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ROLE OF BRAIN NEUROTROPHIC FACTOR IN THE COURSE OF GLAUCOMA

Dildora U.Narzullaeva [1], Shakhzodbek O.Abdullaev [2]

1 Department of Ophthalmology, Pediatric Ophthalmology, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
E-mail: diladora@mail.ru

2 Department of Ophthalmology, Andijan State Medical Institute, Andijan, Uzbekistan
E-mail: sheikhzaidabdullaev@gmail.com

ABSTRACT

Brain-derived neurotrophic factor (BDNF) is one of the important members of the neurotrophic family. Its role is of great importance in the death of ganglion cells in glaucoma. In this review, we would like to highlight the structure, distribution of brain-derived neurotrophic factor, its effect on the survival of retinal ganglion cells and thereby provide a theoretical basis for the neuroprotective treatment of glaucoma.

Key words: Glaucoma, brain-derived neurotrophic factor (BDNF), dead retinal ganglion cells.

INTRODUCTION

Retinal ganglion cells (RGCs), the effector neurons of the retina, form the layer of the same name and consist of a heterogeneous population of various subtypes. Their typology is based on specific somatodendritic and axonal arborization and interneuronal connections that RGCs form in the retina and visual centers of the brain. The main portion of these neurons uses aspartate and glutamate as neurotransmitters, as well as the related oligopeptide N-acetylaspartylglutamate [45]. It is assumed that these mediators play the role of a trigger in the neurotoxic effects that occur in the retina during hypoxia, ischemia and glaucoma, and GCs remain the main target in these diseases [15].

The description of the various morphological types of RGCs was first made by Cajal in 1881. In the human retina, Golgi identified about 20 types of these cells, and H. Kolb et al. described 18 of their types [34]. The position of the dendritic crown of the GC allows us to separate these

cells into three main types: 1) neurons with a diffuse dendritic tree extending in the inner reticular layer; 2) neurons with a stratified dendritic tree, spreading in one or several levels of the inner reticular layer; 3) biplexiform neurons, the dendrites of which extend from the inner reticular layer to the outer one. In the group of diffuse cells, umbrella, bush-like, and garland-like RGCs are identified [41].

RGCs are essential for processing perceptual images, and their loss can lead to irreversible blindness, such as that observed in glaucoma [23]. Optic neuropathies such as glaucoma, the second leading cause of blindness in the world, are associated with loss of RGCs and gradual degeneration of the optic nerve head (ONH); consequently, a characteristic pattern of visual field loss occurs [52,58].

Glaucoma is considered a neurodegenerative disease, similar to Alzheimer's or Parkinson's disease, which leads to progressive atrophy of the optic nerve and irreversible loss of vision [14]. The leading pathogenetic factor of glaucoma is a violation of the outflow of aqueous humor from the anterior chamber of the eye, an increase in intraocular pressure, gradually leading to deformation of the ethmoid plate and compression of the fibers and vessels of the optic nerve. To date, numerous theories have been proposed for the pathogenesis of glaucomatous optic neuropathy. For the most part, these theories are summarized into three main ones, deeply developed by researchers: mechanical (hydromechanical), theory of vascular disorders and metabolic [53]. The neurodegenerative theory will be able to combine all the accumulated data on the pathogenesis of glaucomatous optic neuropathy.

One of the important pathophysiological characteristics of primary open-angle glaucoma (POAG) is damage to retinal ganglion cells. This process occurs as a result of a number of pathogenetic mechanisms, including not only an increase in IOP, but also a violation of autoregulation, the development of ischemia, a deficiency of neurotrophic factors, glutamate-induced excitotoxicity, immunological disorders, calcium metabolism disorders, and oxidative stress. Recently, many authors agree that the destruction of neuroelements of the visual pathway may occur due to the process of secondary transsynaptic neurodegeneration. According to N. Gupta et al (2006), this process combines primary glaucoma with other neurodegenerative diseases, with axonopathy being the key element in their development [24].

