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Molecular Impacts of Vision Impairment: Review Study

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Abstract: The present study was conducted to review the literature towards the importance of molecular basis underlying vision impairment. This study put emphasis on the role of molecular aspects of injury and diabetic related stress on vision impairment. Furthermore, the potential of targeting these molecules as molecular therapies was reviewed. Optic nerve and retina pathology was discussed.

Key words: Optic nerve, vision impairment, retina, molecular mechanisms, pathology

INTRODUCTION

Physiology of optic nerve: The main function of Optic Nerve (OP) is the transmission of visual information from the retina to the brain. ON is made of the axons of Retinal Ganglion Cells (RGCs) (Koch and Lingor, 2016). The exposure of ON to damage causes alterations in vision. Several pathological situations impact the ON such as glaucoma related conditions which involved increased Intraocular Pressure (IOP) and various degenerative processes of the RGCaxons (Bellezza *et al*., 2003; Burgoyne *et al*., 2004; Nickells *et al*., 2012).

MATERIALS AND METHODS

Proteomics of optic nerve: Proteomics studieshave targeted the optic nerve head to determine the role of Peptidyl Arginine Deiminase 2 (PAD2) which is an enzyme that acts to convert the protein arginine to citrulline in a calcium dependent process (Vossenaar *et al*., 2003; Bhattacharya *et al*., 2006). Studies have demonstrated that PADs were involved in demyelinating diseases whereas citrullinationwas involved in other degenerative diseases (Chou *et al*., 1996; Moscarello *et al*., 2002; Scofield, 2004). Studies that have used protein separation revealed the detection of >250 proteins among which were 68 proteins specific to the glaucomatous tissue in glaucomatous optic nerve heads.

Cho *et al*. (2011) conducted a study in the light of the fact that acute increased Intraocular Pressure (IOP) cycle of ischemia-reperfusion causes decreased retinal ganglion cells which agrees with the hypothesis that ischemia-reperfusion participates in the progression of glaucoma. The researchers explored the following parameters: morphological changes, glial cellresponse and expression of inducible Nitric Oxide Synthase (iNOS) in the optic nerve headand retina of the rat following acute high IOP ischemia-reperfusion. Study findings showed that acute high IOP ischemia reperfusion injury induced optic nerve head and retina damage. The results also revealed the over expression of iNOS mostly at theganglion cell layer and inner nuclear layerof the retina and at the optic nerve head. As a conclusion, it has been indicated that the activation of glial cells and over expression of iNOS are thought to play a role in inducing damage to both retina and optic nerve head of the rat after acute high IOP ischemia-reperfusion

According to the study of Sun *et al*. (2010), scientists have developed a model called "retinal ischemia-reperfusion injury model" to approximate clinical conditions including retinal vascular occlusiondisease and acute glaucoma. This model is an animal model which gives results close to human.

Previous studies have shown that the reperfusion is associated with harmful impacts on injured cells through the development of free radicals and inflammatory cytokines (Forman *et al*., 1989; Szabo *et al*., 1991; Hangai *et al*., 1995). Other studies indicated to the damaging role of apoptosis and necrosis on retinal neuronal cells following retinal ischemia-reperfusion injury (Buchi, 1992; Katai and Yoshimura, 1999; Lam *et al*., 1999).

Miki *et al*. (2014) conducted a study to explore the expression of syntaphilinin the rat retina, optic nerve and brain. The results showed the expression of syntaphilin in retinal ganglion cells, in the cell bodies of neurons in the superior colliculus and in the astrocytes of rat optic nerves. Furthermore, the results showed that following optic nerve transection, there was down regulation of syntaphilin gene and protein expression in the optic nerve. Taken together, it was suggested that the expression of syntaphilin in astrocytes at the optic nerve could have a role in axonal injury.

