·Commentary·

TRPC6: an underlying target for human glaucoma

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Abstract

• Glaucoma is one of the leading causes of visual impairment and blindness worldwide. Of known risk factors for glaucoma, an increased in intraocular pressure is most highly correlated with glaucomatous damage. Irrespective of the cause, apoptosis of the retinal ganglion cells is the eventual outcome. It is widely accepted that glaucoma is a neurodegenerative disease that is strongly correlated with central nervous system disorders, such as Alzheimer's disease. These two disorders also share some similarities in pathogenic mechanisms. Recent studies suggest that the transient receptor potential canonical 6 channel could work together with brain-derived neurotrophic factor to promote neuron survival in brain and retina. In this study, we propose that transient receptor potential canonical 6 may contribute to the pathogenesis of human glaucoma and become a potential therapeutic target.

• KEYWORDS: glaucoma; transient receptor potential canonical 6 channel; neuroprotection

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INTRODUCTION

Retinal ganglion cells (RGCs) death is the final step in glaucoma and other ocular neurodegenerative diseases [1]. RGCs have been considered as an attractive reciprocal model to study neurodegenerative disorders in the central nervous system (CNS)[2-4]. At present, the exact mechanisms of RGCs death remain unknown, and there is no effective treatment to combat cell death. The initiation and progression of glaucomatous optic neuropathy and preferential killing of RGCs attributed to elevated intraocular pressure (IOP) [5]. Insufficient blood perfusion caused by increased IOP or ischemia of the optic nerve head may also cause progressive RGCs death with resultant degeneration of the optic nerve and, ultimately, vision loss [6]. Currently, primary treatment of glaucoma is aimed at lowering the IOP[7]. However, some individuals with significantly lowered IOP following treatment show no improvement in glaucomatous optic neuropathy and even progression of the disease [8]. Other factors may, therefore, be implicated in RGCs death, and it is likely that neuroprotection, in addition to lowering of IOP, needs to be considered in glaucoma treatment. Previous studies have demonstrated the potent role of brain-derived neurotrophic factor (BDNF) in promoting neurons survival, including RGCs [9-15]. Recent studies have also revealed that transient receptor potential canonical 6 (TRPC6) participates in BDNF-mediated neuron survival in the CNS and calcium (Ca^{2+}) entry may be involved in early onset Alzheimer's disease (AD) [16,17]. Thus, TRPC6 may contribute to neurodegenerative changes. The potential link between glaucoma and AD has already been identified, with a previous study reporting a high rate of glaucoma among patients with AD [18]. We propose that TRPC6 may play a critical role in signaling cascades involving RGCs survival in glaucoma. BDNF-mediated RGCs survival and TRPC6-mediated Ca^{2+} regulation may be key aspects of the process. Elucidating the potential role of TRPC6 in glaucoma may yield possible therapeutic targets for the treatment of glaucomatous optic neuropathy.

TRANSIENT RECEPTOR POTENTIAL AND TRANSIENT RECEPTOR POTENTIAL CANONICAL

Transient receptor potential (TRP) channels are cation-permeable channels first identified in phototransduction mutation studies of *Drosophila* [18,19]. More than 30 members of the TRP family have been cloned in both vertebrates and invertebrates. TRPs are broadly expressed in a variety of organisms and mediate multiple physiological functions [20-22] such as neurotransmitter release, neurite outgrowth, cell cycle regulation, cell apoptosis and survival via the regulation of Ca^{2+} changes [21,23]. TRPs are also expressed in the transduction of various responses such as mechanosensation [24]. Among the mammalian TRP superfamily, TRP canonical (TRPC) channels show the most structural similarity to the *Drosophila* TRPs [25]. The TRPC family (TRPC1-7) can be divided by homology and function into four subfamilies: TRPC1, TRPC2, TRPC4/5, and

TRPC3/6/7 [21]. The roles of TRPC6 are explained based on the following aspects.

