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Review

Protective treatments and their target retinal ganglion cells in diabetic retinopathy

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ABSTRACT

Diabetic retinopathy(DR)is one of the complications of diabetes which could cause severe vision loss. Retinal ganglion cell(RGC)injury has been confirmed prior to micro-vascular damage. Over the past few decades, a number of animal and clinical studies have confirmed that RGC impairment leads to an early deterioration of vision in DR. Inhibition of aldose reductase (AR), advanced glycation end product (AGE), oxidative stress, glutamate toxicity, and an inflammatory response may play important roles in protecting RGCs in DR. Furthermore, nicotinamide mononucleotide adenylyl transferase-1 (Nmnat1), neurotrophins and neurotrophic factors may become new therapeutic targets. Photobiomodulation (PBM) may be used as adjunctive therapy in protective treatment of RGCs. In this review, we highlight and discuss protective treatments and their targets which have shown great promise for treatment of RGC injury in DR.

1. Introduction

It is estimated that the number of people with diabetes worldwide will rise to 592 million by 2035 (Guariguata et al., 2014). DR is a complication of diabetes which leads to impaired vision and even blindness (Lin and Gupta, 2017; Liew et al., 2014). In the past, DR was considered only as a type of retinal microvascular disease; however, there are a growing number of studies indicating that RGC impairment in the retina occurs in the early stages of DR, which may precede visible retinal vasculopathy (Sohn et al., 2016a; Jonsson et al., 2016). Further clinical data suggest that RGC loss is consistent with experimental studies on DR, and that such RGCs damage is progressive in the development of subsequent DR (Ng et al., 2016; Salvi et al., 2016). Oxidative stress, inflammatory factors, reduction of nerve growth factors, the excitatory toxicity of glutamate, and other mechanisms increasing metabolism are closely related to the damage of RGCs (Kim et al., 2016; Barber et al., 2011; Cui et al., 2016; Huang et al., 2014). At present, new progress is being made in the prevention and treatment of RGC injury in DR, in order to prevent or delay visual dysfunction and reduce the burden of diabetes-induced blindness. In the following we will discuss protective treatments and their target RGCs in DR.

2. Inhibition of aldose reductase

Aldose reductase (AR) is a type of rate-limiting enzyme which has a crucial role in the mechanism of diabetic retinopathy. High glucose levels increase the production of aldose reductase and activate the polyol pathway metabolism, which may lead to impairment of RGCs in DR (Ino-Ue et al., 2000). The accumulation of aldose reductase (AR) is closely related to metabolic processes and may take part in the progress of RGC impairment in DR (Greifenhagen et al., 2016; Kim et al., 2015a).

Recent studies have demonstrated that inhibition of AR relieved RGC injury by inhibiting the expression of extracellular signal-regulated kinase (ERK), 1/2 phosporylation, and nuclear factor-kappa β (NF-kβ) in mice with DR (Ding et al., 2014). This evidence points to a crucial role of AR inhibitors in protecting RGCs in DR. Epalrestat is a type of AR inhibitor currently applied in clinical settings. A clinical trial analysis showed that epalrestat could prevent progression of DR in Japanese patients over 3 years old (Hotta et al., 2012), possibly by inhibiting the polyol pathway to protect RGCs (Hotta, 2010). Epalrestat has been used for the treatment of diabetic neuropathy and retinopathy in the Japanese market since 1992. Side effects of epalrestat include nausea, vomiting, and diarrhoea, and it may also increase hepatic enzymes (Schemmel et al., 2010). Treatment with epalrestat for AR-induced diabetic neuropathy has a good curative effect and the safety and efficacy of epalrestat has been confirmed in clinical trials. At the same time, epalrestat was also found to be effective in slowing progression of DR; therefore, epalrestat preparation to prevent AR-related RGC injury may be a promising therapeutic target.

