Review Article

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Autonomic Regulation of the Function of the Vitreous Body and Retina

Lychkova AE1*, Severin AE2, Torshin VI2, Starshinov YP2, Sdobnikova SV3, Ashrafov RA4, Ashrafova SR4, Golubev YY5 Golubeva GY6 and Puzikov AM1

1Department of Health, Moscow's Clinical Research Center, Moscow, Russia
2Russian People's Friendship University, Moscow, Russia
3Research Institute of Eye Diseases, Moscow, Russia
4Center for Laser Surgery, Moscow, Russia
5Russian National Research Medical University, Moscow, Russia
6City Clinical Hospital, Moscow, Russia

*Correspondence: Lychkova Alla Edward, Department Head of the Moscow's Clinical Research Center, DZM, Shosse Enthusiasts 86, 111123, 11-1-53, Amundsen 129343, Moscow, Russia, Tel: (+7) 962-965-4923; E-mail: lychkova@mail.ru

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Abstract

The data of the literature on the structure and physiology of the vitreous body and the retina in normal and pathological conditions are presented. The mechanism of vitreous detachment and its role in the development of vitreoretinal proliferation are described. Described adren-choline-peptide and NO-ergic mechanisms in signal transduction of the vitreous body and retina. Pharmacological and surgical methods of treatment of vitreoretinal proliferation are briefly described.

Keywords: Vitreous body; Retina; Detachment; Vitreoretinal proliferation

Introduction

Vitreous Body (VB) is a transparent, colourless, gel-like mass containing water with an admixture of salts, sugars, hyaluronic acid, a network of collagen fibers II, IX, XI types and few cells (mainly phagocytes, contributing to the removal of foreign substances from the field of view). The viscosity of the vitreous body is 2-4 times higher than that of water, according to VB gel-like consistency [1]. The vitreous body fills the volume of the eyeball by more than 3/4 and at the same time has a complex system of internal circulation [2].

Structure

Vitreous body includes anterior, posterior and cortical parts, as well as a central zone. The most important area of VB is its cortical part. The outer layer of the vitreous body has a thickness of 100-200 microns, which has a greater density of collagen fibers and a greater concentration of hyaluronic acid as compared to the central part. Cortical gel is comparatively more stable and more resistant to age-related changes [1]. The VB contains two channels (optociliary and lenticular) and three rows of cisterns, a bursa premacularis and a precapillary space [1,3-5].

The posterior part of VB is bordered by the retina and optic nerve disc. The posterior division of VB is a broad strip seal of collagen fibers arranged parallel to IBM. In the VB base area, the collagen fibers are arranged perpendicular to the retina. Various diseases of the posterior segment of the eye, such as haemorrhagiccoedema form of diabetic retinopathy, persistent vitreoretinal care are accompanied by pathological changes in posterior division of VB.

The vitreous body, as noted, contains a three-
dimensional network of randomly oriented collagen fibers. Collagen fibers of the VB are located separately by electrical charges. With age, the charge is reduced and there is a convergence of fibers [4]. There is another opinion that collagen fibers are electrostatically neutral, so they do not form joints and allow the volume of VB to expand, giving plasticity to the system [6]. With age, the gel is liquefied (syneresis process), resulting in cells and other organic clusters floating freely in the vitreous body.

Spots and filaments may appear in the field of view; the sudden appearance of floating filaments may indicate a layer of VB [7].

The second component of the vitreous body - spongy polymer rings of hyaluronic acid. Numerous negatively charged groups in molecules of hyaluronic acid cause volumetric changes due to physical and chemical changes. Molecules of hyaluronic acid give the system high elasticity. This dual mesh-collagen fibers and hyaluronic acid molecules that fill the space between them gives stability to the vitreous body. Violation of the structure of the vitreous gel is due to the dissolution of molecules of hyaluronic acid. This destabilizes the collagen network, which partially subsides, resulting in the formation of areas of high concentrations of collagen, interspersed with areas of vitreous dilution. It is believed that vitreous degeneration is preceded by a vitreous detachment [3].

Bursa premacularis from the retina has the form of an elongated oval and is a closed cup-shaped cavity. Its front wall forms an intravitreal membrane with numerous holes, giving it the form of a “sieve”. The posterior wall is formed by a thin membrane of VB, which is covered internally with a layer of spongy substance, except for the area which corresponds to the foveal zone of the retina [2,3,8].

