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Review Article

ROLE OF CALCIUM IONS IN AQUEOUS HUMOUR DYNAMICS AND POTENTIAL OF CALCIUM CHANNEL BLOCKERS AS OCULAR DRUG DELIVERY AGENTS IN THE MANAGEMENT OF GLAUCOMA

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ABSTRACT

Objective: Glaucoma, a progressive optic neuropathy, is the leading cause of irreversible blindness worldwide. Pharmacologic treatment for glaucoma is directed towards lowering intraocular pressure (IOP) to slow disease progression and delay visual field loss. The effect of calcium channel blockers on intraocular pressure and aqueous humor dynamics remains still controversial, although preliminary evidence suggests that these drugs may be beneficial in the management of ocular hypertension and low-tension glaucoma. There is evidence of the role of calcium ions in the physiology of aqueous humor. This study aims to systematically review and summarize the role of calcium ions in the secretion and dynamics of aqueous humor and the potential use of CCB's as new pharmacologic options for the treatment of glaucoma. **Conclusion:** After a complete review of the action of calcium channel blockers on the physiology of aqueous humor dynamics we have found out the potential effect of these agents in Glaucoma and how calcium channel blockers can be utilized in the ocular therapy of Glaucoma.

Keywords: Glaucoma, Aqueous humor dynamics, IOP, Calcium Channel Blockers.

INTRODUCTION

Glaucoma is an optic neuropathy that is described by the advanced degeneration and functional deterioration of the optic nerve, including the optic nerve head (ONH) and the retinal nerve fiber layer (RNFL), resulting in a progressive reduction in visual sensitivity and, in some patients, blindness [1]. It has been projected that 60.5 million people were affected by primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) globally in 2010 [2-3]. In 2013, the number of people (aged 40 - 80 years) with glaucoma worldwide was estimated to be 64.3 million, which is predicted to increase to 76.0 million in 2020 and 111.8 million in 2040 [4].

There are different types of glaucoma. The significant feature of this group of conditions is optic disc excavation (also known as cupping), a distinctive deformation and remodeling of the ONH in response to intraocular pressure (IOP)-related biomechanical stress and strain that can occur at any level of IOP. The two key types are open-angle glaucoma and angle-closure glaucoma, which are largely distinguished according to the anatomic configuration of the aqueous humor (that is, natural, clear fluid in the anterior chamber in front of the lens) outflow pathway [5]. In open-angle glaucoma, the trabecular meshwork outflow pathway is reachable to the aqueous humor and is often blocked internally, whereas it is blocked by the iris in angle-closure glaucoma. If the trabecular meshwork outflow pathway is blocked internally or by the iris, the IOP is increased and this might lead to ONH damage.

Management of glaucoma stresses on lowering the intraocular pressure (IOP), which remains the chief tried technique of treatment. It is recommended by the American Academy of Ophthalmology that initial treatments aim to reduce IOP in primary open-angle glaucoma (OAG) by 25% from baseline [8].

Role of IOP: IOP is determined by the balance between aqueous humor production by the ciliary body and aqueous humor outflow. Aqueous humor exits the eye through two drainage routes, the trabecular meshwork, and the uveo - scleral outflow pathway. IOP rises when aqueous humor outflow is obstructed [6]. Elevated intraocular pressure (IOP) previously was considered the cause of POAG and was part of the definition of POAG but now is recognized as a major risk factor for disease incidence and/or progression. The association between elevated IOP and vision loss is not straightforward as normal pressure glaucoma, or glaucomatous pathology without elevated IOP represents about 50% of glaucoma diagnoses.

Lowering IOP is the most common treatment by far, generally through topical application of pharmaceuticals and/or surgery [7].

ROLE OF CALCIUM IN AQUEOUS HUMOUR DYNAMICS

The divalent cation Ca^{2+} works as a secondary messenger in many signaling pathways, such as membrane excitability and synaptic transmission, in the central nervous system including the retina [17]. In healthy neurons, Ca^{2+} dependent cascades influence a variety of cellular functions including exocytosis, gene transcription, and membrane trafficking and intracellular respiration [9]. Axonal degeneration in glaucoma bears several striking similarities to that in other neurological diseases.

These include:

(1) Abnormal processing of the amyloid precursor protein

(2) Dependence on target-derived trophic support

(3) Involvement of different Ca^{2+} mediated cascades [10-12].

The pathways of aqueous humor inflow and outflow have potentially calcium-dependent components. With regard to aqueous humor formation, the hydrostatic component from arterial blood pressure and pressure in the vessels serving the ciliary body is clearly calcium-dependent, taking into account the well-established systemic vascular actions of the calcium channel blockers [13]. Also, the osmotic pressure component induced by the active secretion of ions by the inner, non-pigmented ciliary epithelium could be modulated by calcium [14]. With regard to aqueous humor outflow, calcium ions may have a direct role by modulating the episcleral venous pressure, and some experimental data suggest that calcium influences the outflow facility by maintaining the structural integrity of both the trabecular meshwork and the inner wall of Schlemm's canal [15]. Blockade of calcium channels could have several effects on aqueous flow dynamics:

(1) A reduction in the production rates either by a reduction in systematic arterial pressure (and thus ciliary body perfusion)

and/or by an osmotic effect through the modification of calcium and other ion flux in the ciliary epithelium.

