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REVIEW

Pathophysiology of primary open-angle glaucoma from a neuroinflammatory and neurotoxicity perspective: a review of the literature

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Abstract

Purpose Glaucoma is the leading cause of blindness in humans, affecting 2% of the population. This disorder can be classified into various types including primary, secondary, glaucoma with angle closure and with open angle. The prevalence of distinct types of glaucoma differs for each particular region of the world. One of the most common types of this disease is primary open-angle glaucoma (POAG), which is a complex inherited disorder characterized by progressive retinal ganglion cell death, optic nerve head excavation and visual field loss. Nowadays, POAG is considered an optic neuropathy, while intraocular pressure is proposed to play a fundamental role in its pathophysiology and especially in optic disk damage. However, the exact mechanism of optic nerve head damage remains a topic of debate. This literature review aims to bring together the information on the pathophysiology of primary open-angle glaucoma, particularly focusing on neuroinflammatory mechanisms leading to the death of the retinal ganglion cell.

Methods A literature search was done on PubMed using key words including primary open-angle glaucoma, retinal ganglion cells, Müller cells, glutamate, glial cells, ischemia, hypoxia, exitotoxicity, neuroinflammation, axotomy and neurotrophic factors. The literature was reviewed to collect the information published about the pathophysiologic mechanisms of RGC death in the POAG, from a neuroinflammatory and neurotoxicity perspective.

Results Proposed mechanisms for glaucomatous damage are a result of pressure in RGC followed by ischemia, hypoxia of the ONH, and consequently death due to glutamate-induced excitotoxicity, deprivation of energy and oxygen, increase in levels of inflammatory mediators and alteration of trophic factors flow. These events lead to blockage of anterograde and retrograde axonal transport with ensuing axotomy and eventually blindness.

Conclusions The damage to ganglion cells and eventually glaucomatous injury can occur via various mechanisms including baric trauma, ischemia and impact of metabolic toxins, which triggers an inflammatory process and secondary degeneration in the ONH.

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Keywords Glaucoma · Retinal ganglion cells · Cell death · Glutamate · Intraocular pressure · Neuroinflammation

Introduction

The primary open-glaucoma is a progressive optic neuropathy characterized by changes in the optic nerve and associated visual field defects [1]. This pathological condition produces gradual apoptotic death of retinal ganglion cells (RGCs).

Previously, the importance of intraocular pressure (IOP) in disease progression was confirmed [2]. IOP represents the primary risk factor for developing glaucoma. It is widely known that both the incidence and progression of glaucoma can be controlled by decreasing intraocular pressure [2, 3]. The impact of IOP on the pathogenesis of glaucoma is generally explained by two principal complementary to each other theories: vascular (indirect) and mechanical (direct) [4]. According to vascular theory, increase in IOP leads to the compression of capillaries resulting in impaired blood flow to optic nerve head (ONH) and, ultimately, in chronic ischemic injury of optic nerve. This, however, cannot explain why patients often develop glaucoma while their IOP is within normal parameters [5]. It is when the mechanical theory contributes to the overall picture. The above-mentioned theory attributes the development of glaucomatous optic neuropathy to direct compression of axonal fibers of RGCs [4]. As these axons pass through lamina cribrosa when exiting the eye, the latter thought to be the primary site for axonal injury [6]. Therefore, it was postulated that alterations in lamina cribrosa structure lead to differential susceptibility to IOP-induced damage [7, 8]. The histological data showing compaction and fusion of the layers of the lamina cribrosa, in addition to loss of axons, glial cells and capillary vessels at an early stage of glaucomatous damage support this hypothesis [9–12].

Compression of axonal fibers may lead to morbid changes at biochemical level. As an example, impaired axoplasmic transport from the lateral geniculate nucleus to the retina in glaucoma results in a reduction in the distribution of neurotrophins such as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF) [6] (Fig. 1). This in turn leads to the lack of trophic support to RGC bodies and their axons undergoing pressure-related injury [4].

Among other biochemical alterations reported in the literature overexpression of transforming growth factor β2 (TGF-β2) particularly stands out. TGF-β2 causes fibrosis in the trabecular meshwork, preventing the drainage of the aqueous humor, resulting in an increase in IOP and consequent death of RGCs [13].

Neuronal damage leads to accumulation of various types of substances including free radicals, potassium and calcium ions and excitatory amino acids in the extracellular space. Buildup of molecules such as glutamate induces damage to neighboring RGCs creating a vicious circle of chronic neurotoxicity that resolves in marked cell death [14].