In the literature, there are increasingly more works indicating the presence of close connections between primary open-angle glaucoma and neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease [9]. According to AU Bayer (2001), the incidence of glaucoma in patients with Alzheimer's disease is 25.9%, while in the control group this figure is 5.2% [7]. Confirmation of the relative similarity of these two pathological conditions is the detection of visual field defects in patients with Alzheimer's disease, reminiscent of the picture of

glaucomatous damage to visual functions [55]. Of course, they are united by an increase in incidence with age, selective damage to a certain type of neurons, and a similar mechanism of death of nerve cells [54].

The metabolic theory of the occurrence of glaucoma is based on the important role of destruction of intraocular structures, causing the destruction of the GCS and/or irreversible excavation of the OND. The metabolic theory explains the increase in IOP and the development of GON by the effects of peptides, free radicals, lipoids and others on drainage structures, the retina and the optic nerve.

In modern literary sources, important importance is given to the role of mitochondria in apoptosis, aging and neurodegenerative diseases, to which some researchers include glaucoma [18]. Therefore, mitochondrial dysfunction in POAG in the light of metabolic theory is currently being actively studied. It is believed that primary damage in glaucoma develops as a result of a decrease in the energetic power of mitochondria in the axons of retinal ganglion cells. In particular, it was revealed that neurodegenerative changes in the pathways of the visual analyzer are determined by zones of glucose hypometabolism (energy metabolism disorders), which are commonly called mitochondrial dysfunction [29].

Mitochondria play a special role in the development of neurodegenerative diseases. Mitochondrial pathology may be one of the key links in the pathogenesis of POAG [29]. Structural and functional changes in mitochondria lead to “oxidative stress” and excitotoxicity (from the English excitotoxicity - toxicity that develops during excitation). The basis of the pathology in excitotoxicity is the disruption of calcium homeostasis and activation of N-Methyl-D-aspartate (NMDA) receptors. Indirect evidence that the phenomenon of excitotoxicity is also present in glaucoma is the positive neuroprotective effect of antagonists of NMDA receptor mediators. In an experiment on animals with a long-term increase in IOP, a slowdown in the death of optic nerve axons was noted when memantine was administered. In monkeys, visual functions were preserved for a long time, and when recording an electroretinogram, only minor changes were revealed [25]. NMDA receptor antagonists are thought to reduce excitotoxicity by stabilizing cell membranes that have been destabilized by mitochondrial dysfunction and decreased ATP production [57].

An important role in metabolic changes is attributed to cytotoxic mechanisms, according to which damaged ganglion cells release L-glutamate, which serves as a neurotransmitter. L-glutamate activates neuronal NO synthase, which leads to increased NO production and the formation of free radicals (superoxide anion) in mitochondria. The result of this reaction is peroxynitrite, which is highly neurotoxic and causes damage and death of ganglion cells [30].

The metabolic theory includes the neurotrophin hypothesis, according to which all substances necessary for the nutrition of GCS, primarily the neurotrophic factor BDNF (brain derived neurotrophic factor), are synthesized in the brain and retrogradely move to the eye using axonal transport (AT). Axonal transport is one of the central processes that ensures the growth, regeneration and functional activity of RGCs and their axons. A decrease in AT delays the retrograde movement of neurotrophins and turns on the apoptosis mechanism [13, 16].

As mentioned above, neurotrophins are transported into the retina in a retrograde manner. They are responsible for regulating the growth, function and survival of neurons. Long-term retrograde transport of neurotrophins is likely *mediated by* endosomal signaling [17]. Neurotrophins bind to tropomyosin receptor kinase (Trk) receptors on axon terminals, which are then retrogradely taken up by the cell body [5]. In glaucomatous conditions due to high IOP, retrograde transport is thought to be blocked at the optic nerve head and RGCs do not receive BDNF and tropomyosin receptor kinase B (TrkB) support for survival. Thus, neurotrophin deprivation causes cell death, and therefore adjuvant therapy may be a potential approach in the treatment of glaucoma.

Currently, more and more data are appearing in foreign and domestic literature on the important role of neurotrophic factors for the physiology and pathology of the nervous system. Neurotrophic factors are regulatory proteins of nervous tissue that promote proliferation, differentiation, maintenance of the viability and functioning of neurons.