Precapillary space is separated from the optic disc by a thin border plate of the retina, in which there are holes for the passage of vessels. It is believed that through these holes the flow of intravitreal fluid into the perivascular spaces of the optic nerve is carried out [3].

### Membrane

There are two different clinical and anatomical states of the vitreous body: before and after VB. Up to the VB layer, the true membrane as a separate anatomical formation is not determined histologically (there is only some increased density of collagen in the outer layers of the cortex). After the VB detachment, as a result of certain morphological transformations, a distinct membrane is formed, defined both ophthalmologically and histologically [9]. The contractile activity of the VB's fibrocellular membranes which are formed as a result of penetrating injury of the eye is shown with the help of strain gauges. Serotonin, norepinephrine of bitartrate, angiotensin II, prostaglandins PGF1α, bradykinin and vasopressin caused a reversible reduction of the membrane. Membrane relaxation occurred under the influence of papaverine hydrochloride and diltiazem. VB membranes, which play an important role in retinal detachment processes, are largely similar to smooth muscles and contractile tissues [10].

Presence of adrenergic receptors on membranes [11,12] is shown. Highly selective agonist α2-adrenoreceptor brimonidine with local administration is in the vitreous body and aqueous fluid of the human eye [13]. Measurement of the tissue level of the drug should take into account the possibility of its finding in a bound state with melanin. Melanin binding leads to the accumulation of brimonidine in the vitreous body of rabbits and primates with chronic administration of the drug [14].

Normally, the cortex is in contact with the surrounding tissue through the basal lamina. In the posterior part, the basal lamina is a basal membrane of the inner processes of the Muller cells of the retina, called the Internal Limiting Membrane (ILM). ILM forms the tenth layer of the retina and is located on the border with the vitreous body. ILM is the only true membrane of the retina. The membrane contains collagen fibers, proteoglycans (mainly hyaluronic acid), basal membrane and plasma membrane of Muller cells [15,16]. Morphologically, it is randomly intertwined fibers of collagen type IV associated with glycoproteins with individual interweaves of collagen fibrils from the bark of the adjacent VB. Vitreous surface of the ILM is smooth, the retinal has an uneven terrain, due to the depression of the glial cells of the nerve fiber layer. The thickness of the ILM is 0.5-3.2 microns with thinning (up to 0.01 microns) in the foveolar region; ILM disappears along the edge of the optic disc, where it is replaced by a basal astrocyte membrane, devoid of collagen, thickness of only 20 nm (Central meniscus of Kuhnt). Normally, ILM prevents the migration of cells and molecules larger than 20 nm in vitreous body, functioning together with the bark of VB as a “molecular sieve” [3,6].

Important places of solid attachment of VB to the retina and ciliary body: the base of VB, the optic disc, peritoneal...
area, in the course of major retinal vessels [3]. The strength of VB attachment is ensured by the interweaving of its collagen fibers into the basal membrane of the ciliary epithelium and Muller cells strictly at right angles. With age, the attachment density of VB is somewhat reduced, but in this area, the detachment of the vitreous body normally never occurs.

Vitreous body contains permanent (hyalocytes) and transient (fibroblasts, macrophages, monocytes and histiocytes) cells. It is believed that the single sources of these cells are monocytes. More often, cells are found in the base of VB, zinc ligaments, in the cortical layer, directly in the retina and optic disc. The number of hyalocytes depends on location and age, during their life the number decreases. Transient cells are determined in the cortical layer, in the optic disc, in the course of retinal vessels and in the area of the toothed line.

There are no lymph vessels in the retina and vitreous body. Choroid rich in blood vessels is separated from the retina by a dense layer of pigment epithelium, therefore, under physiological conditions; the evacuation of metabolic products is carried out mainly through the retinal capillary venous network.