The pattern and progression of visual field loss due to RGCs death vary among glaucoma patients, suggesting certain variability in the magnitude of the mechanism responsible for cell loss. In experimental models of glaucoma, it was observed that not all RGCs die simultaneously [15]. Moreover, the estimation of ganglion cells' death rate is proportional to the magnitude of the damage produced [16].

The reason for the initiation of ganglion cell death in glaucoma involves several molecular pathways, and several explanatory theories based on different experimental models of glaucoma have been proposed [17]. Here we will review some of these theories such as ones attributing RGCs death to hypoxia, chronic intermittent ischemia, excitotoxicity, defective axon transport and the presence of trophic factors. This review aims to compile published experimental and clinical data that explain the pathophysiological mechanisms of RGC death in primary open-angle glaucoma.

Hypoxia

Increased IOP is not the only factor responsible for damage to retinal cells, but an important causative agent of glaucoma as in some cases it is sufficient to induce the symptoms [18], making it one of the key risk factors for this disease and for related RGCs death [1, 3, 19].

RGCs have been shown to have a selective susceptibility to IOP increase [20]; however, the exact underlying mechanisms of selective loss of RGCs are yet to be elucidated [21]. Several authors suggest that

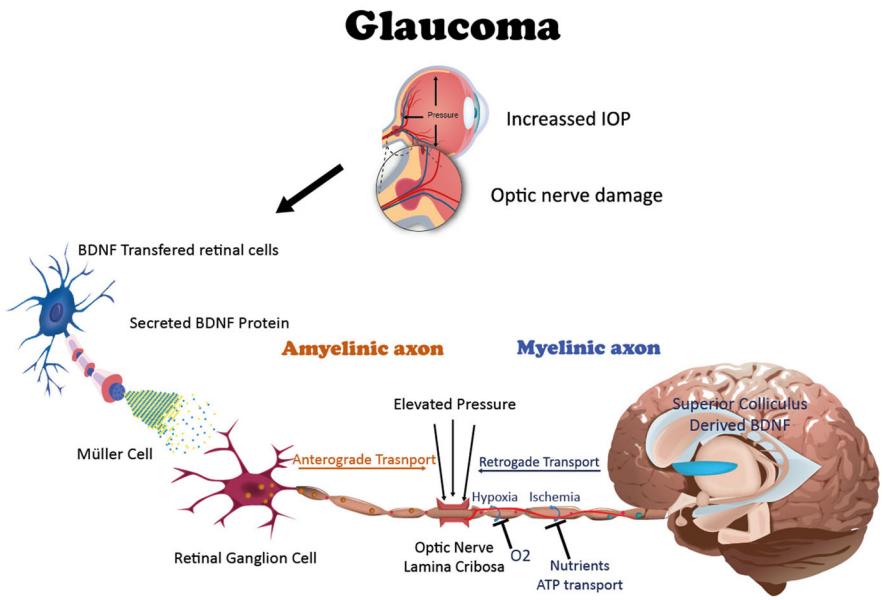

Fig. 1 Increased intraocular pressure leads to damage to the optic nerve head. Increased pressure in the lamina cribrosa from the optic nerve triggers an alteration in the choroidal, anterograde and retrograde obstruction of axonal transport in the ONH, where the axons leave the eye. This reduces the transmission of trophic signals such as brain-derived neurotrophic factor (BNDF) and nerve growth factor (NGF) from terminal axons to neuronal cell bodies, as well as the transport of nutrients and oxygen to the layers of the retina that produce hypoxia and ischemia. Non-myelinated RGCs axons are highly active and energy dependent, which correlates with a high number of mitochondria in this segment of the optic nerve. Changes in energy supply cause an alteration in the axoplasmic flow from the lateral geniculate nucleus and the superior colliculus to the RGCs, contributing to the reduction in neurotrophins and axon damage. Müller cells can be neuroprotective after injury due to the release of neurotrophic factors, such as BDNF, but depending on the time course of the injure can participate in inflammatory processes

multifactorial vascular insufficiency of the ONH plays an important role in the pathogenesis of glaucomatous optic neuropathy [22]. The main source of blood supply to the ONH is the posterior ciliary artery through the choroid and the short posterior ciliary arteries [22]. In this way, the outermost layers of the retina receive oxygen from the choroidal circulation, whereas the inner layers of the retina receive oxygen from the retinal circulation [23].

