GLOBAL JOURNAL OF BIO-SCIENCE & BIOTECHNOLOGY

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FIGHTING THE BLINDNESS: WHAT ELSE WE CAN DO?

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ABSTRACT
285 million people are visually impaired worldwide: 39 million are blind and 246 have low vision. About 90% of the worlds visually impaired live in developing countries. 80% of all visual impairment can be avoided or cured. Glaucoma is a major cause of worldwide irreversible blindness. Bilateral blindness will be present in 5.9 million people with open-angle glaucoma and 5.3 million people with angle-closure glaucoma in 2020. Currently, glaucoma is recognized as an optic neuropathy and the loss of vision in this eye disease is attributed to degeneration of the axons of the retinal ganglion cells. Retinitis pigmentosa (RP) represents a group of progressive hereditary diseases of the retina that lead to incurable blindness and affect two million people worldwide; RP has been known to be initiated by photoreceptor apoptosis as a final common pathway at the cellular level, irrespective of gene mutations. This review discusses pharmacological agents believed to be useful in the prevention and the treatment of different blinding eye diseases. New intervention as pharmacological neuroprotection by calcium channel blockers remains an important strategy to limit the morbidity of these eye diseases representing significant health problem.

KEYWORDS: glaucoma, retinal degeneration, ocular inflammation, cataract, pharmacotherapy.

INTRODUCTION

285 million people are visually impaired worldwide: 39 million are blind and 246 have low vision. About 90% of the world's visually impaired live in developing countries. 80% of all visual impairment can be avoided or cured (WHO, Oct. 2011). Glaucoma is a major cause of worldwide irreversible blindness. Bilateral blindness will be present in 5.9 million people with open-angle glaucoma and 5.3 million people with angle-closure glaucoma in 2020 (Quigley and Broman, 2006).. Currently, glaucoma is recognised as an optic neuropathy and the loss of vision in this eye disease is attributed to degeneration of the axons of the retinal ganglion cells.Retinitis pigmentosa represents a group of progressive hereditary diseases of the retina that lead to incurable blindness and affect two million people worldwide (Busskamp *et al* .,2012) and principally characterized by progressive rod-dominant photoreceptor degeneration in the initial stage and eventual cone photoreceptor degeneration in later stages. Patients with retinitis pigmentosa (RP) mainly complain of night blindness and photophobia in the early stage, followed by gradual constriction of the visual field, decreased visual acuity, and color blindness in later stages. The prevalence of RP is roughly 1 in 4,000-5,000 people, and the condition is common in both Asian and Western countries (Liesegang *et al* .,2002). Significant features of RP include heterogeneity in both clinical and genetic characteristics. The severity and progression of RP vary from patient to patient even in the same family, despite affected members presumably sharing the same causative gene mutation. Molecular genetic studies have also demonstrated that a primary lesion in RP involves photoreceptor and/or retinal pigment epithelial cells in which many causative genes are specifically expressed under physiological conditions. Photoreceptor or retinal pigment epithelial cells are known to degenerate mostly through apoptosis (Chang *et al* .,1993), which is now understood as a final common pathway for RP at the cellular level. The general consensus is that intracellular concentrations of calcium ion are increased in apoptosis (Nicotera and Orrenius, 1998; Fox *et al*., 1999; Delyfer *et al* ., 2004; Sanges *et al*., 2006; Paquet-Durand *et al*., 2007 Sasati and Kaneko, 2007).