Currently, the entire variety of neurotrophic factors can be divided into subfamilies:

1) “neurotrophins” or nerve growth factor subfamily (NGF, BDNF, NF-3, NF-4/5);

2) glial factor subfamily (GDNF, NTR, ART, PSP);

3) “neuropoietins” or the ciliary factor subfamily (CNTF, LIF, IL-6);

4) other neurotrophic factors.

Nerve growth factor (NGF) was the first growth factor identified in the 1950s for its trophic (survival and growth promoting) effects on sensory and sympathetic neurons [38]. Later, in 1982, BDNF was discovered as the second member of the "neurotrophic" family of growth factors by isolation and purification from pig brain. It has been shown to promote the survival of a subpopulation of neurons in the dorsal root ganglion [6]. Since the discovery of NGF and BDNF, other members of the neurotrophin family have been described, such as neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), ciliary neurotrophic factor (CNTF), and glial cell-derived neurotrophic factor. lines (GDNF), each of which has its own profile

of trophic effects on subpopulations of neurons in the nervous system [27]. These molecules have several similarities, including their homology in sequence, structure and processing. They are synthesized as proneurotrophins, immature precursors, and converted to mature proteins after proteolytic cleavage [50]. These molecules bind to the tropomyosin receptor kinase (Trk) and p75 neurotrophin receptor (p75NTR) receptors, and their affinity for each of these receptors depends on their maturity [40]. Mature neurotrophic factors (NTFs) have high affinity for Trk receptors, which leads to cell survival and growth, while proneurotrophins have high affinity for p75NTR, which mainly causes cell apoptosis.

Neurotrophic factors play an important role at the stages of prenatal and postnatal neurogenesis. In embryogenesis, they participate in the formation of cell phenotype, influence the cytoarchitectonics of the cerebral cortex, in ontogenesis they control the growth and differentiation of neurons, and in the postnatal period they contribute to the formation of new synaptic connections [3].

One of the most studied factors from the neurotrophin subfamily is brain-derived neurotrophic factor (BDNF). It was originally isolated from pig brain in 1982, then cloned in 1989 [37], after which it was shown to have an important role in regulating the viability and differentiation of various neurons (sensory, motor, ganglion, dopaminergic, cholinergic and GABA). -ergic neurons) [6]. Brain-derived neurotrophic factor (BDNF), a potent trophic factor, is predominantly expressed in the central nervous system (CNS) and is critical for synaptic and structural plasticity. BDNF is a polypeptide with a molecular weight of 27.2 kDa, which is synthesized by proteolysis of the preBDNF protein (proBDNF). Each monomer consists of 120 amino acids and can only exhibit biological activity upon dimerization. BDNF and preBDNF activate two different types of receptors: the first interacts with the receptor tyrosine kinase family (TrkB), and the second interacts with the tumor necrosis factor receptor family (p75NTR). At the same time, BDNF activates the processes of neuronal differentiation, inhibits proapoptotic proteins and regulates the level of intracellular Ca^{2+}, which stimulates the secretion of the neurotrophin itself; and preBDNF triggers a cascade of reactions that lead to cell apoptosis [47]. This neurotrophin is found in large quantities in the thalamus, neocortex, cerebellum, hippocampus and cerebral cortex. This is explained by the fact that BDNF can be formed with the help of various types of glial cells: astrocytes, Schwann cells, oligodenrocytes, microglia.

The source of BDNF in serum is platelets, which bind, store and release neurotrophin in response to external stimuli [44], which explains its high content at the systemic level [1, 11]. Research shows that BDNF is involved in the pathogenesis of any organic lesion of the central nervous system -

neurodegenerative, ischemic, traumatic, as well as in the mechanisms of development of mental illnesses - schizophrenia, affective disorders such as anxiety and depression.