An alteration in the quality or quantity of blood supply in the capillaries of the ONH could influence the increase in IOP [1]. Among the factors which can affect the perfusion of ONH are poor vascular autoregulation, local vasospasm and mechanical compression of the microvasculature in the lamina cribrosa [24]. If one of these occurs, the tissues in the ONH could suffer from hypoxia due to altered local supply of oxygen [24] (Fig. 1).

Research on the human optic nerve reveals that there are certain portions in the nerve structure that have greater mitochondrial demands for energy production (ATP) [22]. Each subcellular component of RGC such as dendrites, cell body, non-myelinated axons (including intraocular and ONH) and myelinated axons (including intraorbital and intracranial) presents different energetic demands, associated with its structure, function and extracellular environment [22]. These differences are due to the uneven distribution of mitochondria, ATP production and oxygen pressure. The ATP gradients will guide mitochondrial movement, increasing the concentration gradients of oxygen, glucose and pH in the different regions of the neuron. Thus, RGC bodies and axons located near superficial retinal vessels have a high oxygen pressure, which influences the higher production of ATP, proportional to oxygen distribution and consumption [25, 26].

The mitochondrial activity is markedly higher in the unmyelinated regions [17] with mitochondria being mainly concentrated in the laminar and prelaminar regions of lamina cribrosa [6]. Unmyelinated nerve fibers exit the eye via lamina cribrosa and

become myelinated on its posterior side [10]. In cases of hypoxia, generated by IOP, the optic nerve in the lamina cribrosa may be at a greater risk due to the alteration in the ATP production and delay in energy transport between the myelinated and non-myelinated axons [27].

It is commonly known that ganglion cells are loaded with glutamate that can be increasingly released in the extracellular space due to cellular injury [1]. Excess of glutamate in the intercellular medium causes cell damage and cellular death due to its excitotoxic effect [4, 28]. Neuronal loss results in activation of glial cells. Astrocytes may aggravate the damage of ganglion cells and microglia as they can alter ionic homeostasis or prevent the communication of information to regions outside the retina on the ONH [1]. In unmyelinated ONH, astrocytes are predominant glial cell type providing axonal support [29]. In glaucomatous lamina cribrosa, astroglial cells were shown to undergo morphological changes similar to the ones during inflammatory response in the CNS [30]. Reactive astrocytes release pro-inflammatory factors (such as nitric oxide, prostaglandins, cytokines) and gliotransmitters including glutamate which can aggravate the condition of RGCs [1]. Moreover, as astrocytes participate in the formation of blood-retinal barrier their activation leads to dysregulation and increased vascular permeability [31, 32] and ultimately a distortion of blood-retinal barrier [33].

Another type of glial cell altered under hypoxic conditions is Müller cells. These cells are found in retina where they perform an important role in regulating retinal metabolism. Müller cells functions include metabolism of glucose, vascular regulation, ion exchange and control of neurotransmitter level [33]. Under hypoxic conditions, activity of Müller cells is weakened due to changes in energy demand, which contributes to a slow growth in the concentrations of glutamate in the extracellular environment [1, 34]. The cytotoxic effect of a small increase in glutamate concentration does not generate toxicity for healthy retinal neurons, but does so for RGCs [1].

Ischemia

Retinal pigment epithelium is a simple layer of pigmented cells located between the neural retina and the choroids [35]. This region is responsible for the formation of blood-retinal barrier that is mainly constituted by endothelial cells. Tight junctions between the cells of pigment epithelium and vascular endothelium control transport of liquids and solutes through the barrier, as well as prevent the entry of toxic molecules and components circulating in plasma into retina [35]. Therefore, damage to the pigment epithelium of the retina can cause alterations in the mechanisms of retinal and choroidal circulation, modifying the permeability of the blood-retinal barrier causing accumulation of toxins in the retina [36].

Choroid provides vascularization of retina sustaining the pigment epithelium and photoreceptors. A reduction in parasympathetic activity often seen in patients with glaucoma causes the decrease in choroidal blood flow leading to retinal ischemia [37]. In addition to producing photoreceptor damage and visual field loss, ischemia can induce auto-reactive compensatory vasodilation in the retinal vessels [38]. Nitric oxide (NO) is the main mediator of vasodilation. It is involved in a number of physiological and pathological processes in the retina [4]. There are three existing isoforms of nitric oxide synthase (NOS) differing in their origin: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS). IOP elevation results in an increase in endothelial constitutive NOS (ecNOS) expression in the lamina cribrosa after 12 h of IOP elevation [39]. An increase in the expression of ecNOS in the ONH endothelium is related to glial cell damage, axonal delay as a compensatory mechanism, which increases local levels of ATP, and subsequent metabolic disturbances [40].