Understanding of the role of extracellular calcium transport across cell membranes in modulating various intracellular signaling processes, including the initiation of the apoptotic cascade, represents part of the rationale for interest in investigating calcium-channel blockers for neuroprotection in such blinding eye diseases as glaucoma and retinitis pigmentosa. The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that calcium channel blockers may be useful in the prevention and the treatment of different eye diseases. Calcium channel blockers, which alter the intracellular calcium concentration by modifying calcium flux across cell membranes and affect various intracellular signaling processes, have been long and widely used to treat essential hypertension and certain types of cardiac diseases such as angina pectoris. Among five subtypes of calcium channels, only specific agents for L-type calcium channels have been used as therapeutics. Calcium antagonists induce vasodilatation at smooth muscle cells and are neuroprotective through their intracellular decrease of K^+. Calcium channel blockers generally dilate isolated ocular vessels and increase ocular blood flow in experimental animals, healthy humans, patients with open-angle glaucoma (Luksh *et al* ., 2005; Koseki *et al* ., 2008; Araie and Yamaya, 2011) and in patients who have

vascular diseases in which considerable vascular tone is present. As well, contrast sensitivity in patients with normal tension glaucoma was found ameliorated by calcium channel inhibition (Yu *et al* ., 1999; Boehm *et al* ., 2003). Neuroprotective effect of calcium channel blockers against retinal ganglion cell damage under hypoxia was shown by Yamada *et al* . (2006), and also by Garcia-Campos *et al*.(2007). Apoptosis, genetically programmed mechanism of cell death in which the cell activates a specific set of instructions that lead to the deconstruction of the cell from within, is now understood as a final common pathway for retinitis pigmentosa. Apoptosis can thus be considered as a therapeutic target for retinitis pigmentosa (Doonan and Gotter, (2004); Cottet and Schorderet, (2009)). These findings suggest that calcium channel blockers may potentially inhibit ganglion cells and photoreceptor apoptosis in glaucoma and retinitis pigmentosa respectively (Araiet and Yamaya, 2011; Nakazawa, 2011).There are potentially multiple biological bases for the protective effect of calcium channel blockers on eye structures, as was shown above.

NIFEDIPINE

Yamazaki *et al* . (2002) evaluated the pharmacologic effects of several Calcium channel blockers, including nifedipine on the retinal degeneration of Royal College of Surgeons (RCS) rat, which is the most extensively studied animal model for understanding the molecular pathology in inherited retinal degeneration, such as retinitis pigmentosa. The authors concluded that nifedipine is not beneficial for the preservation of photoreceptor cells in RCS rats. Takano *et al*., (2004) also recognized that nifedipine is not able to preserve photoreceptor cells in rd mouse and cannot be used to treat patients with retinitis pigmetnosa. Otori *et al*. (2003) in the experimental study of calcium channel blockers protective effect against glutamate neurotoxicity in purified retinal ganglion cells has found that nifedipine does not inhibit glutamate-induced apoptotic cell death. Harris *et al*., (1997) investigated in observational study ocular hemodynamic and visual function changes in patients with normal-tension glaucoma after treatment with nifedipine during 6 months (30mg per day). Mean intraocular pressure, retrobulbar hemodynamics, visual field mean sensitivity were unchanged after treatment, however contrast sensitivity was improved. The authors concluded that nifedipine fails to provide uniform visual function or retrobulbar hemodynamics responses in patients with normal –tension glaucoma, but those patients who do show improved visual function also show improved indices of retrobulbar perfusion. The limitation of this study include small sample size without control group.

VERAPAMIL

Ettl, *et al*. (2004) investigated the efficacy of verapamil eye drops for inhibition of diabetic cataract in rats. The authors stated that Verapamil eye drops 0.2% administered three times daily are effective in inhibiting the progression of lens opacities in streptozotocin diabetic rats. These encouraging findings need to be confirmed by further studies. Siegner *et al*., (2000) have evaluated the impact of calcium channel blockers on intraocular pressure in the primate eye and found that topical application of all classes of calcium channel blockers, especially verapamil, caused significant intraocular pressure reductions, while ocular hypotensive effects in humans were not substantial (Araie and Mayama, 2011). Combination of verapamil with antiglaucoma medications may provide a useful alternative for reducing intraocular pressure in patients with primary open-angle glaucoma.

