European Journal of Pharmacology 739 (2014) 96–105

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Calcium channels and their blockers in intraocular pressure and glaucoma

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ARTICLE INFO

Article history:
Accepted 17 October 2013
Available online 1 December 2013

Keywords:
Glaucoma
Intraocular pressure
Blood flow
Neuroprotection
Calcium channel blocker
Visual field

ABSTRACT

Several factors besides high intraocular pressure assumed to be associated with the development and progression of glaucoma, and calcium channel blockers (CCBs) have been an anticipated option for glaucoma treatment by improving ocular perfusion and/or exerting neuroprotective effects on retinal ganglion cells with safety established in wide and long-term usage. Decrease in IOP has been reported after topical application of CCBs, however, the effect is much smaller and almost negligible after systemic application. Various CCBs have been reported to increase posterior ocular blood flow in vivo and to exert direct neuroprotection in neurons in vitro. Distribution of the drug at a pharmacologically active concentration in the posterior ocular tissues across the blood–brain barrier or blood–retina barrier, especially in the optic nerve head and retina where the ganglion cells mainly suffer from glaucomatous damage, is essential for clinical treatment of glaucoma. Improved visual functions such as sensitivity in the visual field test have been reported after administration of CCBs, but evidences from the randomized studies have been limited and effects of CCBs on blood flow and direct neuroprotection are hardly distinguished from each other.

Contents

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http://dx.doi.org/10.1016/j.ejphar.2013.10.073

1. Introduction

Primary open-angle glaucoma (POAG) is a multifactorial optic neuropathy associated with characteristic morphologic changes at the optic nerve head (ONH), peripapillary retina and retinal nerve fiber layer, and it is associated with gradual visual field loss. The disease prevalence varies among races and ranges between 0.5% and 10% (Rudnicka et al., 2006). Population-based surveys have indicated that 80 million people worldwide are affected by glaucoma and 11.2 million are bilaterally blind. It is estimated that glaucoma will become the second most common cause of blindness in the world by 2020 (Quigley and Broman, 2006).

Elevated intraocular pressure (IOP) was previously considered the sole factor causing glaucoma. It is now, however, recognized as a major factor but only one of the risk factors related to the disease incidence and/or progression. Although reducing IOP is the evidence-based mainstream POAG treatment,(Collaborative Normal-Tension Glaucoma Study Group, 1998a,b; Heijl et al., 2002; The AGIS Investigators, 2000; Leske et al., 2007; Lichter et al., 2001; Musch et al., 2009), studies have indicated that medical or surgical IOP reduction does not always halt progression of the disease, especially in patients with normal IOP (normal tension glaucoma; NTG) (Drance et al., 2001; Collaborative Normal-Tension Glaucoma Study Group, 1998a; The AGIS Investigators, 2000; Leske et al., 2007). Visual field damage slowly but significantly progresses in some cases even after sufficiently low IOP is achieved after surgical intervention (Hagiwara et al., 2000; Shigeeda et al., 2002), suggesting the presence of important factors besides high IOP in glaucoma pathogenesis.

Among various IOP-independent factors assumed to be associated with glaucoma, impaired ocular perfusion is probably the only factor for which the contribution to POAG incidence and/or progression was confirmed by population-based or prospective cohort studies (Bonomi et al., 2000; Leske et al., 1995; Leske et al., 2007, 2008, 2001; Tielsch et al., 1995). Ocular circulation is impaired in glaucoma and ocular hypertension patients (Ciancaglini et al., 2001; Evans et al., 1999; Galassi et al., 2003; Gherghel et al., 2001; Liu et al., 1999; Yaoeda et al., 2003) and compromised local circulation is probably correlated with visual field deterioration (Satilmis et al., 2003; Schumann et al., 2000; Yamazaki and Drance, 1997). Thus, improvement of local ocular circulation may be beneficial in the treatment of glaucomatous optic neuropathy.

Another possibility in the treatment of glaucoma is neuroprotection, which is a promising treatment strategy for many central nervous system (CNS) disorders, including stroke or traumatic brain injury. Glaucoma is currently recognized as one of the multifactorial neurodegenerative disorders of neurons and neuroprotection can be a potent IOP-independent option in the treatment of glaucomatous optic neuropathy.