EXPRESSION AND FUNCTION OF TRPC6

TRPC6 is widely expressed in mammalian brain and retina. In rat brain, TRPC6 was reported in dentate gyrus in the hippocampus [25], cerebellar granule neurons (CGNs) in the cerebellum [16], and substantia nigra in the midbrain [26]. In retina, TRPC6 was expressed in RGCs [27-29], rods [30], and many other cell types[31,32].

TRPC6 is a key player in neuron pathophysiological functions [16, 33-35]. It was essential in BDNF-mediated neuron growth cone turning and intracellular Ca^{2+} elevation [33]. Down-regulation of TRPC6 led to apoptosis and blocked the BDNF-protective effect in CGNs, and overexpression of TRPC6 could protect CGNs against serum deprivation-induced cell death [16]. TRPC6 promoted neuron dendritic growth via the CaMKIV-CREB pathway [34], which suggested that TRPC6 was important during brain development [35].

In retina, preliminary work has been conducted in TRP channels research. Wang *et al*[36,37] showed that constitutively active TRPCs resulted in retinal degeneration because of Ca^{2+} overload. TRPC channel blockers can suppress light-evoked currents in rat photosensitive RGCs [28]. TRPC may also mediate basal Ca^{2+} entry in retinal pigment epithelial (RPE) cells [32] and Müller cells [31]. Activating TRPC6 channel prior to ischemia has early neuroprotective effects on RGCs *in vivo*, and the protection of TRPC6 was also BDNF-mediated [29].

As a potent neuroprotective agent, BDNF appears to be a good candidate for therapeutic treatment for some CNS disorders such as AD [38,39]. BDNF-dependent pathways of neuron survival in the CNS may share similarities with that of RGCs in retina. In fact, BDNF had long been known to influence RGCs survival, both during retinal development and following lesioning [9-13]. TRPC has been clarified as the key downstream target for the neuronal protective effect of BDNF [16]. TRPC6 is required for the neuroprotective effect of BDNF.

POTENTIAL DISEASE–RELATED MECHANISMS

The potential link between AD and glaucoma indicates that TRPC6 might be involved the pathogenesis of glaucoma. Ca^{2+} is a ubiquitous and versatile intracellular messenger, which regulates many cellular activities such as neuronal excitability, synaptic plasticity, and neurotoxicity. Dysfunction of Ca^{2+} homeostasis can result in many CNS-related cognitive and neuropathological problems.

AD is a chronic neurodegenerative disease. Although the molecular basis has not been fully established [40,41], TRPC6-induced dysfunction of Ca^{2+} homeostasis may be the key step. It is generally accepted that abeta deposits, which renders neurons vulnerable to excitotoxicity and apoptosis by disruption of intracellular Ca^{2+} homeostasis and production of neurotoxic factors, are central to its neuropathology [42]. Previous report showed that the overexpression of presenilin-2 and AD-linked presenilin-2 variants influenced TRPC6-enhanced Ca^{2+} entry into HEK293 cells. Thus, TRPC6 in AD may be a promising focus for research[43].

A high prevalence of glaucoma had been found in AD patients [44-46], with many AD patients exhibiting typical glaucomatous optic neuropathy, such as enlarged optic disc cupping, damaged retinal nerve fibers, and a defective visual field. To some extent, glaucoma had been proposed to be a form of ocular AD [1]. Therefore, it is reasonable to believe that the underlying pathways of the two diseases may be similar. Future studies may reveal a similar mechanism of TRPC6 activity in glaucoma and AD.

TRPC6, PRESSURE AND GLAUCOMA

TRPC6 is also associated with pressure-related changes in many diseases. High TRPC6 levels have been found in numerous tissues including the lung, stomach, colon, esophagus, and myometrium [47]. TRPC6 can be directly activated by mechanical stimulation [48,49]. The intravascular pressure-induced depolarization and constriction of small arteries and arterioles was regulated by TRPC6[50]. Moreover, TRPC6 expression was up-regulated in pulmonary arteries hypertension of rats [51]. Podocin, together with TRPC6 and possibly other TRPCs, forms complexes with other transmembrane proteins may act to sense glomerular pressure [52]. These characteristics of activation make TRPC6 serving as an environmental pressure sensor, translating extracellular cues into intracellular signals.