Unfortunately, side effects of epalrestat have limited its clinical

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application. In order to solve this problem, the study of a new preparation of epalrestat or other AR inhibitors is urgently needed. Pterin-7-carboxamides, derivatives of coumarin-thiazole and oxadiazole, benzothiadiazine derivatives, and others have been shown to have better aldose reductase inhibitory activity and lower toxicity than epalrestat (Saito et al., 2016; Ibrar et al., 2016; Zhu et al., 2016). Phytochemicals from molecular docking studies showed that protein-ligand interactions are better with these than with epalrestat, sorbinil or ranirestat (Antony and Vijayan, 2015). As phytochemical reductase inhibitors are widely sourced, have less adverse side effects and other characteristics, they have a new prospect for the protection of ganglion cells in patients with DR. The study of these drugs is in early experimental stages, lacking clinical trials support, so these new AR inhibitors need further study on their role in protection of RGCs in DR.

Tonicity response element binding protein (TonEBP) is a transcription factor which increases under hypertonic conditions (Cheung and Ko, 2013). Moreover, TonEBP increases AR by up-regulating the enzyme activity of AR, promoting ganglion cells injury in diabetic mouse retinae (Park et al., 2014). Studies by Seong-Jae Kim et al. have further reported that high glucose-induced expression of TonEBP increased in the ganglion cell layer (GCL) of streptozotocin-induced rats, leading to an increase in, AR which may lead to apoptosis of RGCs in the DR (Kim et al., 2014a). Aralia grows in the northeast of China and possesses anti-apoptotic, anti-oxidant, anti-inflammatory, and anti-tumor properties (Liu et al., 2016a; Otsuka et al., 2014; Zhang et al., 2013; Hwang et al., 2015); therefore, *Aralia elata* extract may be effective in the prevention or treatment of RGC injury in DR. In addition, the safety of Aralia application has been proven in dogs, and a measurement of 100 mg/kg proved a safe application dosage for humans (Li et al., 2016). Interestingly, a recent study further confirmed that Aralia extract could prevent diabetes-induced apoptosis of RGCs in the retina. Indeed, a two-month treatment with Aralia extract effectively reduced levels of TonEBP by blocking phospho-p38 mitogen-activated protein kinase (MAPK) expression, then further inhibiting AR activity, thereby protecting RGCs from apoptosis in the retina of diabetic mice (Kim et al., 2015b). To our knowledge, Aralia belong in Chinese traditional medicine, with the drug products hepatoprotectants (Aralia Gantai Capsule)used in the clinical market. Aralia has made some progress in the treatment of diabetes (Jung et al., 2012). Importantly, it contains natural active ingredients which may reduce the incidence of cardiovascular disease, allergies, and so on; therefore, Aralia extract may be a novel and effective prevention and treatment for RGC injury in DR.

3. Inhibition of advanced glycation end product

Experimental and clinical researches have revealed that hyperglycemia increases the expression of advanced glycation end product (AGE), which is the last product of non-enzymatic glycation. A study has shown that AGE is closely related to DR (Maeda et al., 2015) and leads to cells degeneration in the ganglion cell layer (which may include RGCs) in the retinal explants of rats (Lecleire-Collet et al., 2005). Inhibition of AGE accumulation may be a therapeutic target for RGC injury in DR.

Aminoguanidine (AG) is an inhibitor of protein glycation. In addition, it has immunoregulation (de Souza Ferreira et al., 2016), anti-apoptotic (Du et al., 2013), and recovery of deficit cognition (Alipour et al., 2016) effects. Direct evidence for these effects is provided by results indicating that AG induces AGE reduction in diabetic rat retinae (Luo et al., 2012). In a recent study, a thirteen-week treatment with AG significantly reduced the level of AGE. Furthermore, in this study, AG effectively inhibited apoptosis of ganglion cells in seven-week-old male Zucker diabetic fatty rats (Kim et al., 2014b). This result is consistent with the previous idea that AGE may cause RGC damage in DR and also indicates the potential ability of AG to slow the progression of ganglion cells damage in DR. Whether it can be successfully applied in early stages of RGC injury in patients with DR needs further study. Litsea (Litsea japonica) belongs to a family of plants which contains a biologically active substance used to reduce inflammatory cytokines (Koo et al., 2014), called metalloproteinases (Jeong et al., 2015). An extract of Litsea japonica inhibited AGE formation (IC50 7.4–72.0 μM) in a diabetic zebrafish model (Lee et al., 2017), which shows that the extract may be an AGE inhibitor and have a protective effect on RGCs. In diabetic mice, oral administration of the extract of Litsea japonica to 7-week-old male mice for 12 weeks reduced accumulation of AGE in the neural retina and markedly inhibited apoptosis of RGCs (Kim et al., 2015c). These results suggested that the extract of Litsea japonica may be beneficial for RGC injury by inhibiting AGE in DR.