A sufficient number of works are devoted to the study of BDNF in Alzheimer's disease. It has been established that in this group of patients in the advanced stage of the disease, the level of BDNF and its matrix ribonucleic acid is reduced in the blood serum and cerebrospinal fluid without significant differences in the concentration in these biological fluids. The degree of BDNF reduction correlated with the severity of clinical manifestations of the disease. However, in the early stages of Alzheimer's disease, an increase in this neurotrophin in the cerebrospinal fluid and blood serum is shown, which, according to the authors, may be compensatory in nature [20].

The fact that BDNF is expressed in various structures of the eye is evidenced by many studies. In animals, the protein is found in the inner and outer layers of the retina, in the nerve fiber layer [28]. Other sources of BDNF are trabecular cells and Müller glial cells. BDNF also reaches retinal ganglion cells through the bloodstream and through the intershell spaces of the optic nerve. After these cells remain in an environment with low levels of oxygen and glucose, increased secretion of both neurotrophin and its receptor is observed. These data, according to researchers, indicate the important role of BDNF in response to ischemic processes in glaucoma [35].

Experimental models of glaucoma have shown that in retinal cells there is a decrease in the amount of BDNF, which is determined only in the layers of ganglion cells and nerve fibers. The TrkB receptor, which is found in the above layers of the retina normally, is detected in greater quantities in glaucoma, which, according to the authors, may be a compensatory process in response to a lack of BDNF [28].

The experiment reveals a violation of the axoplasmic transport of BDNF with an increase in IOP. The neurotrophin and its receptor accumulate at the optic nerve head directly behind the sclera and reach ganglion cells in significantly lower concentrations compared to control eyes in both acute and chronic increases in IOP. According to some data, with an acute increase in IOP to high levels, retrograde transport of BDNF is reduced by 74%. Vesicles containing BDNF also accumulate in the intraocular areas of the axons of retinal ganglion cells, which indicates a violation of the anterograde transport of neurotrophin [49].

It has been established that in patients with POAG, as the disease progresses, there is a significant decrease in the concentration of BDNF at both systemic and local levels. A certain correlation is found between the content of neurotrophin in

tears and the stage of the disease, the number of scotomas in the central visual field, the ratio of the areas of excavation and the optic nerve head, and the thickness of the retinal nerve fiber layer (RNFL). Another study also noted the importance of BDNF in the pathogenesis of glaucomatous optic neuropathy. The authors showed that low values of neurotrophin in the tear fluid (TF) correspond to more pronounced glaucomatous changes, assessed using parameters of the optic nerve head and RNFL. A significant relationship has been established between the level of BDNF and indicators of light sensitivity of the eye, as well as such perimetric indices as MD and PSD. During dynamic observation, a greater progression of the glaucomatous process was noted in patients with a low content of neurotrophin in the SF compared to the control group, which indicates its prognostic significance in this disease.

Diagnostic criteria for glaucoma have been widely discussed, and specific recommendations are now followed. Currently, diagnosis is largely based on the detection of abnormal changes in the optic disc and visual field using various tools such as fundoscopy, optical coherence tomography (OCT) and standard automated perimetry. However, it is assumed that most currently used methods can detect the disease only when 30%–50% of the RGCs have been irretrievably lost. However, early detection of glaucomatous damage is ideal for preventing progressive loss of glucocorticoids [4]. Therefore, it is important to search for biomarkers that can predict the onset and/or progression of disease and can be objectively measured and assessed as an indicator of biological processes in both normal and pathological conditions [22]. For example, examining the relationship between systemic BDNF levels and the risk of developing and/or rate of progression of glaucoma may be useful in predicting its possible usefulness as a biomarker [48]. It would also be interesting to study the relationship of BDNF levels with treatment outcome and prognosis. This assumption is based on the observation that BDNF levels are significantly lower in the serum, aqueous humor and tear fluid of patients with early stages of POAG [51]. A similar correlation of BDNF levels was observed in patients with Alzheimer's disease [8,21]. Because BDNF is also generated by some non-neural cells, it remains controversial whether the source of systemically detected BDNF is actually neuronal tissue. However, studies have shown that systemic BDNF levels correspond to brain BDNF levels [46]. Blood concentrations of BDNF in different species have been reviewed in detail [32]. The authors suggest that BDNF levels in blood and plasma closely reflect BDNF levels in brain tissue. These results not only provide insight into the pathophysiology of the disease, but also indicate the possible use of systemic BDNF levels as a

biomarker to monitor the onset and progression of neurodegenerative diseases such as glaucoma and Alzheimer's disease.

