Glaucoma Pathophysiology

Glaucoma is a progressive neurodegenerative disease that represents the major cause of irreversible blindness.

1. Introduction

Glaucoma is a progressive neurodegenerative disease and one of the major cause of irreversible blindness. The number of worldwide glaucoma patients will increase from 76.5 million in 2020 to 111.8 million by 2040, mainly due to aging population [1][2]. Glaucoma presents the loss of retinal ganglion cells (RGCs), thinning of the retinal nerve fiber layer, and cupping of the optic disc [3]. Glaucoma is formed by heterogeneous diseases showing varying clinical presentations. Aging, high intraocular pressure (IOP), and a genetic causes are the major risk factors for glaucoma [3]. Primary open-angle glaucoma (POAG) is the major presentation in countries. However, 30% of patients have normal tension glaucoma (NTG) [4]. The etiology of POAG is well-known with mechanical and/or vascular mechanisms. The mechanical process implicates compression of the axons due to increased IOP, while the vascular mechanism shows events in which blood flow and ocular perfusion pressure are decreased to the posterior pole leading to damage [5][6]. Vascular or perfusion dysregulations in NTG show different clinical features, including migraine headaches, Raynaud's phenomenon, or sleep apnea [7]. In high IOP glaucoma, both the anterior and posterior segments are affected, as extensive affection is detectable in the trabecular meshwork (TM) and along the inner retina-central visual pathway [8].

Lithium, introduced in 1949, is the most used drug for chronic mental illness, including bipolar disorder with depressive and manic cycles. Lithium remains a first-line treatment for bipolar disorder, manic-depressive illness, [9], traumatic brain injury [10], and numerous neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's diseases [11]. In acute treatment of mania, the efficacy of lithium is well established [12]. Numerous studies have presented that lithium can diminish manic relapses, even if its efficacy was lower in reduced depressive relapses [13]. In parallel, some studies have shown that lithium may diminish suicides and suicide attempts in patients suffering from mood disorders [14]. Lithium therapeutic mechanisms remain complex, including several pathways and gene expression, such as neurotransmitter and receptors, circadian modulation, ion transport, and signal transduction processes [15]. Recent studies show that the benefits of lithium extend beyond just the therapy of mood. Neuroprotection against excitotoxicity or brain damage are other action of lithium [16]. Moreover, recent findings have investigated the role of lithium in glaucoma [17][18] but its actions remain unclear. Nevertheless, recent studies have highlight possible mechanisms of lithium action through the WNT/beta-catenin pathway in glaucoma [19][20]. The combination of lithium and atypical antipsychotics (AAPs) has been the main common choice for the treatment of bipolar disorder [21]. Due to the possible side effects of the first-generation antipsychotics, the second-generation antipsychotics (also called AAPs) were gradually introduced in therapy [22]. Currently, no studies have focused on the possible actions of AAPs in glaucoma.

2. Pathophysiology of Glaucoma

In primary open-angle glaucoma (POAG), responsible for IOP elevation, the IOP upregulation implicates the TM occlusion inducing by the iris tissue [8]. The chronic contact between the TM and iris leads to permanent affection of the TM. TM dysregulation and its diminished cellularity are the first stage to high tension glaucoma (HTG). Numerous factors, including oxidative stress (OS) and aging, as well as environmental factors, are implicated as the promotors of TM damage [23]. OS could be enhanced in the morphological alterations of the TM of glaucomatous eyes, due to it stimulating inflammatory response. Chronic inflammation and OS modulate each other, creating a vicious circle influencing the cellular responses. The cultures of TM presented a NF-$\varkappa$B pathway activation after exogenous stimulation such as IL-1 or H_2O_2. The NF-$\varkappa$B pathway stimulation leads to a significant expression of the endothelial leukocyte adhesion molecule-1 (ELAM-1), IL-1β and IL-6 [24]. ELAM-1 belongs to selectin families, which are cell adhesion molecules. ELAM-1 presence in POAG is a main factor for the onset of TM endothelial dysregulation [25]. In glaucoma, a progressive loss of TM cells

was observed, due to the combination of both aging and stress conditions [26]. In HTG, the TM dysregulation involves both inflammation and reprogramming mechanisms with OS damage and endothelial dysregulation [27]. IL-6, IL-1, and TNF-alpha induce ECM reprogramming and alter cytoskeletal interactions in the glaucomatous TM [25].