The receptor of AGE (RAGE) is the most characteristic of the receptors of AGE. RGC injury may be prevented by inhibiting RAGE. A study has confirmed that inhibition of RAGE was beneficial for the prevention of diabetic retinopathy (McVicar et al., 2015). Glucagon-like peptide-1 (GLP-1) is a type of incretin hormone that takes part in glucose homeostasis. A study has shown that intravitreal GLP-1 injections increase the survival rate of RGCs in rats with crushed optic nerves (Zhang et al., 2011). Correspondingly, further animal experiments showed that GLP-1 could inhibit the expression of RAGE by decreasing NF-κβ (Chen et al., 2016). Further studies are needed to confirm that GLP-1 may protect RGCs by targeting RAGE in DR. GLP-1 has been wide clinical applications, but is mainly used for reducing blood sugar; its protective effect on RGCs by targeting RAGE needs further animal and clinical trials.

In conclusion, AGE and RAGE may be therapeutic targets and we may reduce the expression of AGE and RAGE, or block a combination of AGE and RAGE, to protect RGCs in DR. Further animal and clinical studies are needed to confirm efficacy for this treatment for DR.

4. Inhibition of oxidative stress injury

An increased level of oxidative stress in diabetes plays an accelerative role in the progression and pathogenesis of diabetic retinopathy. Oxidative stress creates a vicious cycle of macromolecular damage by increasing the production of more reactive oxygen species (ROS) and nitrogen species (RNS), and activating several metabolic pathways, which in turn dysregulate cellular and molecular mechanisms associated with DR (Zheng and Kern, 2009). One particular example is oxidative stress-induced RGC death by the renin-angiotensin system (Ozawa et al., 2013). In another study, superoxide dismutase (antioxidant defence) application for three hours or five hours significantly reduced ROS levels in both 20 week db/m and db/db mice retinae, quickly improving the function of RGCs in db/db mice (Xiao et al., 2012). These results further indicate that oxidative stress plays a crucial role in mediating RGC injury in diabetic retinae and we may slow down progression of RGC damage by inhibiting oxidative stress in DR.

Lutein is one of the carotenoids. In recent years, animal studies have found that lutein is of vital importance in RGC protection (Zhang et al., 2016), which may be related to the reduction of oxidative stress (Li and Lo, 2010). ROS production was increased in the retinae of one-month-diabetic mice using dihydroethidium measurements; however, a lutein-supplemented diet prevented accumulation of ROS, further inhibited ERK activation, and increased synaptophysin, an increase in ganglion cell number was measured in the retinae of lutein-fed diabetic mice (Sasaki et al., 2010). These results suggest that lutein may inhibit local oxidative stress and protect RGCs by decreasing ROS. Additionally, astaxanthin belongs to the carotenoid group found widely in plants, algae and seafood. Astaxanthin has many physiological functions, such as being anti-carcinogenic (Liu et al., 2016c), anti-inflammatory (Jiang et al., 2016) and an anti-oxidant (Al-Amin et al., 2016). Astaxanthin easily passes through the blood-retina barrier and protects RGCs from oxidative stress damage in-vitro and in-vivo (Nakajima et al., 2008). Moreover, the antioxidant properties of astaxanthin is superior to lutein