Today, good glaucoma intervention, whether a pharmaceutical or surgical procedure, aims to slow the progression of optic neuropathy and reduce visual field defects by lowering IOP just enough to maintain good visual function. Several published clinical trials have clearly demonstrated that lowering IOP can slow the progression of vision loss in both early and late stages of the disease. However, as has been reported in many cases, patients with excellent IOP values experienced visual deterioration despite extensive therapy [30]. Even with significant improvements in therapeutic precision and knowledge of disease progression, a subset of people with glaucoma are prone to aggressive progression, possibly due to non-IOP-related factors contributing to GCS loss. In addition, there has been no significant evidence that non-IOP-lowering drugs can alter the progression of glaucoma, and none have been shown to provide neuroprotection to restore retinal and neuronal function in clinical trials [42].

Neuroprotection is an ideal therapeutic approach for glaucoma to maintain the life of RGCs [2]. The goal of neuroprotection in glaucoma is to preserve the optic nerve independent of IOP reduction and thus prevent or delay RGC apoptosis and axonal degeneration [56]. The rationale for the use of NTFs as therapeutic agents in glaucoma is their ability to promote RGC survival, axonal regeneration, and enhancement of neuronal function and connectivity such that their protection is not limited to the preservation of remaining viable RGCs in the setting of glaucoma, but also promotes the regeneration of already lost nerve cells. Experimental studies by different authors have established that exogenous BDNF is able to delay apoptosis of retinal ganglion cells. ML Ko et al (2001) studied the effect of neurotrophin upon three-time intravitreal injection into the eyes of rats with IOP increased by 2.5 times. According to their data, after the second and third injections, cell survival was 91.3 and 82.7%, respectively, which turned out to be a statistically significant difference from the results obtained in the control group [33]. In addition to BDNF injections, a group of authors led by Domenici L. (2014) proved the effectiveness of instillation of neurotrophin dissolved in saline into the conjunctival fornix of mice and rats. Even one drop at a concentration of 12 mg/ml increased the level of BDNF in the retina of the studied animals [19].

Recently, there has been growing interest in the possible use of genetic engineering to deliver BDNF to retinal cells. Good results have been achieved in in vitro studies: it has been shown that “infection” of retinal ganglion cells with an adeno-associated virus is possible, and infected cells are capable of producing BDNF [39]. Similar results were obtained by intravitreal injection of BDNF DNA

into animals using a viral vector, resulting in increased synthesis of neurotrophin and a significant neuroprotective effect of therapy [43]. Recently, the possibility of "non-viral" gene delivery systems has been studied [12]. A group of authors proved that the induction of 3D spheroids of limbal MMSCs contributes to a significant increase in the production of BDNF and can be considered as a cell drug for safe and long-term neuroprotection in the treatment of optic neuropathies [10] . Stem cell therapy is another approach with the potential to modulate BDNF signaling either by enhancing its production *through* activation of multiple neuroprotective pathways or by acting as a nanocarrier. Stem cell-derived GCS are an ideal treatment option to replace diseased or dead GCS; however, the complexity of retinal architecture makes the idea of cell replacement challenging for functional restoration. Alternatively, transplantation of stem cells such as mesenchymal stem cells (MSCs) also holds great promise due to their ability to secrete exosomes, which can serve as extracellular vesicles encapsulating BDNF [26].

Conclusion.

BDNF plays a role in multiple pathophysiological pathways (TGF- *β*, etc.) and may serve as a promising candidate for the development of treatments aimed at improving the survival of GCS in glaucoma. It is possible to use BDNF as a biomarker of the glaucomatous process, since early diagnosis of glaucoma creates a greater chance of entering the "therapeutic window" and resisting irreversible - consequences. All of the above requires further research in this area.

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