DILTIAZEM

Frasson *et al* ., (1999) first reported the effects of D-cis-diltiazem, a benzothiazepin calcium channel antagonist which blocks both cyclic-nucleotid-gated cation channels (CNGC) and voltage-gated calcium channels (VGCC) on photoreceptor protection in rd1 mice, several investigators have reported positive and negative effects of calcium channel blockers on animal models of retinitis pigmentosa (Bush *et al* ., 2000; Pearce-Kelling *et al* ., 2001; Yamazaki *et al* ., 2002; Hart *et al* ., 2003; Sato *et al* ., 2003; Takano *et al* ., 2004; Vallazza-Deschamps *et al* ., 2005; Sanges *et al* ., 2006; Takeuchi *et al* ., 2008). The intracellular concentration of calcium ions is subsequently elevated, leading to photoreceptor apoptosis (Frasson *et al*., 1999). Sanges *et al*. (2006) demonstrated that systemic administration of D-cis-diltiazem reduced intracellular concentrations of calcium, downregulating calpains and photoreceptor apoptosis in rd1 mice. Direct inhibitory effects of D-cis-diltiazem on L-type VGCC have been reported by Hart *et al.* (2003), and D-cis-diltiazem effectively blocks photoreceptor light damage in mouse models by inhibiting photoreceptor apoptosis (Valazza-Deschamps *et al* ., 2005). In contrast, L-cis isomer inhibits L-type VGCC similarly to D-cis isomer (Cia *et al*., 2005).

The difference in action between D-cis and L-cis-diltiazem on photoreceptor apoptosis suggests that CNGC might also be important for photoreceptor neuroprotection (Frasson *et al*., 1999). Despite these studies, however, Pawlyk *et al*.(2002) and Takano *et al*. (2004) found no rescue effects of D-cis-diltiazem on retinal degeneration in rd1 mice, and Bush *et al*. (2000) also reported that D-cis-diltiazem was ineffective for photoreceptor rescue in rhodopsim P23H transgenic rats. The effects of diltiazem on animal models of retinal degeneration remain controversial.

Pasantes-Morales *et al* . (2002) in human study reported that a combination of D-cis-diltiazem, taurin, and vitamin E has beneficial effects on the visual field progression, although the study did not clarify whether diltiazem alone demonstrated beneficial effects. Otori *et al*. (2003) evaluated the effect of diltiazem on inhibition of glutamate-induced apoptotic retinal ganglion cells death and concluded that application of diltiazem do not appear to reduce apoptosis. Investigating the pharmacokinetics of diltiazem after subconjunctival and topical administration in rabbits and effect on wound healing after the creation of conjunctival flaps, Oruc *et al.* (2000) have found that topical and subconjunctival diltiazem successfully penetrated the aqueous humor, but did not appear to affect wound healing.

Based on antioxidative action of calcium channel blockers, which have recently been shown, another therapeutic target is ocular inflammation. Animal study of intraperitoneal injections of either nilvadipine, diltiazem, or vehicle have not found a beneficial inhibitory effect of diltiazem on the pathogenesis of ocular inflammation

through the suppression of inflammation-related molecules (Ishida *et al*., 2010).

NIMODIPINE

Nimodipine is an isopropyl calcium channel blocker which readily crosses the blood-brain barrier due to its high lipid solubility. Its primary action is to reduce the number of open calcium channels in cell membranes, thus restricting influx of calcium ions into cells.

Several clinical trials have unequivocally shown that nimodipine is capable of preventing neurological deficits secondary to aneurysmal subarachnoid haemorrhage. The results of the VENUS (Very Early Nimodipine Use in Stroke) study do not support the concept that early nimodipine exerts a beneficial effect in stroke patients (Horn *et al* ., 2001). On the other hand oral nimodipine showed an enhanced acute reperfusion if applied within 12 hours of onset of acute stroke (Infeld *et al* ., 1999). Yamada *et al*., (2006) in experimental in vitro model revealed that nimodipine have a direct neuroprotective effect against retinal ganglion cells damage related to hypoxia.

