ischemia [19].

The role of serotonin is not limited to the intensification of proliferative processes, but also involves the initial expansion of the vessels in response to retinal ischemia due to stimulation of NOS synthase followed by depletion of this enzyme and development of ischemic retinal lesions.

Glaucoma

Currently, the multifactor development of primary open-angle glaucoma is universally recognized, therefore, the focus of surgical and therapeutic efforts on lowering the intraocular pressure needs a certain correction. Today, in the treatment of patients with primary open-angle glaucoma, one of the main problems is the stabilization of visual functions after intraocular pressure is normalized. The main causes of disease progression are unresolved chronic hypoxia and ischemia of eye and brain tissues [7].

One of the ways to correct circulatory disorders of the central nervous system is the use of serotoninactive drugs. In the pathogenesis of primary open-angle glaucoma, an important role may play a violation of the permeability of the blood-brain barrier and a violation of the serotonin balance in the visual analyzer and anterior segment of the eye. With increased permeability of the blood-brain barrier, some metabolites that do not normally penetrate the brain are transported into it and block serotonin receptors that provide a normal neuronal-astrocyto-vascular function. Thus, conditions are created for the development of ischemia and apoptosis of the optic nerve and cortical portion of the visual analyzer [8].

The serotonergic system is involved in the regulation of the blood supply to the eye, the formation of moisture in the anterior and posterior chamber of the eye, and regulation of intraocular pressure, as well as in the trophic function of the retinal neurons.

We conducted a morphological study of the eye structures of rabbits of two groups, whose age was different for 12 months: animals of the older age group and senile age. In rabbits of senile age there is an increase in the activity of the serotonergic system against the background of a simultaneous relative decrease in the activity of the adrenergic and, to a lesser extent, cholinergic systems.

Conclusion

Serotonin and its receptors are present in almost all structures of the eye and the visual analyzer as a whole, and 5-HT plays one of the key roles in the normal form-forming processes of the eye and the realization of photo-optical functions. In particular, the local synthesis of serotonin is carried out by the enzyme tryptophan hydroxylase in the amacrine cells of the retina and in the cells of the photoreceptor. Expression of the full nomenclature of serotonin receptors, mainly in the proliferative regions during the formation of the retina, has been established. These receptors, acting as mediators of mitogenic effects of serotonin, can play a significant role in the process of secondary neurogenesis. The role of serotonergic structures in preventing ischemic damage to the eye is postulated. Activation of the serotonergic system (eg, age), as, in particular, our studies showed, leads to dilatation of blood vessels and increased fibrogenesis in the lacrimal gland.

Excess or deficiency of serotonin as well as other associated neurotransmitters, a violation of vegetative homeostasis leads to the development of pathology. In particular, hyperserotoninemia can be a factor of pathogenesis in the development of myopia: it increases the proliferation of fibroblasts and promotes

scleral remodeling; modulates the magnitude of intraocular pressure and changes the neurotrophic processes in the retina of the eye. The possibilities of using serotonin, its receptors in the prevention and treatment of retinal pathology merit further research and practical use.

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