Hamorrhages in vitreous body accumulate toxic substances that have a cytotoxic effect on the microstructure of VB cells, inner shells of the eye and on the biochemical processes occurring in them [6]. 66.4% of cases, blood clots and fibrous elements localized in the Central part of the VB, presumably, in the area of the projection of lentil-related macular channel and adjacent tanks [3]. Blood introduced into the vitreous body, had pronounced toxic effects on eye tissues, increased permeability of the blood aqueous barrier altered acid-base balance VB, and violated the metabolic processes in it, increasing the intensity of free radical reactions, the content of histamine. Vitreous hamorrhage is accompanied by intensification of lipid peroxidation with toxic retinal damage. Activation of lipid peroxidation is a key mechanism in the development of diabetic retinopathy, playing an important role, in particular, in the development of hypoxia. The presence of angio-genic and angio-inhibitory factors of VB, which control the proliferation of cell endothelium, was established [17].

VB membranes play an important role in the pathogenesis of diabetic retinopathy. Despite their long-term histological study, the common terminology regarding proliferative membranes has not developed - they are considered a fibrovascular tissue, a combination of newly formed vessels with glial tissue [18], it is also proposed to classify them as gliosis. This may be due to the complexity of the origin and structure of proliferative membranes. Proliferative membrane includes glial tissue, collagen fibers, fibroblasts, shaped blood elements, my fibroblast-like cells, macrophages and some other components [19,20].

The role of glial tissue in the pathogenesis of proliferative diabetic retinopathy remains controversial. Glial cells in epiretinal membranes obtained during vitrectomy are common. It was found that glial cells are usually found in epiretinal membranes behind the edge of newly formed vessels. This allowed us to assume that glial cells and their extracellular matrix are the basis for the subsequent growth of newly formed vessels [21]. However, S. A. [22] considers that glial cells are not necessary for non-vascular growth [22].

Cellular fibronectin of the epiretinal membrane which is distributed diffusely, is produced by the membrane itself, can promote cell proliferation and migration [23].

**Myopia**

In myopia there is an increase in the anteroposterior size of the eyeball by primarily changing the size of VB. Different pharmacological drugs in form-deprivation myopia worked on the expansion of the cavity of the VB more efficiently in the axial than in the equatorial direction [24]. Unlike other drugs, nicotine blockers effectively prevented the expansion of VB in all directions [25]. That is, nicotine cholinergic receptors can regulate eye growth, but in small doses of their blockade, it increases the development of myopia in the development of exophthalmos. The nicotine receptor blocker chlorisondamine also inhibits the growth of the eye during myopia and shifts the level of refraction towards hyperopia [25].

The middle (vascular) tunic of the eye plays a major role in metabolic processes. It has three parts: part iris, part of the ciliary body and the choroid - choroid.

The inner tunic of the eye, adjacent to the vitreous body, perceives light irritation and turns them into successive nerve impulses, is the retina. It consists of two sheets - the inner light - sensitive, containing photoreceptor neurosensory cells with their processes - rods and cones, and the outer-pigment. The anterior parts of the retina, covering the iris and ciliary body,
belong to the accommodation apparatus.

In the retina of vertebrates are found about thirty mediators: serotonin, acetylcholine, dopamine, glycine, GABA, glutamate (GLU) and a number of peptides. The processes of excitation and inhibition in the retina largely depend on the quantitative ratios of mediator substances.

**Cholinergic system**

One of the main retinal neurotransmitters is acetylcholine. The presence of acetylcholine at the first stages of ontogenetic development of the retina and brain of striped fish, determined by the immunoreactive test for acetylcholinesterase, testifies to the important neuromodulatory role of the cholinergic system [26]. Amacrine cells of rabbit retina expresses muscarinic receptors [27]. It was believed that choline acetyltransferase are only found in the amacrine cells. Relatively recently shown histochemically: the presence of choline acetyltransferase also in the ganglion cells of the retina of the rat. Cholinergic ganglionic cells are present in the rat retina [28]. It is not excluded that acetylcholine, produced by acetylcholine transferase, can act not only as a neurotransmitter, but perform other typical non-neural AH functions [29], for example, trophic signalling, regulation of cell life cycle and participation in intercellular contacts. In this context, it becomes clear why it was impossible to find choline acetyltransferase in ganglion cells of the retina.

The release of acetylcholine in the retina is mediated by P2X- purinoreceptors. In the retina of the mouse detected P2X1-, P2X2-, P2X4-, P2X5-, P2X6- and P2X7- receptors. P2X3 receptors are expressed by dendrites of cholinergic amacrine cells and appear to influence the function of these cells in the mouse retina [30]. The reaction to the light of cholinergic amacrine cells mediates endogenous NO released in the retina [31].