Michelson *et al* ., (2006) have evaluated the impact of nimodipine on retinal blood flow in double-blind, two-way, crossover study of healthy subjects and found that orally administered at a dosage of 30 mg three times a day nimodipine significantly increases retinal perfusion in healthy subjects. Based on experimental findings Shahsuvaryan (2008) investigated the efficacy of nimodipine in the prospective comparative clinical interventional study of patients with nonarteritic anterior and posterior optic neuropathy. The author stated that increase in visual acuity was higher in the posterior ischemic neuropathy subgroup than in the anterior ischemic subgroup. Visual field testing during the follow-up also revealed positive transformation of visual field defects size and location, which correlated to visual acuity changes. These encouraging findings need to be confirmed by double-blind study.

Nimodipine has also been shown to significantly inhibit the growth of new vessels in experimental rat model of retinopathy of prematurity (Juarez *et al* ., 2000). Vascular endothelial growth factor (VEGF) can induce cell proliferation by activating the calcium channel in cell membrane through the influx of calcium increased.

Another animal study (Kong *et al* ., 2004) also have found a beneficial inhibitory effect of nimodipine on proliferative retinopathy by blocking the influx of calcium and expression of VEGF.

The impact of nimodipine on ocular circulation in normal tension glaucoma have been evaluated in many clinical studies.

Piltz *et al* ., (1998) have described a performance-corrected improvement in visual field deviation and contrast sensitivity in patients with normal tension glaucoma (NTG) and in control subjects in a prospective, placebo-controlled double-masked study after oral administration of nimodipine (30 mg twice a day). Other authors (Michalk *et al*., 2004) also stated that a single dose of 30mg nimodipine normalizes the significantly reduced retinal blood flow in NTG patients with clinical signs of vasospasmic hyperactivity. Luksch *et al*., (2005) have examined the impact of 60 mg nimodipine in NTG patients 2 hours after oral administration. Results disclosed that nimodipine increased the blood flow of the optic nerve head by 18% and improved color-contrast sensitivity.

Thus, nimodipine is potentially useful calcium channel blocker for eye disorders treatment due to its high lipid solubility and ability to cross the blood-brain barrier.

NILVADIPINE

Recent experimental evidences suggest that Nilvadipine appear to have beneficial effects on different ocular structures. Ogata *et al* ., (2000) have evaluated the effects of nilvadipine on retinal blood flow and concluded that this agent may directly and selectively increase retinal tissue blood flow, while having only minimal effect on systemic circulation including arterial blood pressure. Another experimental study conducted by Uemura and Mizota (2008) have also advocated the use of nilvadipine for the treatment of glaucoma or other retinal diseases that have some relation to apoptosis, based on claims that nilvadipine has high permeability to retina and neuroprotective effect to retinal cells. Otori *et al* ., (2003) in the experimental study of different calcium channel blockers protective effect against glutamate neurotoxicity in purified retinal ganglion cells has found that nilvadipine significantly reduce glutamate-induced apoptosis.

Systemic administration of nilvadipine has been shown to be effective for protecting photoreceptors in royal college surgeons rats (Yamazaki *et al*., 2002), rd1 mice (Takano *et al* ., 2004), and heterozygous rd2 (rds) mice (Takeuchi *et al* ., 2008). In addition to direct effects of calcium channel blockers on intracellular concentrations of calcium ion in photoreceptor cells, other indirect effects are expected such as increased expression of fibroblast growth factor (FGF) 2 (Takano *et al* ., 2004) and ciliary neurotrophic factor (CNTF) in the retina (Takeuchi *et al* ., 2008), and increased choroidal blood flow (Koseki *et al* ., 2008). In the latest animal study of intraperitoneal injections of nilvadipine Ishida *et al* ., (2010) have found a beneficial inhibitory effect of this drug on the pathogenesis of ocular inflammation through the suppression of inflammation-related molecules. Several clinical trials have shown the effectiveness of nilvadipine in retinitis pigmentosa and glaucoma.