Calcium channel blockers (CCBs) have been an anticipated option for the treatment of glaucoma from this viewpoint (Fig. 1). CCBs, which alter calcium influx across cell membranes and intracellular $Ca2+$ levels, are widely used to treat angina pectoris, essential hypertension and certain arrhythmias (Abernethy and Schwartz, 1999a). CCBs have potential for preventing the onset or progression of glaucomatous optic neuropathy by improving ocular perfusion and/or exerting neuroprotective effects. Data on the clinical safety of CCBs have accumulated, and indicate a substantial advantage for CCBs as an alternative treatment.

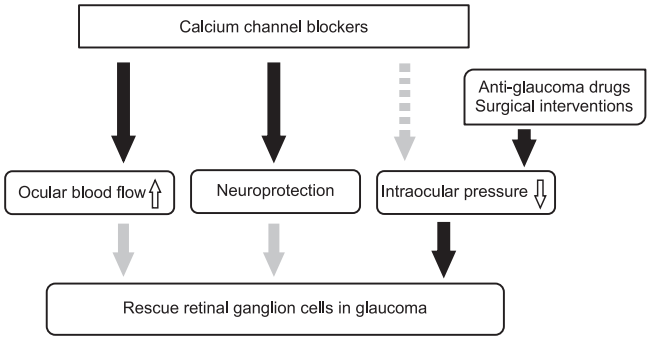

Fig. 1. Mechanisms for glaucoma treatment using calcium channel blockers.

This paper aims to provide a concise overview of the involvement of calcium in glaucoma. It reviews studies on the effects of CCBs or agents with calcium blocking activities on IOP, ocular blood flow, neuroprotection and visual function.

2. CCBs and IOP

A high IOP level is known to be a major risk factor for the development and progression of glaucoma. It has been demonstrated by a number of randomized studies that lowering IOP is the main objective of glaucoma treatment, not only in glaucomatous eyes with an IOP higher than the normal range (The AGIS Investigators, 2000), but also for those with a normal IOP (Collaborative Normal-Tension Glaucoma Study Group, 1998a,b). There have been a number of topical antiglaucoma drugs available that have been shown to have a significant effect on IOP reduction via different mechanisms. The effect of CCBs on IOP is much smaller than other treatments; however, the change in IOP should not be disregarded when considering glaucomatous optic neuropathy. In general, CCBs cause weak IOP reduction after topical administration, though they are not commonly used clinically, and their effect on IOP after systemic administration is insignificant.

The effect of CCBs on IOP has been studied in animals and humans and many studies have reported their effect after topical administration rather than systemic administration. Most studies have agreed that topical CCBs induced significant IOP reduction for several hours.

Topical diltiazem showed IOP reduction in normal rabbits (Santafe et al., 1997), steroid-induced ocular hypertensive rabbits (Melena et al., 1998), water-loading induced ocular hypertensive rabbits (Santafe et al., 1999) and normal cynomolgus monkeys (Siegner et al., 2000). Topical nifedipine induced IOP reduction in normal rabbits (Segarra et al., 1993) and normal cynomolgus monkeys (Siegner et al., 2000). Topical verapamil reduced IOP in normal rabbits (Santafe et al., 1996; Segarra et al., 1993), normal monkeys (Siegner et al., 2000) and normal humans (Abreu et al., 1998; Netland et al., 1995, 1996), as well as in humans with ocular hypertension (Abelson et al., 1988; Goyal et al., 1989). Topical flunarizine showed IOP reduction in normal rabbits (Campana et al., 2002; Maltese and Bucolo, 2003; Osborne et al., 2002), achymotrypsin-induced ocular hypertensive rabbits (Campana et al., 2002), normal cynomolgus monkeys (Siegner et al., 2000) and laser-induced ocular hypertensive cynomolgus monkeys (Wang et al., 2008).

The extent of the IOP decrease after topical CCBs seems to be small, and has been reported as an approximately 2 mmHg reduction in normal humans after topical verapamil (Abreu et al., 1998; Netland et al., 1995, 1996). In most of these studies, a cross-over ocular hypotensive effect on fellow untreated eyes has been observed. This may be attributed to the distribution of topically applied CCBs in the fellow eye through systemic circulation or a consensual reaction mediated by the CNS (Gibbens, 1988).

Systemically applied CCBs have much smaller effects on IOP. Intravenous verapamil showed IOP reduction in rabbits (Green and Kim, 1977; Payne et al., 1990) but oral verapamil showed no significant effects on the IOP in rabbits or humans (Beatty et al., 1984). Oral diltiazem had an insignificant effect on IOP in rabbits