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Review Article

Regulation of Corneal Functions by the Nervous System

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Summery

In the functioning of the eye, the cornea performs two functions: protective against mechanical (and infectious)damage and optical – providing the function of vision. The cornea has a complex innervation. The corneal epithelium contains 5-HT4-, 5-HT6- and 5-HT7-receptors localized on the basal surface of corneal epithelial cells and capable, after their activation, of inducing the synthesis of cAMP mediating the transport of Cl-ions. . In addition, the 5-HT7 receptor, a relatively recently cloned subtype of serotonin receptors, modulates the phase of rapid eye movement during sleep. Sympathetic innervation of the cornea affects the properties of receptors and membranes, reducing the permeability of the apical membrane to Cl-ions and reducing the sensitivity of beta-adrenergic receptors. The physiological role of α1- and β-adrenergic receptors and their secondary messengers phosphatidylinositol and cAMP is to regulate homeostasis and corneal fluid transport. In the sensory nerves of the rat cornea, the presence of calcitonin gene-associated peptide, substance P and galanin was noted; in sympathetic – (NPY) and parasympathetic – galanin, NPY, M-enkephalin and VIP. Cholinomimetics, with the mediating role of cGMP, stimulate the growth of the corneal epithelium.

Keywords: Adrenergic system; Cholinergic System; Cornea; Peptides; Purines; Serotonin

The eye is a peripheral organ that perceives light radiation and transforms it into a set of afferent signals that form a visual sensation.The main elements of the optical system of the eye are the cornea, lens and pupil [1].

Cornea

In the functioning of the eye, the cornea performs two functions: protective against mechanical (and infectious) damage and optical – providing the function of vision. The transparent corneal epithelium is a highly specialized basal and stratified squamous cells that are renewed during life from a population of stem cells. Stem cells are localized in the corneal limbus, and their condition is maintained by various external and internal factors, such as the local cellular environment, survival factors, and anti-inflammatory factors (cytokines). Under conditions of homeostasis and following its violation, limbal stem cells divide, producing daughter subpopulations of stem cells that grow transiently in size, which proliferate, migrate and, differentiating, replace the lost cells. With a decrease in the productivity of limbal stem cells, corneal cells are replaced by cells of the neighboring conjunctiva, which is fraught with painful sensations, decreased visual acuity and even amblyopia [2]. Direct innervation of epithelial cells and keratocytes was noted in the human cornea. The presence

of vesicles, mitochondria and glycogen in the nerve fibers of the stroma and epithelium indicates the possibility of the presence of serotonin, other classical and peptidergic neurotransmitters in the cornea [3].

The Serotonergic System

The structures of the eye have a well-developed serotonergic innervation [4,5,8,9]. The study of the role of neurotransmitters in ontogenesis began with serotonin. The vertebrate visual system is a convenient object of study, a model of the formation of the nervous system. Serotonin and a number of other molecules, including transcription factors and membrane receptors, determine the type of retinal cells [10].Serotonin and its receptors are present in almost all structures of the eye and visual analyzer, including in the corneal tissue of rabbits and humans. The presence of serotonin receptors in pig conjunctiva [11], rabbit eye tissues and human ciliary body was established by the method of reversible polymerase chain reaction [12,13]. Using freshly fixed human corneal tissue, a complete characterization of the monoamine receptors of the cornea was obtained using immunohistochemical, immunofluorescence and immunoblotting research methods [14]. In the human conjunctiva, the anterior segment of the eye, the density of 5-HT2A-, 5-HT2B-, 5-HT4-, 5-HT7-mRNA is high and 5–HT5-receptors are low; 5-HT2C- and 5-HT6-receptors were not detected [15,16] mRNA was also found 5-HT1D and 5-HT1F receptors [11]. The question of the physiological role of 5-HT2,3,4-receptors in these structures remains open. Monoamine receptors are present on the basal surface of corneal epithelial cells and are expressed by cells of the endothelial layer (posterior epithelium) [4, 6-9]. A protein component of 5-HT7 receptors was detected in human and rabbit corneal epithelial cells [9]. 5-HT7 receptors were detected by RT-PCR in the culture of human corneal CEPI-17-CL4 cells [9]. The corneal epithelium contains 5-HT4-, 5-HT6- and 5-HT7-receptors localized on the basal surface of corneal epithelial cells and capable, after their activation, of inducing the synthesis of cAMP mediating the transport of Cl-ions. Apparently, 5-HT7 receptors are involved in the modulation of fluid secretion and Cl- in these eye tissues.

