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Pharmacology of novel intraocular pressure-lowering targets that enhance conventional outflow facility: Pitfalls, promises and what lies ahead?

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ABSTRACT

Intraocular pressure (IOP) lowering drugs that are approved for the treatment of glaucoma and ocular hypertension have limited activity on increasing aqueous humor movement through the trabecular meshwork and Schlemm's canal (TM/SC). The TM/SC complex is considered the conventional outflow pathway and is a primary site of increased resistance to aqueous humor outflow in glaucoma. Novel mechanisms that enhance conventional outflow have shown promise in IOP reduction via modulation of several pathways including Rho kinase, nitric oxide/soluble guanylate cyclase/cGMP, adenosine A_1, prostaglandin EP_4/cAMP, and potassium channels. The clinical translatability of these pharmacological modulators based on pre-clinical efficacy models is currently being explored. In addition, identification of pathways from GWAS and other studies involving transgenic rodent models with elevated/reduced IOP phenotypes have begun to yield additional insights into IOP regulation and serve as a source for the next generation of IOP lowering targets. Lastly, improvements in drug delivery technologies to enable sustained IOP reduction are also discussed.

1. Introduction

Glaucoma is an optic neuropathy in which elevated intraocular pressure (IOP) serves as a key risk factor for retinal ganglion cell death. However there are patients with high IOP that do not develop the disease and are termed ocular hypertensives and there are patients with IOP in the seemingly normal range that develop glaucomatous optic neuropathy (Weinreb et al., 2014). Nonetheless, glaucoma is expected to affect 80 million people worldwide (1–4% prevalence) by 2020 with 11 million people considered legally blind (Quigley and Broman, 2006). Decreasing IOP either by pharmacological or surgical intervention is the only proven therapy to prevent or delay the progressive loss of visual fields (VFs) in patients with ocular hypertension and glaucoma (Weinreb et al., 2014). There are currently 5 different pharmacological drug classes of IOP lowering medications (and their combinations thereof) including (1) β-adrenoceptor antagonists (Timolol, Betaxolol, etc.), (2) carbonic anhydrase inhibitors (Acetazolamide, Dorzolamide, Brinzolamide), (3) α_2-adrenoceptor agonists (Brimonidine, Apraclonidine), (4) parasympathomimetics (cholinomimetics like pilocarpine) and (5) prostaglandin analogs (Latanoprost, Travoprost, Bimatoprost, and Tafluprost). Prostaglandin analogs are considered the most efficacious at achieving a target IOP lowering of 20–50% in open angle glaucoma (OAG) patients (Weinreb et al., 2014). However, prostaglandin analogs have numerous side effects including ocular hyperemia, irritation, orbital fat atrophy, hypertrichosis, and uveitis (Alm, 2014).

Despite pharmacological and surgical intervention, up to 45% of patients who were treated to achieve a target IOP-that is 25–30% (6–8 mmHg) lower than un-medicated baseline IOP, continued to show progressive VF loss (Heijl et al., 2002). This outcome reveals three possible issues, 1. These patients would require greater IOP reduction to prevent VF loss, (2) challenges in establishing an *a priori* target IOP to prevent VF loss, or (3) existence of IOP-independent factors that cause progressive VF loss in these high-risk patients. It is also important to note that 42% of primary open angle glaucoma (POAG) patients require 2 or more medications to effectively control their IOP (Kass et al., 2010). Based on the Early Manifest Glaucoma Trial, it was determined that every 1 mm Hg higher mean IOP in the follow up period was associated with 13% higher risk of progressive VF loss for the study population (Leske et al., 2003). Some of the issues with insufficient IOP control and need for multiple IOP lowering medications include poor