Elevation of the IOP, at the lamina cribrosa or the optic nerve head (ONH) step, involves hypoperfusion and damages in reperfusion [28]. Increase in IOP is considered as a major factor of retinal ganglion cells (RGCs) dysfunction, leading to a retrograde transport blockade and the accumulation of neurotrophic factors at the lamina cribrosa instead of reaching the RGC soma [29]. The etiology of POAG remains unclear but numerous risk factors have been shown as causes of its onset, including increased IOP, aging, gender, family history, OS, systemic and ocular vascular factors, and inflammation [30]. The dysfunctions in the protein patterns shown in the aqueous humor (AH) of POAG patients is the consequence of the progressive loss of TM integrity [31]. TM-derived proteins can damage both the retina and optic nerve head (ONG) behavior in the posterior segment of the eye, leading to apoptotic signaling for RGCs and their axons in the ONH. The TM is the most sensitive tissue of the anterior segment of the eye to oxidative stress [32]. Glaucomatous TM cells presented POAG-typical molecular modifications, including ECM accumulation, cell death, dysfunction of the cytoskeleton, advanced senescence, NF-$\varkappa$B pathay activation and inflammatory markers release [24][33]. These results could suggest that the IOP elevation is associated to OS and degenerative processes affecting the human TM endothelial cells (hTMEs). The chronic exposure of TM cells to OS leads to numerous changes in the lysosomal pathway responsible for autophagia [34], as well as cell senescence with an increase in senescence-associated-galactosidase [35]. OS leads to lysosomal dysfunctions and the defective proteolytic activation of lysosomal enzymes with a subsequent diminution in autophagic flux and the activation of cell senescence [8].

3. Oxidative Stress, Inflammation and Glutamate in Glaucoma

Pathogenic processes of the neurodegenerative mechanism lead to the mechanical and vascular stress enhancing mitochondrial dysregulation, chronic oxidative stress (OS) and metabolic stress [36][37], excitotoxicity [38], and neuro-inflammation [39][40]. OS and cell senescence are increased in the aging retina [41][42] and are considered as the main glaucoma risk factors. In the aging retina, OS leads to the stimulation of a para-inflammation [43]. Para-inflammation, in glaucoma, is characterized by a tissue adaptive response to noxious stress [43]. However, a physiological stage of para-inflammation is needed to maintain homeostasis but when tissue is exposed to a chronic stress, inflammation may have a negative role and could be involved in both initiation and progression of the disease [44]. The deregulation of para-inflammation in the retina is a response to stress stimuli especially chronic OS. However, excessive and uncontrolled para-inflammation could implicated inflammatory responses with a release of cytokines/chemokines leading to neuroretina damages [45]. Para-inflammatory dysregulation could be associated to TM dysfunction and increased resistance to aqueous outflow, the main cause of increased IOP in POAG [8].

The mechanisms of reactive oxygen species (ROS) production are activated in several pathological conditions of the retina, such as glaucoma, occlusion of the central artery of the retina and the age-macular degeneration. They are enzymes, including the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the cytochrome P450, the mitochondrial cytochrome oxidase, the xanthine oxidoreductase, and the eNOS decoupled, catalyzing the stimulation of ROS production in the vascular system tissues [46][47]. OS diminishes BH4 bioavailability, but increases BH2, which possessing cofactor activity to compete with BH4 for enhancing eNOS [48].

The TM was the main pathological region of PAOG [49]. IOP can be control by the balance between the production and out flow of the aqueous humor. The TM is composed by layers of trabecular beams and surrounded by elastic fibers, fibronectin and laminin. Abnormalities of the ECM are involved in high IOP [50]. Recently, the WNT/β-catenin pathway have been found to be associated with the development of glaucoma in the TM [51].

To date, the visual loss processes are not entirely elucidated in glaucoma, the ROS production plays an important role in its development [52]. ROS production rates are increased in patients with glaucoma in the acute mood but also in the blood serum [53]. In retinal arteries, a moderately increased IOP leads to ROS production, activation of NOX2 expression, and endothelial dysfunction, leading to the idea of IOP stimulation can damage the vascular function of the retina [54]. Nevertheless, some pathogenic mechanisms are linked to glaucoma, including glutamate excitotoxicity [55], which are not necessarily associated with the elevated levels of IOP [52]. It seems that the death of RGCs during a glaucoma lesion stimulates ROS production in vitro [56]. It has been shown that the ROS production controls the immune response by stimulating the action of antigen glial cells [56]. ROS production affects the retina, and increase the IOP to induce a dysfunction of the support glia, which facilitates the secondary degeneration of the RGCs in glaucoma [57]. The glial cells produced by ROS that affect the retina, and the PIO elevated to induce a dysfunction of the support glide, which facilitates the secondary degeneration of the CGR in the glaucoma [57].