Glaucoma is a typical optic neuropathy with IOP as the main risk factor. The pressure inducing RGCs death remains unclear. Designed to sense pressure, a series of receptors are located throughout the brain and retina pathway. These molecules might allow cells in the retina and optic nerve to respond directly to ocular pressure. Pressure injury may overload the cells with Ca^{2+}, which cause a direct degenerative cascade. The molecules sensing pressure might be the factor translating pressure into neuronal damage. TRPV1, another member of the TRP family, one of the sensor of pressure, has recently been discovered expressed in RGCs and induced apoptosis through the influx of extracellular Ca^{2+} [53]. The possibility that TRPC6, also a pressure-sensitive channel, may exert similar functions or work together is worth investigation.

HYPOTHESIS

Taking the features of TRPC6 already mentioned above into consideration, we hypothesize that TRPC6 may contribute to the pathogenesis of human glaucoma and become a potential therapeutic target. Thus manipulation of TRPC6 activity may provide a novel and promising tool for the treatment of the disease.

In conclusion, glaucoma is a major cause of optic neuropathy and adversely affects the vision and life quality of many people in a large number of developing countries[54,55]. At present, there is no effective treatment strategy to protect

against optic nerve damage induced by intraocular hypertension and other risk factors. There has been little success in the development of neuroprotective agents for retinal damage. Firstly, there is the issue of timing: a drug would have to be administered within a reasonable time of the retinal insult occurring [56]. Secondly, all drugs that have been developed have been characterized by incomplete protection and presented a risk of nonspecific effects, such as glutamate excitotoxicity [57] or other side effects. Thus far, most current studies have focused on reducing IOP. However, targeting IOP lowering will not completely impede the progression of glaucoma in all patients. Neuroprotection has, therefore, become increasingly important as a therapeutic target, with innovative studies underway [58]. Experimental data previously revealed neuroprotective effects of various agents and strategies, such as neurotrophin delivery[59] and blocking of excess glutamate stimulation [60]. Other strategies attempted include stabilization of Ca^{2+} homeostasis [61], prevention of apoptosis, modulation of immunologic status *via* vaccination [62], and induction of endogenous neuroprotective mechanisms. These studies raise hopes for discovering beneficial effects in future clinical trials.

The potential role of TRPC6 as a neuroprotective target is illustrated as follows: 1) The possibility which TRPC6 is involved in neurodegenerative diseases is a reasonable conjecture. Identifying the physiological signals that regulate TRPC6 activity in glaucoma appears to be a clear priority. To date, little work has been done in this area. TRPC6 would become an important and interesting target in glaucoma research; 2)TRPC6 appears to be important in the pathogenetic pathway that leads to apoptosis of RGCs [29]. In different retinal cell types, we could discover whether TRPC6 plays an active role in Ca^{2+} entry pathways. If TRPC6 channel were found to control a variety of biological functions, new and promising drug development could emerge; 3)Targeting TRPC6 may be helpful in protecting RGCs against elevated IOP and other insults. The damage to RGCs occurs at an early stage of glaucoma, even before visual field defects are detected. In general, pressure-induced dysfunction of RGCs precedes cell death; therefore, neuroprotective therapies could be more effective at this stage. Our hypothesis suggests a possible method to detect glaucoma at an early stage and monitor the development of the disease; 4) TRPC6 may enhance our understanding of the mechanisms of RGCs neurodegeneration and provide new insight in optic neuropathy, as well as other neurodegenerative diseases, such as AD. Overall, exciting advances at the laboratory level will continue to drive research on the role of TRPC6 in glaucoma. Future investigations of human glaucoma and AD involving TRPC6 should prove highly rewarding in the years to come.

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