RESULTS AND DISCUSSION

Molecular impacts of diabetes on optic nerve: Diabetic retinopathy is considered the main reason for lowering visual loss and acquired blindness. In diabetic experimental models, axoglial defects in ON may be the first changes from a structural point of view to be observed in ON. In an experimental model, diabetes was induced to investigate the impacts of environmental enrichment on axoglial alterations of the ON. Diabetic animals were housed in either Enriched Environment (EE) or a Standard Environment (SE) for 6 week. The researchers examined several parameters including phosphorylated neurofilament heavy immunoreactivity, microglia/ macrophages (ionized calcium binding adaptor molecule 1 (Iba-1) immunoreactivity, astrocyte reactivity (Glial Fibrillary Acid Protein-Immunostaining (GFAP), myelin (myelin basic protein immunoreactivity) and Brain Derived Neurotrophic Factor (BDNF)) levels. Study findings showed that EE housing was able to inhibit phosphorylated neurofilament heavy immunoreactivity. Furthermore, EE housing prevented the levels of BDNF to be lowered as a consequence of induced diabetes. Taken together, it can be extracted that EE offered neuroprotection in the diabetic visual pathway.

In another study conducted by Ha *et al.* (2012), the role sigma Receptor 1 (σR1) in vision was investigated. σR1 can be considered as a molecular chaperone that provides retinal neuroprotection *in vivo* and *in vitro*. The experiments showed that retinal phenotype of mice lacking σR1 had normal retinal morphology and function in young mice (5-30 week) but there was a loss of RGC as well as disturbance of ON axons consistent with inner retinal dysfunction. Diabetic model was induced to investigate the influences of stress on σR1. Results showed that there were increased alterations in retinal functional in σR1, KO mice including ganglion cell dysfunction. Taken together, it was suggested that σR1 has a crucial role in modulating retinal stress and it may have the potential to be targeted for retinal disease.

It has been suggested that σR1 may act as a unique pharmacological receptor (Jiang *et al.*, 2006). Various studies have emphasized that σR1 has significant roles in chaperone modulating ER stress (Hayashi and Su, 2007; Su *et al.*, 2010). However, several significant influences associated with σR1 ligands have been reported to include pain lowering effect, improved memory and offering neuroprotection which point to the possibility that σR1 can be considered asa significant therapeutic target in various diseases such as ocular and retinal diseases.

The expression of σR1 has been reported in various ocular tissues including lacrimal gland, cornea, iris-ciliary body, lens and retina (Ola *et al.*, 2001; Ha *et al.*, 2012). It has also been reported that σR1 is expressed in ON (Ola *et al.*, 2001; Mavlyutov *et al.*, 2011).

Other studies have reported that Heat shock proteins (Hsps) and crystallinshave important in the pathophysiological process of retinopathy (Heise and Fort, 2011). The increased expression of retinal crystallin has been described as the main characteristic feature of diabetic retinopathy (Kim *et al.*, 2007; Wang *et al.*, 2007; Fort *et al.*, 2009). It has been reported by other studies that various members of Hsps are also overexpressed in the retina because of diabetes. The study of Quin *et al.* (2007) showed that in induced diabetic model, there was overexpression of Hsp70.1A and 70.8 in retina. It has been interestingly found that the levels of Hsp90 was not influenced whereas the levels of Hsp25 were reduced in diabetic models (Losiewicz and Fort, 2011). In another study, Kim *et al.* (2007) studied the expression of Hsp90 in the retina of diabetic rats and the results showed that the levels Hsp90 were overexpressed at 24 week of age.

Several studies across the literature have pointed to the therapeutic option at molecular level. In some studies, alpha B-crystallin was systemically introduced into models of stroke and retinal ischemia with promising results to protect cells (Arac *et al.*, 2011; Fuehrer *et al.*, 2011). Furthermore, studies showed that the introduction of alphaB-crystallin12 h following stroke led to reduced stroke volume and inflammatory cytokines (Arac *et al.*, 2011; Kim *et al.*, 2011).

Kim *et al.* (2008) conducted a study to examine the role of PKC in neuronal apoptosis through Akt in the retinas of diabetic rats. Study findings showed that there was increased activity, in rat diabetic model, in ganglion cell death, PKC activity. Furthermore, the results showed decreased binding ability of Akt-HSP90. As a conclusion, PKC activation participates in neuro-retinal apoptosis in diabetic rats through inhibiting Akt-mediated signaling pathways.

CONCLUSION

The present study reviewed the literature about the molecular aspects of vision impairment resulting either from injury to retina and ON or from stress including diabetes. Animal models are mainly used to induce injury or diabetes. Various animal models showed that molecular mechanisms improve our understanding of various pathogenesis as well as the possibility of using molecular mechanisms in therapeutic options.

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