Several studies have shown that patients with glaucoma present an overexpression of the iNOS and eNOS enzymes in astrocytes of the optic nerve [41, 42]. Meanwhile iNOS has a very potent neurotoxic effect and is thought to be involved in the death of ganglion cells in glaucoma [43], some authors suggest that overexpression of eNOS would have neuroprotective effect mediating a rise in blood flow in the ONH [41]. Astrocytes and other glial cells could also cause the death of ganglion cells in glaucoma by producing glutamate and tumor necrosis factor alpha (TNF-α) and influencing blood flow to the optic nerve, as has been documented experimentally [44]. Increases in nNOS have also been observed, following ischemia-induced pressure rise by occlusion of blood vessels [45].

In glaucoma, there is degeneration of RGCs and their axons in the optic nerve [46], which can be induced by elevated IOP generating axonal loss. These damages are associated with disruption of neurotrophic factor, glial activation, tumor necrosis factor release, increased oxidative stress, mitochondrial dysfunction and immune system deregulation [47, 48] (Fig. 2).

Microglial activation is a common feature of various neurodegenerative diseases including glaucoma. Under glaucomatous conditions, microglia is overactivated by increased IOP and upon activation can trigger neurotoxicity in the CNS and induce inflammatory response in the retina by producing proinflammatory factors such as interleukin 1β (IL-1β) [49]. IL-1β is a part of the innate immune response in the CNS, and its production is controlled tightly. Toll-like receptors (TLRs) and nod-like receptors (NLRs) are two key pattern recognition receptors (PRRs) essential at the onset of the innate immune response [50]. TLR4 has been shown to play a central role in retinal lesions and CNS ischemia. Neuronal death after ischemic injury activates intense inflammatory response, which triggers TLR4 signaling and induces the transcriptional activation of pro-IL-1β, which is then proteolytically processed through