**The adrenergic system**

The content of biogenic amines in vitreous body, retina, choroid and sclera of chicken was measured by liquid chromatography. Dopamine is found mainly in the retina; it is much smaller in the vitreous body; in the choroid it contains 1/3, in the sclera - 1/20 part of the level in the retina [32]. The dopamine released by the retina may be one of the messengers regulating the growth of the adjacent sclera.

Amacrine cells affect the transmission of the signal from bipolar to ganglion cells and organize complex properties of the receptive fields of the output neurons of the retina. Each mediator is confined to a certain morphological class of amacrine cells. Thus, acetylcholine in all animals studied so far is in amacrine cells, glycine - in bi-stratified amacrine cells, which are insertion neurons on the way of the signal from the rods. In conditions of dark adaptation they are connected in an electrical syncytium, with cone cells and bipolar cells. Dopaminergic amacrine cells in the light divide this syncytium. The exceptions to the rule of morpho-mediator unity are GABAergic amacrine cells. There are up to 8 different types of them. The GABA neurons usually contain another neurotransmitter.

**The peptidergic system**

In the retina, a number of peptides were found to stimulate the release of neurotransmitters. Stimulators of serotonin release are neurotensin, LEU-enkephalin and somatostatin; dopamine is released with the participation of neurotensin and LEU-enkephalin; glycine is released with neurotensin [33]. In the retina locates peptides and γ-aminosalicilova acid. The key role of peptides can be traced, since ontogenesis of the Central nervous system. Substance P modulates the activity of the cholinergic system in the future, in the early postnatal period of the existence of the retina of the rabbit [34].

In the course of ontogenesis changes in the expression of substance P in the rabbit retina and, more importantly, substance P plays an important role in the formation of neurons and neural circuits in the retina [35]. The influence of neuropeptides, serotonin and other neurotransmitters is noticeable starting from the first trimester of human embryo development. Cholinergic neurons appear simultaneously with neuropeptides. The newly formed peptidergic fibers spread in the direction of cholinergic centers, with which they can interact. In the CNS peptidergic neurons are localized with different neurotransmitters. For example, in the area of facial nerve nuclei, fibers containing encephalin and substance P coexist with cholinergic and catecholaminergic neurons, indicating the possibility of multilateral interaction. In the interpeduncular nucleus, peptidergic neurons function as interneurons, clearly modulating the afferent inputs to the nucleus. It is believed that the interaction of neurotransmitters with peptides plays an important role in the initial stage of morphogenesis of the Central nervous system, including human retina [36].

**Glutamatergic system**

One of the main neurotransmitters of retinal ganglion cells is glutamate. Glutamate receptors participate
in synaptic transmission of retinogeniculate and retinocollicular signalling pathways [37].

Visual receptors, rods and cones transmit signals to bipolar and horizontal cells using glutamate. Glutamate is released in the dark when the receptors are depolarized, and stops to stand out in the light when they are hyperpolarized.

Nitrergic system

Nitric oxide synthesis follows the activation of N-methyl-D-aspartate (NMDA) receptors, and NO acts as a retrograde messenger, giving a signal to the growth of retinal afferents [38]. Nicotine stimulates the synthesis of NO photoreceptor, horizontal, bipolar, ganglion and Muller cells. Acetylcholine can activate the No/cGMP signalling pathway in the inner and outer retina. This indicates the interaction of nitrergic and cholinergic systems in the regulation of the activity of retinal cells. Donator NO nipradilol stimulates axonal regeneration of retinal ganglion cells of cats [39].

Pathology of vitreous Body and Retina

The main group of diseases of the posterior segment of the eye in need of vitreoretinal intervention consists of diabetic macular edema, idiopathic macular rupture, vitreomacular traction syndrome [15,40-42].

Proliferative vitreoretinopathy is a fibrous lesion of the vitreous body and retina. There are primary proliferative vitreoretinopathy, when the first signs of the disease are found outside of predisposing diseases and injuries and a secondary proliferative vitreoretinopathy, in which the occurrence of the disease is associated with damage to the eyes. The most common causes of secondary proliferative vitreoretinopathies are retinal detachment, retinal rupture, eye injury especially penetrating with CT and retinal damage, severe and traumatic abdominal surgery on the eyeball, as well as diabetes and a number of other diseases. One of the most important reasons for the emergence of progressive neovascularization and proliferation, traction retinal detachment are pathological fusions between the internal compartments of the retina and the posterior compartments of CT in their direct contact [43].

