Normal Tension Glaucoma

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Glaucoma is a neurodegenerative disease of the eye, which involves degeneration of retinal ganglion cells (RGCs): the output neurons of the retina to the brain, which with their axons comprise the optic nerve. Glaucoma is usually associated with elevated intraocular pressure (IOP), but there is a subtype of glaucoma, termed normal tension glaucoma, that presents with normal IOP.

Keywords: Normal Tension Glaucoma ; Neuroprotection ; Oxidative Stress ; Retinal Ganglion Cell ; Optic Nerve ; Drug Repositioning

1. Introduction

Glaucoma is a neurodegenerative disease of the eye and it is one of the major causes of blindness. It is usually associated with sustained elevation of intraocular pressure (IOP), damage to the optic nerve, and death of retinal ganglion cells (RGCs). The cell body of RGCs is located in the retina and they project their axons to the brain nuclei through the optic nerve. To date, more than 40 subtypes of RGCs have been identified and how they respond to injury has been studied in various models [1][2][3][4]. Glaucoma therapy mainly focuses on reducing IOP and this approach prevents or slows down disease progression. However, the therapeutic effect of this method alone is not sufficient for some patients and disease progression continues despite treatment. In addition, there is a form of glaucoma that shows glaucomatous optic neuropathy without elevation of IOP, termed normal tension glaucoma (NTG). These suggest that there are factors other than high IOP that could be a therapeutic target for glaucoma. One of the factors that was focused upon previously was excitotoxicity, but it is known now that the glutamate level in the vitreous of glaucoma patients is not upregulated; although, glutamate neurotoxicity may still play a part in the pathology of glaucoma [5][6]. Pathogenesis of glaucoma is complex, and it involves multiple factors. Oxidative stress is one of the risk factors for glaucoma and the level of glutathione (GSH), a major antioxidant in the retina [7], is decreased in the glaucoma patient plasma [8][9]. Moreover, a recent report demonstrated that oxidative stress is increased in the common marmoset with pathological features of glaucoma [10]. Studies using animal models indicate that suppression of oxidative stress increases RGC survival [11][12][13][14][15], suggesting that antioxidants are potential candidates for glaucoma therapy. Here, we discuss recent works on the effects of antioxidants in mouse models of NTG and in some glaucoma patients.

2. Effects of Suppression of Oxidative Stress in Rodent Models of NTG

Research into the therapeutic effects of reducing oxidative stress on retinal diseases including glaucoma is growing [16]. Here, we describe findings from some of the studies focusing on those using rodent models of NTG.

2.1. Apoptosis Signal-Regulating Kinase 1

Apoptosis signal-regulating kinase 1 (ASK1) is a member of mitogen-activated protein kinase that plays important roles in cellular responses to oxidative stress and endoplasmic reticulum stress [17][18]. ASK1 plays an essential part in oxidative stress-induced apoptosis through activation of the ASK1-JNK/p38 pathway [19][20]. Therefore, blocking the ASK1 pathway may be useful to prevent neuronal cell death in various neurodegenerative diseases. We have previously reported neuroprotective effects of *ASK1* gene deletion on RGCs in several different mouse models of glaucoma, including retinal ischemia, optic nerve injury (ONI) and GLAST KO mice (GLAST/ASK1 double KO mice) [21][22][23]. These studies demonstrated that deletion of ASK1 decreased oxidative stress levels and increased RGC survival, suggesting that targeting oxidative stress is an effective approach for treatment of glaucoma. Interestingly, it is possible that ASK1 deletion may also have indirect effects on RGC survival, such as by reducing TNF-α production by macrophages, microglia and astrocytes [24][25], in which TNF-α is reported to mediate neurodegeneration in glaucoma [26]. Recently, ASK1 has attracted much attention because of its pathogenic role in non-alcoholic steatohepatitis (NASH), which led to the ASK1 inhibitor selonsertib entering human clinical trials [27][28]. It is intriguing to test the effects of the ASK1 inhibitor on various animal models of glaucoma and explore its therapeutic potential for glaucoma.

2.2. Valproic Acid

Valproic acid (VPA) is a short chain fatty acid and it has been used clinically worldwide for treatment of epilepsy since 1970s. Mechanisms of action of VPA are complex and there are multiple pharmacological actions, including increasing GABA synthesis, inhibiting histone deacetylases and neuroprotection [29][30][31]. We reported that VPA suppresses glaucoma-like retinal degeneration in GLAST KO mice, a mouse model of NTG, by reduction of the oxidative stress level in the RGCs and by stimulation of the BDNF-TrkB pathway [32][33]. Antioxidant properties of VPA have been demonstrated by other groups, for example, in the brain following ischemia/reperfusion injury [34] and in motor neurons following spinal cord injury [35]. It is possible that VPA acts as a histone deacetylase inhibitor and upregulates gene expressions of antioxidant enzymes such as superoxide dismutase and catalase [36]. Intriguingly, some studies reported that oral administration of VPA in patients with retinitis pigmentosa, an inherited retinal dystrophy that is characterized by selective degeneration of photoreceptors, improved visual function, demonstrating clinical efficacy in retinal diseases [37][38][39]. VPA is a drug that is already approved for clinical use in treatment of various conditions with relatively minor side effects. Use of VPA for retinal diseases in clinical settings has not been considered yet, but recent data indicating its therapeutic efficacy in glaucoma and retinitis pigmentosa suggest that VPA is a suitable candidate for ‘drug repositioning’, which is an application of known drugs to new medical conditions to save time and cost that is required to establish the safety of the drug. Findings from numerous studies indicate that VPA may be effective in treatment of glaucoma and retinitis pigmentosa, and further studies are required to determine if it is suitable for treatment of retinal diseases.