Ohguro (2008) reported the photoreceptor rescue effects of nilvadipine in a small patient group. Nakazawa *et al* ., (2011) expanded his nilvadipine study for RP patients to confirm the results. Although both treated and control groups are still small, authors results have shown significant retardation of the mean deviation (MD) slope as calculated by the central visual field (Humphry Visual Field Analyzer, 10-2 Program) after a mean of 48 months of observation. As these pilot studies are small-sized and cannot completely exclude possible biases, a large-scale, randomized, multicenter human trial of calcium channel blockers is required in order to evaluate their efficacy as therapeutic agents for retinitis pigmentosa. The potential beneficial impact of nilvadipine on ocular circulation in normal tension glaucoma has been evaluated in different clinical studies.

Yamamoto *et al*., (1998), Tomita *et al* ., (1999), Niwa *et al* ., (2000) have found that nilvadipine reduces vascular resistance in distal retrobulbar arteries and significantly

increases velocity in the central retinal artery in patients with normal tension glaucoma. Tomita *et al* ., (1999) also stated that reduced orbital vascular resistance after a 4-week treatment with 2 mg oral nilvadipine consequently increases the optic disc blood flow. Koseki *et al* ., (2008) conducted a randomized, placebo-controlled, double-masked, single-center 3-year study of nilvadipine on visual field and ocular circulation in glaucoma with low-normal pressure. No topical ocular hypotensive drugs were prescribed. The authors concluded that nilvadipine (2 mg twice daily) slightly slowed the visual field progression and maintained the optic disc rim, and the posterior choroidal circulation increased over 3 years in patients with open-angle glaucoma with low –normal intraocular pressure. The results of this study add to the growing body of evidence that nilvadipine may be useful for neuroprotection in glaucoma. Thus, nilvadipine is potentially useful calcium channel blocker for eye disorders treatment due to its hydrophobic nature with high permeability to the central nervous system, including the retina and the highest antioxidant potency among calcium channel blockers.

Other calcium channel blockers

The experimental study conducted by Oku *et al*., (2000), evaluated the effect of topical iganidipine, a new dihydropyridine derivative calcium channel blocker on the impaired visual evoked potential after endothelin-1 injection into the vitreous body of rabbits and have advocated iganidipine eyedrops for the treatment of ischemic retinal and optic nerve disorders for the maintenance of visual function. The latest experimental study (Karim *et al* ., 2006) evaluated a neuroprotective effect of another new calcium channel blocker – lomerizine. The authors stated that lomerizine alleviates secondary degeneration of retinal ganglion cells induced by an optic nerve crush injury in the rat, presumably by improving the impaired axoplasmic flow. Tamaki *et al* ., (2003) also investigated the effects of lomerizine on the ocular tissue circulation in rabbits and on the circulation in the optic nerve head and choroid in healthy volunteers and have found that lomerizine increases blood velocity, and probably blood flow, in the optic nerve head and retina in rabbits, and it also increases blood velocity in the optic nerve head in healthy humans, without significantly altering blood pressure or heart rate.

CONCLUSION

In conclusion, there are potentially multiple biological bases for the therapeutic effect of calcium channel blockers in eye diseases. Taken into account that not all calcium channel blockers are equally effective, the challenge for future laboratory research will be to determine the best type and dosage of calcium channel blockers and also to determine which processes are modulated by these drugs in vivo and therefore are primarily responsible for the apparent beneficial effects observed in the previous studies.

Clearly, further observational studies cannot adequately address many unanswered questions. It is time to conduct a randomized controlled trial to provide direct evidence of the effectiveness of specific type calcium channel blocker in eye diseases. New intervention as pharmacological neuroprotection by calcium channel blockers remains an important strategy to limit the morbidity of these eye diseases representing significant health problem.

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