In addition, the 5-HT7 receptor, a relatively recently cloned subtype of serotonin receptors, modulates the phase of rapid eye movement during sleep [17] and other physiological and behavioral functions, including circadian rhythm, body temperature, learning, memory and behavior. This is confirmed by the fact that the introduction of selective 5-HT7 receptor blockers selectively reduces the phase of rapid eye movement in rabbits and rats; in other words, endogenous serotonin, activating 5-HT7 receptors, tonically enhances the phase of rapid eye movement [17]. Serotonin contributes to an increase in cAMP levels in rabbit corneal tissue culture [4,9]. Nialamide, a monoamine oxidase inhibitor, enhances the cell response to serotonin, but not to epinephrine; therefore, serotonin is metabolized by Monoamine Oxidase-A (MAO-A). Amitriptyline, an inhibitor of neuronal serotonin uptake, does not enhance the stimulation of cAMP synthesis. Lysergic acid diethylamide (inhibitor of 5-HT1,2-receptors) blocks the reaction to serotonin; moreover, the half effect of serotonin blockade is achieved by 50% of the effective concentration of lysergic acid diethylamide, which proves the dose-dependent effect of blockade of effector serotonin receptors.Serotonin receptors capable of stimulating cAMP production by activating adenylate cyclase are 5-HT4-, 5-HT6- and 5-HT7-receptors. Serotonergic neurons in mammals are localized in the nuclei of the suture and reticular formation. The distribution of serotonin receptors has been studied in the brains of healthy volunteers and in human and animal brain preparations. As a result, a high density of serotonin receptors located in the primary visual cortex was shown. This indicates the important role of serotonergic transmission in the modulation of visual afferent activity. In addition, serotonergic neurons are known to regulate local cerebral circulation [18]. It is believed that dysfunction in the neuronal-astrocyte-vascular interaction may be the result of perfusion deficiency in the visual cortex.

The Cholinergic System

Protein and mRNA components of all five types of M1-M5 muscarinic receptors were found in the culture of human corneal and conjunctival cells. M3 receptors are localized in the epithelium and endothelium of the cornea, and are also expressed in the ciliary muscle and epithelium, iris, and trabecular network of the human eye [19]. Muscarinic receptors are chronologically involved in the proliferation of corneal epithelial cells by phosphorylation of p42/44 mitogen-activated protein kinase MAPK [20] in the corneal epithelium, these receptors are involved in the regulation of cAMP [6]. Cholinomimetics, with the mediating role of cGMP, stimulate the growth of the corneal epithelium. Muscarinic receptor agonists are used in the treatment of glaucoma to reduce intraocular pressure.

The Adrenergic System

The cornea receives afferent nerves from the trigeminal ganglion and efferent fibers from the superior plexus. Sympathetic innervation of the cornea affects the properties of receptors and membranes, reducing the permeability of the apical membrane to Cl-ions and reducing the sensitivity of beta-adrenergic receptors, including, as it is believed, to serotonin. Serotonin, by activating its receptors located at the terminals of the sympathetic nerve on the cornea, stimulates the transport of Cl-ions. The adrenergic receptor group includes three subtypes of α1-adrenergic receptors (α1A/D, α1B and α1C), three subtypes of α2-adrenergic receptors (α2A, α2B and α2C), and three subtypes of β-adrenergic receptors (β1, β2 and β3). α1-adrenoceptors mediate their response through G-protein-associated receptors, namely Gp/Gq, and apparently

participate in the regulation of inositol-1,4,5-triphosphate synthesis [6,7]. α2-adrenoceptors realize their capabilities using a set of G-associated proteins, including Gi/G0, as mediators. All types of adrenoreceptors are associated with phospholipase C; activation of the receptors promotes the formation of Inositol Phosphate-3 (IP3) and glycerol (DAG). A negative association of all types of adrenoreceptors with adenylate cyclase and their participation as mediators in the blockade of Camp synthesis has been shown [21]. Secondary messengers stimulate both potential-dependent and independent Ca2+ channels and activate protein kinase C, phospholipases A and D, release of arachidonic acid and cAMP [22].