2.3. N-acetylcysteine

N-acetylcysteine (NAC) is a *N*-acetyl derivative of cysteine that has historically been used as an antidote against paracetamol overdose, and more recently for various medical conditions including bronchopulmonary disorders, renal disorders, and neurological and psychiatric disorders. In neurons, the availability of cysteine is the rate-limiting substrate for the synthesis of GSH, a powerful antioxidant, so supply of NAC that can be rapidly hydrolyzed and converted to cysteine can increase GSH levels that may lead to neuroprotection. We have recently reported that daily NAC administration protected RGCs in EAAC1 KO mice, a mouse model of NTG, by increasing retinal GSH levels and reducing oxidative stress, demonstrating that supplementation of cysteine in neurons via NAC in EAAC1 KO mice restores the retinal GSH levels [40]. These findings demonstrate that NAC exerts neuroprotective effects by its antioxidant properties in EAAC1 KO mice and that NAC may be a potential candidate for glaucoma therapy.

2.4. Spermidine

Spermidine is a naturally occurring polyamine and it is vital for life. It has been reported that decrease in the spermidine concentration is associated with aging in humans, and exogenous application of spermidine increased the lifespan of yeast, flies, worms, and human immune cells [41]. Spermidine has been shown to reduces oxidative stress both in vitro and in vivo: spermidine-treated yeast cells and mouse fibroblast cells are less susceptible to damage induced by H_2O_2 treatment than non-treated cells, and oral intake of spermidine increases the serum level of free thiol groups in mice [41][42]. We reported that oral intake of spermidine suppresses RGC death and visual impairment in EAAC1 KO mice as well as in the ONI model, by reducing oxidative stress levels in the retina [43][44]. We found that spermidine suppresses activation of the ASK1-p38 pathway in RGCs and reduces expression of inducible nitric oxide synthase (iNOS) in microglia in an ONI model [44]. These findings demonstrated that oral intake of spermidine exerts antioxidative effects and it is beneficial for glaucoma therapy. Spermidine is a natural component of our diet and studies reported that blood spermidine levels could be increased by eating food that is rich in spermidine, for example, soybeans and mushrooms [45]. Therefore, the beneficial effects of spermidine are easily attainable by choosing the right food.

3. Effects of Dietary Intake of Antioxidants in Glaucoma Patients

Several clinical studies suggest that dietary antioxidants may be effective for slowing down progression of glaucoma [46]. Indeed, the association of reduced plasma levels of vitamin C and E with primary open angle glaucoma has been indicated [47], and the plasma levels of vitamin E were significantly lower in NTG patients [46]. Studies of African American women aged between 65 and 94 demonstrated that oral consumption of fruits and vegetables that contain high levels of vitamins A and C and carotenoids may be associated with reduced risk of glaucoma [48]. Furthermore, a case study reported that an NTG patient who received dietary supplement containing a mixture of citicoline, homotaurine and vitamin E once a day with a topical brimonidine and brinzolamide drops showed a significant improvement in visual field and stable retinal fiber layer and ganglion cells, suggesting a synergic neuroprotective effect from the dietary supplement [49]. On the other hand, a prospective study indicated that a higher dietary intake of vitamins C, E or A had no effect on risks of glaucoma [50][51]. These contradictory reports suggest that the findings regarding the use of these vitamins for treatment of glaucoma should be taken with caution.

Niacin, also known as vitamin B3, is showing promising results as a therapeutic candidate for glaucoma. Studies from DBA/2J mice demonstrated that oral administration of niacin reduced RGC death [52] and the therapeutic role of niacin in glaucoma was supported by studies of NTG patients indicating that there was a reduced level of dietary niacin intake in NTG patients [53]. Recent clinical trials demonstrated that supplementation with niacin improved inner retinal function in glaucoma patients [54], and the long-term effects of niacin supplementation are under investigation at present.

4. Conclusions

Pathogenesis of glaucoma involves multiple factors, but currently available therapies that are clinically effective mainly target reduction of IOP. Research on exploring novel therapeutic strategies that target oxidative stress is increasing, and combinatory treatment of IOP reduction and suppression of oxidative stress may prove effective. Future studies are required to validate the effectiveness of neuroprotection in glaucoma patients, but neuroprotective strategies in addition to IOP-lowering therapy may benefit many glaucoma patients, particularly those who do not achieve sufficient therapeutic effects with IOP reduction alone.

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