The immune system is controlled by numerous inflammatory factors, including tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF) and tumor growth factor-β (TGF-β) [58]. Inflammation leads to the stimulation of cyclooxygenase 2 (COX-2) [59]. Several cytokines (TNF-α, IL-1) stimulate COX-2 [60]. COX-2 activates ROS production [59][61]. The nuclear factor-ϰB (NF-ϰB) pathway can activate numerous factors leading to COX-2 and inducible nitric oxide synthase (iNOS) over-expressions [62]. Numerous findings have presented that NF-ϰB pathway can activate the expression of both TNF-α, IL-6, IL-8, STAT3, COX-2, BCL-2 (B-cell lymphoma 2), metalloproteinases (MMPs), VEGF [62], and then the overstimulation of the ROS production [63]. Moreover, iNOS is stimulated during chronic inflammation [64].

Numerous studies have presented the mechanism by which OS can activate chronic inflammation [65]. The imbalance caused by OS involves damages of signaling in cells [66]. ROS have a main role both upstream and downstream of NF-κB and TNF-α pathways. The hydroxyl radical is the main harmful of all the ROS. A vicious circle has been observed between ROS and these pathways. ROS are controlled by the NOX system. Furthermore, the modified proteins by ROS may involve the enhancement of the auto-immune response to activate TNF-α and NOX [67]. Nuclear factor erythroid-2 related factor 2 (Nrf2) is mainly associated to OS and inflammation [65]. Nrf2 is a transcription factor binding to the antioxidant response element (ARE) [68]. Numerous studies have shown that Nrf2 could have an anti-inflammatory role through the regulation of MAPK, NF-ϰB, and PI3K pathways [69]. Then, Nrf2 could have a main action against OS damages [70]. Moreover, evidence also have shown that mitochondrial dysfunction could have a significant action in cancer processes [65].

Glutamate is an amino-acid responsible for the brain's primary excitatory neurotransmission. Glutamate is considered as the main neurotransmitter within the cortico-striatal-thalamic circuit involved in OCD [71]. Glutamatergic neurons are embedded in every brain circuit in comparison to dopamine and serotonin which are used by a small minority of neural cells in the brain. Glutamate is the main excitatory neurotransmitter in brain and is present in more than 50% of synapses. This signaling plays a major role for neuronal plasticity, memory, and learning [72]. Rapid neurotoxicity enhanced by neuronal excitotoxin has been observed with abnormal glutamate levels [73]. In neurons, glutamate is stored in synaptic vesicles from which it is released. Glutamate release increases glutamate concentration in the synaptic cleft to bind ionotropic glutamate receptors. SLC1A1 encodes for the neuronal excitatory Na+-dependent amino acid transporter 3 (EAAT3). EAAT1 and EAAT2 are the main astrocyte glutamate transporters whereas EAAT3 is the major neuronal glutamate transporter. Glutamate is converted into glutamine in astrocytes and released. Then, glutamine is take up by neurons to be re-converted into glutamate [74]. The role of the EAAT3 is to control glutamate spillover which affects pre-synaptic N-methyl-D-asparate (NMDA) and metabotropic glutamate receptors activity [75][76]. EAAT3 activity is dysregulated by the overexpression of GSK-3β [77].

In glaucoma, the glutamate pathway dysregulation may enhance RGC death and has been shown to be controlled by the NMDA receptor that, due to its higher Ca2+ permeability, could have a great affinity for glutamate and a slower inactivation [78][79]. In retinal neurodegeneration, the glutamate excitotoxicity is involved in the mtDNA damage or DNA oxidation–related mitochondrial dysfunction [80]. Glutamate excitotoxicity activation in the excitatory signaling leading to neuronal cell death by high levels of glutamate and the over-stimulation of NMDA receptors. The excitotoxic damages to RGCs may be enhanced by the augmentation of glutamate synthesis or the diminution of glutamate clearance [81].

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