(2) An increase in outflow by a reduction in episcleral venous pressure [16].

POTENTIAL OF CCB's IN GLAUCOMA

It is generally accepted that ganglion cells in glaucomatous eyes are initially injured at the level of the optic nerve head, but it remains uncertain whether the insult is primarily mechanical, ischemic-like in nature or due to the release of toxins from surrounding astrocytes and/or microglial cells [18-21]. The evidence for ischemia being involved has strengthened remarkably over the past decade with many studies pointing to vascular insufficiency at the optic nerve head as a component in the pathogenesis of glaucomatous optic neuropathy [22-24]. The hypothesis is, therefore, that ganglion cell death in glaucoma is due to an initial ischemic-like insult to the cell axon and a later insult to the ganglion cell body caused by the elevated extracellular glutamate. Should this idea be correct, then it might be concluded that to attenuate ganglion cell death in glaucoma pharmacologically, it is necessary to counteract the ischemic-like insult to the axon as well as the toxic effect of excessive glutamate [25].

Calcium channel blockers (CCBs) have been an anticipated option for the treatment of glaucoma from this viewpoint. CCBs which alter calcium influx across cell membranes and intracellular Ca^{2+} levels are widely used to treat angina pectoris; essential hypertension and certain arrhythmias [26]. CCBs have the potential for preventing the onset or progression of glaucomatous optic neuropathy by improving ocular perfusion and/or exerting neuroprotective effects.

Thus, it is reasonable that inhibiting primary calcium influx with CCBs should have neuroprotective effects on neurons undergoing apoptotic and necrotic processes. CCBs potentially rescue ischemic RGCs by restoring impaired blood flow in the local ischemic tissue by vasodilation and direct inhibition of the before mentioned calcium-related cell death pathways including ischemia and excitotoxicity-induced apoptosis and necrosis [25]. It is safe to say that these CCB's should be used topically rather than orally in case of glaucoma patients as oral usage can surely cause some or other systemic adverse effects.

HISTORICAL BACKGROUND AND PREVIOUS STUDIES

Over the decades' many researchers have conducted experiments using CCB's for the treatment of glaucoma owing to the role of calcium ions on the aqueous humor dynamics. Many of these researches show a promising role of calcium channel blockers in lowering of IOP. During 1993-1997 Santafe *et al.* studied the effect of topical CCB's Diltiazem and Verapamil in rabbits [15, 28-30]. In 1983 Monica *et al.* also conducted experiments of calcium blocking agents and their effects on IOP [31]. During 1993-1995 Netland *et al.* found the effect of CCB's in open-angle glaucoma and also conducted color Doppler ultrasound analysis of ocular circulation after their topical application [32-33]. Plitz and Bose *et al.* in 1998 found out the effect of Nimodipine in glaucoma patients [34]. In 1998 Kelly *et al.* and Abelson *et al.* found out the IOP lowering effect of CCB's in normal subjects [14, 35]. There were some negative results also as studies conducted by Beatty *et al.* in 1983 showed IOP elevation after CCB's administration [36]. In 1989 Goyal *et al.* studied the hypotensive effect of Verapamil [37]. In the year 2000 Niwa *et al.* showed the Nilvadipine on ocular blood flow in NTG and Siegner *et al.* showed the effect of CCB's alone and in combination with anti-glaucoma medications [38-39]. In the year 2004 Hara *et el.* showed the clinical potential of Lomerizine on retinal neuronal damage [40]. During 2005 Luksch *et al.* and Saito *et al.* independently effect of Nimodipine and it is color contrast activity in patients and Neuroprotective effect of novel CCB on rat ganglion cells [41-42]. The most recent work on CCB's were done in 2008 individually by Koseki *et al.* Uemura *et al* and Wang *et al* by a placebo-controlled 3 year study of CCB on visual field and circulation, protective effect against retinal ischemia by Nilvadipine and effect of flunarizine, a calcium channel blocker, on intraocular pressure and aqueous humor dynamics in monkeys respectively [43-45].

DISCUSSION: Through historical background studies we have found out that initial work has been done to find out the IOP lowering effect of calcium channel blockers in the treatment of glaucoma. By studying the aqueous humor dynamics also, we have found out the potential role of calcium ions in the secretion of the same and the approaches which can be used to block the calcium ions and the beneficial effect of calcium channel blockers which can be utilized as new pharmacologic agents in glaucoma. But more preclinical and clinical data is required for the utilization of these agents in glaucoma therapy.

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