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adherence to glaucoma therapy (e.g. too many doses per day, non-refilling of prescriptions, etc.), poor safety/tolerability profiles and loss of pharmacological effectiveness over time. Decreasing the patient burden from undergoing glaucoma surgeries to lower their IOP is also an important consideration due to 1–2% risk of endophthalmitis (Rai et al., 2012). Combination drug therapy within a pharmacological class is less effective compared to combinations of drugs from two different pharmacological classes of glaucoma medications. The advent of new fixed combination IOP lowering drugs for glaucoma (Brinzolamide/Brimonidine; Dorzolamide/Timolol; Timolol/Brimonidine) has offered new avenues to improve patient adherence. However, most classes provide more effective IOP lowering when used with prostaglandin analogs (Lerner and Goldberg, 2010). The identification of additional novel target mechanisms to complement the existing armamentarium of topical treatments for glaucoma is therefore necessary for improving IOP control.

While all above drug classes act either on the uveoscleral pathway and/or aqueous humor formation, none of these are targeting the major site of resistance to aqueous humor outflow in glaucoma, namely, trabecular meshwork/Schlemm's canal (TM/SC; termed as conventional outflow pathway) (Saccà et al., 2015). While cholinergic agonists (Pilocarpine) or adrenergic agonists (Dipivefrin, an epinephrine prodrug) can increase conventional outflow facility, there are generally unacceptable adverse/side effects related to the pharmacological action of these drugs including miosis/mydriasis, hyperemia, systemic/cardiovascular reactions, etc. Moreover, cholinergics indirectly increase outflow facility by their contractile actions on longitudinal ciliary muscle which in turn pulls on the scleral spur rather than via direct actions on the outflow pathway. Therefore, novel pharmacological targets which can affect the conventional outflow pathway are highly desirable given that this region accounts for the 70–90% of aqueous humor drainage out of the eye (Tamm, 2009).

This review article will focus mainly on novel drug targets that potentially increase conventional outflow facility. Additionally, the potential advantages, pitfalls/disadvantages and pre-clinical to clinical translatability (where applicable) will also be briefly discussed.

2. New targets of the conventional outflow pathway

2.1. Rho kinase or ROCK inhibitors

Rho kinase inhibitors have received great attention lately as promising IOP lowering drugs as they appear to target the TM/SC and cause tissue relaxation, thus increasing conventional outflow facility (Challa and Arnold, 2014). Briefly, Rho-GTP, a small G protein binds to Rho-associated coiled-coil forming protein kinase (ROCK) and causing catalytic activation. In turn, ROCK phosphorylates myosin light chain (MLC) resulting in contraction of smooth muscle or TM tissue. ROCK can also phosphorylate and inactivate myosin phosphatase (MLP), thereby prolonging the contractile state of the target tissues. Knockout of either ROCK1 or ROCK2, which exhibit 92% homology in their kinase domains, in mice lowers IOP compared to cohort controls (Liao et al., 2007; Whitlock et al., 2009).

There are several small molecule ROCK inhibitors that have been developed for clinical evaluation which target both ROCK1 and ROCK2 isoforms. ROCK inhibitors cause the relaxation of the actin-myosin complex via the dephosphorylation of MLC. As a result, both TM and SC cells have been shown to undergo changes in cell shape, reduction in stress fibers, decrease in focal adhesion and phosphotyrosine immunolabelling as well as a reduction in the expression of junctional proteins including ZO-1 and claudin-5 (Thieme et al., 2000; Rao et al., 2001; Kameda et al., 2012). Studies involving *ex-vivo* anterior chamber ocular tissue perfusion as well as *in-vivo* IOP lowering efficacy studies revealed that inhibition of Rho kinase pathway effectively increased conventional outflow facility (Honjo et al., 2001; Rao et al., 2005; Tian and Kaufman, 2005; Tokushige et al., 2007). Typically, preclinical IOP lowering was between 2 and 13 mmHg across different species (mostly, rabbits and monkeys) lasting 6–12 h post-topical ocular dosing (Challa and Arnold, 2014).