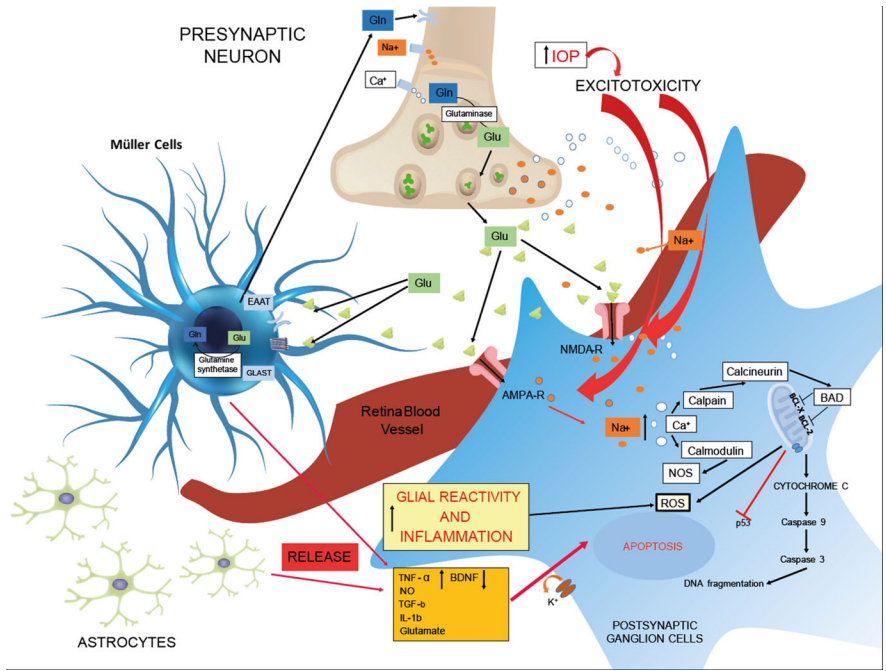

Fig. 2 Müller cells remove the excess of extracellular glutamate from the retinal tissue prevent it from spreading beyond the synaptic region. Glutamate (Glu) is synthesized in neurons from local precursors such as glutamine (Gln), which is released by glial cells as astrocytes and Müller cells. Once released, glutamine is absorbed at the presynaptic terminals and is metabolized into glutamate by the enzyme glutaminase. Glutamate is released at presynaptic termination into extracellular medium and neighboring glial cells capture excess glutamate through excitatory amino acid transporters (EAATs) and glutamate aspartate transporter (GLAST). Uptaken glutamate is transformed into glutamine by the glutamine synthetase, which is further transported back to neurons as a precursor for glutamate synthesis. Overstimulation of AMPA receptors (AMPAR) permits the influx of Na^+ ions and the efflux of K^+ ions and the increase in glutamate release mediating glutamate excitotoxicity and contributing to sensitization of NMDA receptors, as it facilitates the extrusion of magnesium molecules. The increase in IOP and stimulation of AMPA and NMDA receptors intensifies entry of extracellular calcium into ganglion cells. Calcium entry leads to calpain activation which cleaves calcineurin. Calcineurin initiates apoptosis in RGCs through the dephosphorylation of the pro-apoptotic protein Bcl-2-associated death promoter (BAD) that induces cell death stimulating the release of cytochrome C from mitochondria. Calcium also activates calmodulin inducing the NOS expression and the production of reactive oxygen species (ROS). After IOP elevation, astrocytes and other glial cells could also cause the death of ganglion cells in glaucoma by producing nitric oxide (NO), tumor necrosis factor alpha (TNFα), transforming growth factor β (TGF-β), interleukin 1 beta (IL-1β) and glutamate, influencing blood flow to the optic nerve causing neurotoxicity and inflammation

inflammasome activation [51]. In a murine model, retinal ischemia induced by rise in IOP was shown to directly increase TLR4 expression that in turn triggered caspase-8 signaling that activated the NLRP1-type receptor family and IL-1β production [52].

It was observed that in an early phase of acute glaucoma IOP-induced ischemia did not significantly stimulate the activation of caspase-3, thus suggesting that the inflammatory response of caspase-8 may be responsible for the death of RGCs in glaucoma [50]. Hence, those results demonstrate that caspase-8 is a key link between TLR4 and inflammasomes in the processing of IL-1β and this pathway contributes to the induced death of RGCs. Targeted inhibition of TLR4 and caspase-8 signaling significantly attenuates retinal ischemic damage and death of ganglion cells by regulating inflammasome activation and IL-1β production [50].

The optic nerve experiences a chronic ischemic injury associated with IOP, which leads to loss of axons, glial cells and capillaries. Damage to the retina or the ONH could potentially activate retinal astrocytes [53]. Recurrent injury of the ONH and constant inflammatory process could cause astrocytic reactivity in the region [54] or depolarization of astroglial cells leading to a propagation of optic nerve depression causing changes in the voltage of ganglion cells and photoreceptors [55]. Ischemia can prone astrocytes to trigger disruptions in axoplasmic transport and induce biochemical changes in lamina cribrosa and alterations in the cellular matrix. Furthermore, under ischemic conditions astrocytes tend to release potentially toxic for surrounding neurons compounds such as nitric oxide, TNFα, TGF-β and glutamate. All these changes may contribute to glaucomatous neuropathy [29].

Ischemia and ocular trauma may result in a release of glutamate from necrotic cells and/or a failure of ionic homeostasis and the initiation of the depolarization-induced excitotoxicity cascade [45]. Therefore, RGCs do not only suffer from initial ischemic insult, but surviving neurons may subsequently be damaged by excessive levels of extracellular glutamate and excitotoxicity. This additional damage is often referred to as secondary degeneration and has been a focus of neuroprotective strategies. Excitotoxic damage causes an increase in intracellular calcium, which activates NOS. Nitric oxide (NO) combines with superoxide forming highly reactive species of peroxynitrite that causes DNA breakage and oxidative stress. In addition, NO binds to guanylyl cyclase producing cyclic GMP which also leads to cell death [4].