The possibility of expression of α-adrenoreceptors by corneal epithelial and endothelial cells is discussed. The expression of α1-adrenoreceptors by intact corneal epithelial and endothelial cells was shown by direct measurement of radioligand coupling; later data obtained using preparations of destroyed cells did not confirm the expression of α-adrenoreceptors [6]. There is functional evidence of the presence of α2-adrenoreceptors in the corneal tissue and in the endothelium of the border vessels of the cornea [14]. beta-adrenergic receptors are located on the apical surface of corneal epithelial cells [4]. In addition, it has been shown that α1-, β1- and β2-adrenergic receptors are present in freshly prepared preparations of the human cornea [4], where they mediate reactions to endogenous catecholamines. C.B. Nielsen, P.J.Nielsen [23] found a decrease in the thickness of the human cornea by the adrenomimetic isoprenaline; however, later R.J. Walkenbach et al. [5,6] did not confirm the effect of α1-adrenoreceptors on corneal thickness in vitro; β-adrenoreceptors of corneal epithelial cells associated with stimulation of adenylate cyclase and CAMP-dependent protein kinase, as well as with chloride secretion, participate in the regulation of corneal thickness [6]. β-adrenoreceptors with the participation of cAMP prevent epithelialization of corneal lesions. The adrenergic effect is promoted by prostaglandins PGE1.

The physiological role of α1- and β-adrenergic receptors and their secondary messengers phosphatidylinositol and cAMP may also be involved in the regulation of homeostasis and corneal fluid transport.The interaction of the adrenergic and serotonergic systems is shown in the work of Cavallotti C. et al. [8], who used spiroperidol as a ligand of D2-dopaminoreceptors in the study of the rabbit cornea. A spiroperidol agent for 5-HT 2-serotonin receptors is also known. This drug, in our opinion, is a combination of the 5-HT2-receptor blocker spiperone and the D2-blockers haloperidol, which caused its dual effect on receptor structures and at the same time revealed their presence. The close anatomical and functional relationship of the sympathetic and peptidergic systems in the tissues of the eye is evidenced by the results of experiments with chronic denervation of these tissues .

The Peptidergic System

The innervation of the dog's cornea is represented by a rich anterior stromal plexus and characteristic bundles of horizontally oriented nerve fibers of the epithelium converging at one point of the perilimbal part of the cornea. Fibers containing the substance P have been found in most eye tissues. In the cornea, these fibers, together with fibers containing Calcitonin Gene-Associated Peptide (CGRP), form the basis of peptidergic sensory innervation. A high content of substance P was detected by immunohistochemical method in the cornea, conjunctiva, episclera, trabecular network, iris and ciliated body of the anterior segment of the rat eye [24-26]. More than 99% of the nerve fibers of the dog's cornea contain both substance P and calcitonin gene-associated peptide, approximately 30% - tyrosine hydroxylase. In the sensory nerves of the rat cornea, the presence of calcitonin gene-associated peptide, substance P and galanin was noted; in sympathetic – Neuropeptide Y (NPY) and parasympathetic – galanin, NPY, M-enkephalin and VIP. The release of substance P into a watery liquid has been shown in case of inflammation of the eye, and inhibitors of substance P block the inflammatory process.

Conclusion

The cornea, as an element of the optical system of the eye, has a complex and multifaceted innervation that allows it to perform a protective and visual function. The cornea has a well-developed serotonergic innervation. The corneal epithelium contains 5-HT4-, 5-HT6- and 5-HT7-receptors localized on the basal surface of corneal epithelial cells and capable, after their activation, of inducing the synthesis of cAMP mediating the transport of Cl-ions. In addition, the 5-HT7 receptor modulates the phase of rapid eye movement during sleep and other physiological and behavioral functions, including circadian rhythm, body temperature, learning, memory and behavior. The introduction of selective 5-HT7 receptor blockers selectively shortens the phase of rapid eye movement in rabbits and rats; that is, endogenous serotonin, activating 5-HT7 receptors, tonally enhances the phase of rapid eye movement. Muscarinic receptors are chronologically involved in the proliferation of corneal epithelial cells by phosphorylation of p42/44 mitogen-activated protein kinase MAPK ; in the corneal epithelium, these receptors are involved in the regulation of cAMP. Cholinomimetics , with the mediating role of cGMP , stimulate the growth of the corneal epithelium. Sympathetic innervation of the cornea affects the properties of receptors and membranes, reducing the permeability of the apical membrane to Cl-ions and reducing the sensitivity of beta-adrenergic receptors and serotonin receptors to serotonin. Sympathetic innervation of the cornea affects the properties of receptors and membranes, reducing the permeability of the apical membrane to Cl-ions and reducing the sensitivity of beta-adrenergic receptors, among others). In the sensory nerves of the rat cornea, the presence of calcitonin gene-associated peptide,

substance P and galanin was noted; in sympathetic – Neuropeptide Y (NPY) and parasympathetic – galanin, NPY, M-enkephalin and VIP.

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