Trauma to the retina and diabetes is caused by local inflammation with a release of large amounts of active substances, stimulates the regeneration of tissues. At the same time, as well as with conventional skin damage, the restoration of the retina in case of damage is provided by the appearance of dense glial and fibrous tissue, that is, a scar is formed. In this case, the vitreous body is always involved in the process—there are dense fusions (traction) between the retina and the vitreous body, that is, areas of tension of the retina. Depending on which area of the retina similar proliferative changes develop, it is accepted to allocate anterior and posterior proliferative vitreoretinopathy. With the development of proliferation there is a local thickening of the retina, then fibrous membranes, which are reduced over time, forms the folds of the retina. With the appearance of retinal folds or strong traction on the part of VB increases the likelihood of retinal detachment, with the development of which the severity of the proliferative process is further enhanced.

A retinal detachment, which appears due to proliferative changes, differs in their severity, steady progression, and has a high probability of recurrence after surgical treatment. Retinal detachment in the absence of surgical treatment leads to complete blindness and subatrophy of the eyeball. If a subatrophied eyeball reduces in volume, in addition, there are persistent inflammatory reactions in the eye with a high risk of sympathetic ophthalmia, that is, involvement in the inflammatory process pair eye. When epiretinal fibrosis changes occur in the outer layer of the retina-the internal limiting membrane. The latter thickens and shrinks over time. If changes occur in the Central area of the retina, there is local swelling, thereby reducing visual acuity, distorted surrounding objects [20,44].

Diagnosis and treatment

Modern research methods, such as optical coherence tomography, can be very useful in the early diagnosis of proliferative changes, helping to assess the structural changes of the retina, their severity and dynamics of the disease.

Recently the greatest research interest is the study of the posterior of the cortical layers of VB, as it is generally accepted that the main anatomical feature that is aimed vitreoretinal impact in the treatment of these diseases, are these layers [2,5,15].

Methods of separating the posterior cortical layers of the vitreous body from the retinal ILM can be divided into two directions – pharmacological and surgical [15,45-50].

The appearance of unexpressed proliferative changes in the Central zone of the retina, it is recommended that watchful waiting, re-screening and, preferably, data of optical coherent tomography of the retina.
Pharmacological vitreolysis is a conservative effect of enzymes on the vitreoretinal connection [48]. Experiments using a series of enzymes (chondroitinase, hyaluronidase, dispute and others) have demonstrated the feasibility of this approach for treatment of posterior detachment of the vitreous body from the point of view of its security. However, the relatively low efficiency of the obtained results requires the search for new, more adapted for this purpose, enzymatic preparations [49-51]. With the obvious progression of the disease, and reducing visual functions, surgical treatment is recommended — vasectomy.

Vasectomy consists in removing the diseased ST, fibrous membranes, the expansion of the retina with silicone oil. After about 1 month of silicone oil removed from the cavity of the eye, replacing the saline solution. Anti-inflammatory drugs are also used, reducing the severity of postoperative inflammation and the likelihood of subsequent relapse. The standard of modern vitrectomy is to perform a full-fledged three-portal access through which the removal of VB, including its intact layers up to the Subtotal vitrectomy, with the greatest difficulty is the isolation and removal of the posterior cortical layer from the internal limiting membrane of the retina [51-53].

In recent years, the development of vitreoretinal surgery was marked by a number of new positions that allowed reaching a qualitatively new level in the treatment of patients. First of all, it concerns the use of micro invasive three-port vitrectomy technique, the use of a single cutting tool with a diameter of 25 G, 27 G, a new generation of light guides and endovitreal instruments. All, taken together, allowed to reduce dramatically the trauma of operations, reduce the time of rehabilitation of patients and to improve the functional results of surgical treatment.

Reference


12. Dong C-J, Guo Y, Agey P, Wheeler L, Hare WA. Nimodipine enhancement of alpha2 adrenergic modulation of NMDA receptor via a mechanism