Excess of glutamate in the extracellular medium during ischemic processes increases calcium intake. Calcium activates caspases which are normally present in inactive form under physiological conditions. Caspases generate a cascade of reactions activating the proteases necessary for initiation of apoptosis. The type of caspase activated in this process appears to be different depending on a cell type. For instance, the expression of caspase-3 is upregulated mainly in the inner nuclear layer and in the outer nuclear layer of the retina [56]. Caspase-3 activation precedes the appearance of cells with fragmented DNA in these layers. Other authors have described the presence of caspase-1 in the outer nuclear layer after ischemia [57]. However, in the same experimental model, it was shown that beside caspase-3 activation in the inner layers of the retina ischemia also induced a 55-kDa Serine/threonine-protein kinase N1 (PKN) cleavage fragment [58]. The molecular size of the fragment corresponds to molecular size of the constitutively active fragment of PKN which appearance depends on the duration of reperfusion and is related to cell death. Therefore, inhibition of caspase-3 reduces the expression of PKN and decreases cell death in the retina [58].

Excitotoxicity

Astrocytes and Müller cells form the macroglia cells of the retina, which are responsible for supporting the neuronal functions. Astrocytes are found in the vicinity of nerve fibers and RGCs to regulate retinal vascularization and maintain the retinal endothelial barrier [59–62]. Müller cells interact with neurons and are responsible for maintaining the metabolic functions of neurons. Müller cells supply the neurons with trophic substances, remove metabolic wastes and maintain the osmotic and homeostatic regulation of the neuronal environment [59–62].

After several periods of IOP elevation, astrocytes in the vicinity of the lamina cribrosa close to the ONH undergo morphological changes as the decrease in their expression of Glial fibrillary acidic protein (GFAP) [63]. Despite this, astrocytes are considerably more resistant to metabolic changes and extended

periods of hypoxia and ischemia than neurons [22]. In the cases of glaucoma, astrocytes can increase GFAP expression, presenting morphological changes in astrogliosis, hypertrophy and hyperproliferation as an indicator of retinal stress, contributing to retinal degeneration associated with axonal loss of RGC and remodeling of the ONH [64]. Homeostasis is affected by decreased expression in carbonic anhydrase and potassium channels, affecting the base acid regulation system and osmotic balance [28, 65–69].

Müller cells are neuroprotective under physiological conditions, but may fail in this function under pathological stimulation and instead contribute to neuronal degeneration. Usually the Müller cells remove the extracellular glutamate from the retinal tissue prevent it from spreading beyond the synaptic region. The main transporter for glutamate uptake in Müller cells is glutamate aspartate transporter (GLAST) [65]. Glutamate is synthesized in neurons from local precursors. The most common precursor for glutamate synthesis is glutamine released by glial cells as astrocytes and Müller cells. Once released, glutamine is absorbed at the presynaptic terminals and is metabolized into glutamate by the mitochondrial enzyme glutaminase. In addition, glutamate can be synthesized by transamination of the Krebs cycle intermediate α-ketoglutarate and metabolization of glucose by neurons in Krebs cycle. Glutamate is released at presynaptic termination into extracellular medium, and neighboring glial cells are able to capture excess glutamate through excitatory amino acid transporters (EAATs). Glutamate that was uptaken is transformed into glutamine by the glutamine synthetase, which is further transported back to neurons as a precursor for glutamate synthesis (Fig. 2).

In glaucoma, the decrease in GLAST expression leads to glutamate excitotoxicity, neuronal death in the retinal tissue and degeneration of the photoreceptors [21, 28, 70, 71]. Studies have shown that subcutaneous injections of glutamate lead to severe destruction of the inner layers of retina, especially of the ganglion cell layer [72]. More recently, it has been suggested that the glutamic and aspartic amino acids are key mediators of lesions in the CNS and, therefore, of the optic nerve and retina. Elevation of the aforementioned amino acids in the vitreous plays an important role in the pathogenesis of glaucoma due to their excitotoxic effect [73].

The excitotoxic action of glutamate is mainly mediated by the overstimulation of the NMDA receptor at postsynaptic terminations. Elevated levels of glutamate alter this receptor and initiate a cascade of events that finally leads to apoptosis of RGCs. In addition, overstimulation of AMPA receptors (AMPAR) may also play a role in glutamate-mediated excitotoxicity. They permit the influx of Na^+ ions and the efflux of K^+ ions and the increase in glutamate release. In an acute phase of neuronal trauma, sodium entering the cell causes edema. Depending on the severity of the damage, the cell can recover or lose its function and die. Later, augmentation of calcium influx alters calcium homeostasis, hereby initiating a wide variety of biochemical reactions [4]. Additionally, activation of the AMPA receptor contributes to sensitization of NMDA receptors, as it facilitates the extrusion of magnesium molecules. Concomitant with activation of ionotropic receptors activation of metabotropic receptors may also produce a surge of calcium in the extracellular space by facilitating the release of intracellular deposits of this ion [74].