Several ROCK inhibitors such as RKI-983/SNJ-1656 (Novartis/Senju), AR-13324 (Rhopressa®; dual ROCK and norepinephrine transporter inhibitor), AR-12286 (Aerie), and AMA0076 (Amakem) have entered clinical trials (reviewed in Wang and Chang (2014)). These ROCK inhibitors were dosed either as twice-daily or once-daily drops in healthy volunteers, ocular hypertensive (OHT) and primary open angle glaucoma (POAG) patients. It appears that IOP reduction by ROCK inhibitors in preclinical models is greater than that observed in clinical studies involving volunteers or OHT/POAG patients. For example, RKI-983 (0.1%; single dose) caused an IOP reduction of 28% (10 mmHg decrease) at 3 h and 21% (8 mmHg decrease) at 6 h in an unilateral ocular hypertensive monkey model of glaucoma whereas the fellow normotensive monkey eye exhibited an IOP reduction of 20% (5 mmHg decrease) and 17% (4 mmHg decrease) at the same time points post-dose (Fig. 1) (Chen et al., 2014). In normal volunteers, RKI-983 (0.1%; b.i.d) caused 15% (2 mmHg) reduction at 2 h, 23% (3 mmHg) reduction at 4 h through 12 h, similar to the findings in normal monkey eyes (Tanihara et al., 2008). Moreover, RKI-983 (0.1%; b.i.d) was also less efficacious in patients with OHT/glaucoma wherein IOP reduction was 18–20% (4-4.5 mmHg reduction) (Inoue et al., 2015). RKI-983 exhibited a dose-dependent increase and incidence in conjunctival hyperemia (16–100% over a dose range of 0.003–0.1%) in normal human volunteers and POAG/OHT patients (Tanihara et al., 2008; Inoue et al., 2015). Aerie's AR-13324 (highest dose-0.2%) caused a

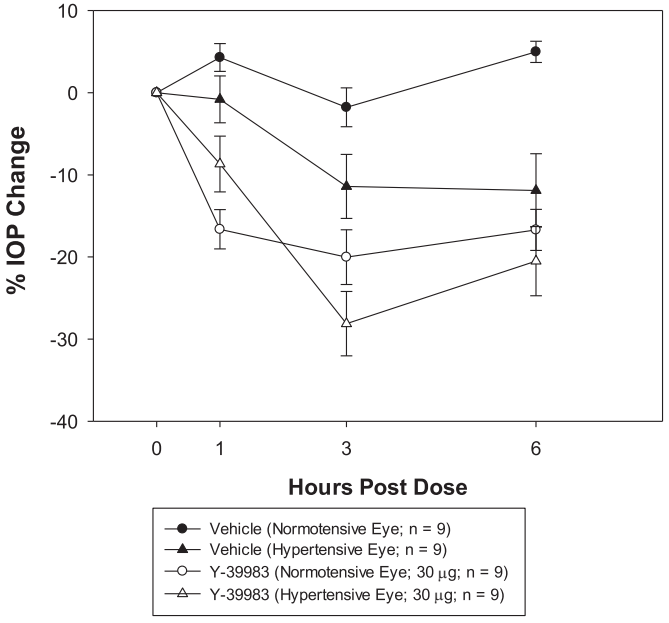

Fig. 1. Effect of a single topical ocular dose of 0.1% Y-39983 (ROCK inhibitor, RKI983) on IOP in normotensive and laser-trabeculoplasty induced hypertensive eyes of cynomolgus monkeys. A single 30 µl drop of Y-39983 or vehicle was applied bilaterally in monkey eyes and IOP was measured using an pneumatonometer in two groups of conscious monkeys at indicated time points. Percent IOP change was determined by subtracting IOP readings at indicated time points post-dose from the pre-dose baseline IOP value, which was set at 100%. Average (± S.E.M) baseline IOP of hypertensive eye was 38.1 ± 1.5 mmHg whereas it was 26.4 ± 1.1 mm Hg in normotensive eye (n=9 monkeys per group). All animals were dosed between 8:00-9:00 AM.

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