Calcium activates catabolic enzymes, phospholipases, superoxides, free radicals and kinases, causing further release of extra glutamate. Consequently, chronic neurotoxicity in glaucoma gives rise to marked cell death due to interruption of calcium homeostasis [4]. The increase in IOP intensifies entry of extracellular calcium into ganglion cells. Calcium entry leads to calpain activation, which is a cysteine protease that cleaves calcineurin. Calcineurin initiates apoptosis in RGCs through the dephosphorylation of the pro-apoptotic protein Bcl-2-associated death promoter (BAD) that induces cell death stimulating the release of cytochrome C from mitochondria [75] (Fig. 2).

It was previously shown that glutamate or NMDA inhibitors are capable of impeding apoptosis of the ganglion cells [4]. Studies conducted with the use of animal models describe the effect of intravitreal injection of different doses of *N*-methyl-D-aspartic acid (NMDA) and inhibitors of p38 and PI3K [76]. Introducing NMDA led to apoptotic death of RGCs. Prior to this, there was a significant increase in p38 and Akt concentrations in the ganglion cell layer and in the inner nuclear layer of retina. Thus, it was concluded that p38 MAP kinase pathway is pro-apoptotic, whereas the PI-3 kinase-Akt pathway is antiapoptotic in RGC death induced by NMDA [76].

The growth in intracellular calcium concentration also stimulates the activation of the calmodulin-dependent NOS. The colossal entry of calcium into the mitochondria causes formation of a pore in the internal mitochondrial membrane and therefore leads to a failure in the electrochemical potential, decrease in ATP levels and an increase in reactive oxygen species (ROS) [77]. ROS activate caspases, phospholipases, proteases and endonucleases, as well as NOS. ATP deficiency hinders the function of ATP-dependent pumps located in the cytoplasmic membrane, causing a massive inflow of water and Na^+ ions leading to cellular swelling or death from necrosis. Damage to mitochondria and DNA induces the activation of genes responsible for apoptosis. Cell death triggers the release of various neurotoxic substances that can initiate apoptosis in previously undamaged cells, a process known as secondary degeneration. Therefore, any damage can be propagated beyond its original extent by secondary degeneration [4].

Axotomy

Several studies indicate that glaucoma is a disease occurring only in the white matter and that the loss of RGCs bodies is due to retrograde degeneration [78–80]. The ONH is accompanied by a progressive disappearance of RGC axons leading to a loss of around 80% at 4 weeks [81] that finally causes a progressive loss of axons, leading to blindness. Precise mechanism of axotomy-induced cell death is still unclear; however, there is evidence that it is of an apoptotic nature [78].

Apoptosis is controlled by the caspase family of cysteine proteases. Caspases are represented by starter caspases (caspase-2, caspase-8, caspase-9, caspase-10); effector caspases (caspase-3, caspase-6, caspase-7) and cytokine-processing caspases (caspase-1, caspase-4, caspase-5, caspase-11, caspase-12, caspase-13, caspase-14). It is recognized that after optic nerve axotomy in rats, mRNA levels of the pro-apoptotic proteins Bcl-2 and Bcl-XL are decreased [82]. Also, both caspase-3 and caspase-9 appear to be involved in apoptotic death of RGCs in this model [83, 84]. In addition, it has been demonstrated that cytochrome c levels are upregulated at day one after axotomy reaching a maximum at 3 days and decreasing thereafter [85], highlighting their role in RGCs apoptotic death.

The apoptosis of ganglion cell bodies in patients with glaucoma is consistent with retrograde degeneration following axonal injury and consistent with theories of vascular, mechanical and target trophic factor [4, 86]. It was observed that RGCs in glaucoma with increased IOP exhibit obstruction of orthograde and retrograde axonal transport at the ONH, where their axons exit the eye [8, 10]. This possibly inhibits the transmission of trophic signals from axon terminals to neuronal cell bodies [78]. It has been suggested that optic nerve-axotomized RGCs die because of deprivation of neurotrophic factors from the superior colliculus. The neurotrophin BDNF and NGF are also involved in the reduction in RGCs apoptosis rates after axotomy [87–89]. The protective effect of BDNF is due to reduction in activity of caspase-9 and caspase-3 in a PI3K-dependent mechanism [90]. In addition, PI3K pathway can be activated by insulin-like growth factor 1 (IGF1) protecting the ganglion cells in an axotomy model of glaucoma [91].

Some studies have shown that p38a activation in RGCs occurs early after axotomy and plays an important role in apoptosis [92]. Inhibition of p38 MAP kinase activity can ameliorate glutamate-related RGC apoptosis in vitro and axotomy-induced RGC death in vivo [92]. Other studies have reported that abnormal activation of glutamate receptors and high levels of intraocular glutamate are related to RGC apoptosis after optic nerve axotomy [93–95]. The inhibition of AMPA/kainate receptors attenuates the RGCs death more effectively than inhibition of NMDA receptors [4], indicating participation of this type of receptors in the apoptotic response.

Deregulation of calcium homeostasis can lead to degeneration of axons [96, 97]. In a murine model of optic nerve damage, the activation of calpain contributes to the early intra-axonal damage and subsequent axonal degeneration [98]. The calpain alters the retrograde transport and the dephosphorylation of neurofilaments in axons, eventually causing their loss [98, 99].

Trophic factors

Trophic factors are endogenously secreted proteins that act in an autocrine and/or paracrine way

influencing vital cellular processes and thus maintaining cellular homeostasis. In the eye, principal sites of expression of these molecules are retinal pigment epithelium (RPE) and Müller cells. The main paracrine targets of the secreted trophic factors are photoreceptors and choriocapillaris. Glaucoma is characterized by aberrant function and/or eventual death of RPE cells, photoreceptors, choriocapillaris and mainly RGCs [100].

Previous research described that administration of BDNF into the vitreous produces activation of two signaling pathways leading to cell survival: the MAPK and the PI3K/Akt pathways. Following administration of BDNF, MAPK is phosphorylated in ganglion and Müller cells, whereas Akt is only activated in ganglion cells. Hence, it seems that the cooperation of the two pathways is necessary for the neuroprotective effect of BDNF to occur [101].

TGF-β is involved in paracrine signaling and can be found in various tissue types. Typically, all cell types have receptors for TGF-β1 on their surface. At the ocular level, however, TGF-β2 has greater significance. TGF-β2 helps corneal healing and preserves immune privilege in the anterior segment [102]. Under glaucomatous conditions, overexpression of TGF-β2 can lead to fibrosis, increased production and deposition of extracellular matrix proteins in trabecular meshwork cells, hereby blocking the outflow of aqueous humor. Patients with glaucoma have increased levels of TGF-β2 in the aqueous humor compared to healthy controls [13].

TGF-β increases production and remodeling of extracellular matrix through the canonical SMAD pathway, as well as through mitogen-activated kinase (MAP) and Rho-GTPase/Rho kinase pathways [102, 103]. RhoA activates Rho kinase, thus leading to phosphorylation of myosin light-chain (MLC). This suggests that Rho pathway-mediated rigidity of trabecular meshwork and alterations of extracellular matrix are possibly involved in the decrease in flow of aqueous humor and ultimately in IOP growth [103].

In addition to Smad and Rho-GTPase pathways, TGF-β also activates the MAP kinase pathway by phosphorylation TGF-β II receptor. This pathway induces IL-6 and SPARC expression [104].

Conclusion

RGC damage present in open-angle glaucoma can be caused by various mechanisms including baric trauma and ischemia, followed by inflammatory process and excitotoxicity which in turn affect axonal transport and induce degeneration of the ONH.

Ischemic damage, caused by rupture of the blood-retinal barrier or due to alterations in the mechanisms of retinal and choroidal circulation, is capable of inducing chronicity of the disease. In these situations, damaged neurons can release glutamate and/or induce a failure of ionic homeostasis, causing the onset of the cascade of excitotoxicity and consequently death of ganglion cells.

In each patient, the degree of impact and combination of diverse pathological mechanisms may vary greatly. Nevertheless, knowing the exact pathophysiological mechanisms of primary open-angle glaucoma might shift the existing treatment paradigm from solely focusing on decreasing IOP to giving thorough protection to the optic nerve and ganglion cells against apoptosis. The understanding of the involved mechanisms will point out ways to protect the eye against the disease.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliation with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval This article does not contain any studies with human participants and animals performed directly by any of the authors.

Informed consent As this article does not contain any studies with human participants, the concept of informed consent is not applicable.

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