Glaucoma is known to be the second most important cause of blindness worldwide. Moreover, it is the leading cause of irreversible blindness and therefore presents even a greater public health challenge than cataracts. In 2010, glaucoma affected approximately 60.5 million people globally, and with the aging of the population this number is expected to increase to up to almost 80 million by 2020 [1]. Despite this high prevalence, relatively little progress has been made in the management of this neurodegenerative disease over the past decade. Current treatment modalities are directed towards the reduction of intraocular pressures (IOP) and thus far, this is the only therapy shown to be effective in large scale clinical trials [2]. Pharmacological treatment with eye drops is generally the first line therapy to reduce IOP in glaucoma patients. IOP is determined by the balance between aqueous humor (AH) production and outflow. As such, current medications can be divided into two categories: drugs that decrease AH production (β-blockers, carbonic anhydrase inhibitors and α-2 agonists) and those that increase AH outflow by lowering the trabecular resistance [3].

Rho kinase (ROCK) inhibitors constitute a new pharmacological class of potential drugs that decrease IOP via direct effects on the TM and as such increase conventional outflow facility [5]. Experimental data indeed indicate that ROCK inhibitors alter contractility of the TM cells, thereby lowering IOP by facilitating aqueous outflow via relaxation of cells in the TM [6–9]. However, preclinical and clinical studies [10,11] evaluating ROCK inhibitors (such as Y-39883 [Novartis], AR-12286 and AR-13324 [Aerie Pharmaceuticals], ATS907 [Altheos, Inc.], K-115 [Kowa Company, Ltd.] and HA-1077 [Santen Pharmaceutical Co., Ltd.]) have reported mild to severe conjunctival hyperemia, which is caused by mechanism-based smooth muscle relaxation of conjunctival blood vessels. Therefore, a product pipeline of soft ROCK inhibitors was developed by Amakem Therapeutics (Belgium). In general, soft ROCK inhibitors undergo rapid degradation towards a predefined, functionally inactive metabolite [12]. This soft principle might reduce side effects and consequently widen the therapeutic window of ROCK inhibitors. AMA0076 is an example of such a soft ROCK inhibitor. Preclinical and clinical studies (ARVO abstract 2014) have shown that this soft ROCK inhibitor potently reduced IOP...
without causing significant hyperemia [13]. These findings led us to expect that this compound might be a promising candidate as a novel IOP-lowering treatment for glaucoma.

When IOP is insufficiently controlled with the current pharmacological treatments, more invasive therapies, such as laser treatment and/or filtration surgery need to be considered. Glaucoma filtration surgery is indeed the most effective treatment to lower IOP. Unfortunately, excessive postoperative wound healing with subsequent scarring frequently leads to surgical failure resulting in poor postoperative control of IOP and the consequent progression of visual field loss [14]. Therefore, extensive efforts are being made to find novel effective anti-fibrotic adjunctive agents. ROCK might represent a promising target to reduce postsurgical fibrosis, since these compounds have been shown to have anti-inflammatory, anti-angiogenic and anti-fibrotic properties. Indeed, ROCK inhibitors decreased the activation of nuclear factor-κB in stimulated inflammatory cells and subsequently blocked the generation of proinflammatory cytokines [15]. Increased expression of RhoA in endothelial cells significantly promoted migration and the in vitro angiogenic capacity. Furthermore, inhibition of the Rho/ROCK pathway attenuated VEGF-mediated migration and angiogenesis in vitro [16]. Finally, and importantly, in vitro and animal studies have shown that ROCK inhibition inhibited the activation of fibroblast into myofibroblasts, and consequently had profound effects on surgical outcome in a rabbit model of glaucoma surgery. Histological examination of the filtration blebs revealed that treatment with ROCK inhibitors resulted in a significant lack of collagen deposition [17]. Although these results are promising, further preclinical research is necessary to establish the potential of ROCK inhibitors as an adjunctive to glaucoma surgery.

Elevated IOP is not the only risk factor for the development of glaucoma, since glaucoma is known to be a multifactorial disease. Reduction of IOP can slow down disease progression, but many patients continue to experience progressive visual field loss despite proper IOP control. Moreover, reduced ocular perfusion pressure has been identified as a risk factor for glaucoma progression in several large clinical trials. Therefore, novel treatment strategies besides the reduction of IOP are being explored, such as neuroprotective and ocular blood flow enhancing agents. To date, no drugs are licensed for neuroprotection in glaucoma, despite promising results of Memantine and Brimonidine in preclinical studies. Accumulating evidence suggests that ROCK inhibitors are able to directly protect retinal ganglion cells, since co-incubation with these inhibitors significantly promoted ganglion cell survival in deprived cellular conditions [18]. The neuroprotective effect of ROCK inhibitors was also confirmed in vivo; they inhibited experimentally induced apoptosis of retinal ganglion cells in several animal models for glaucoma [19]. The underlying mechanisms responsible for the neuroprotective properties of ROCK inhibitors are not yet fully understood and more profound research is necessary. Interestingly, the vasodilatory effect of ROCK inhibitors is also described at the level of the retina. Vasodilation of retinal blood vessels could subsequently lead to an improved ocular blood flow, which could potentially have a protective effect on retinal ganglion cells [20].

Taken together, ROCK inhibitors have a broad theoretical therapeutic potential in glaucoma. Besides their consistently reported IOP lowering effect, experimental data suggest additional effects that may be relevant for the management of glaucoma: neuroprotection, facilitation of ocular blood flow and prevention of filtration failure. These features make ROCK inhibitors a promising new target for the treatment of glaucoma. For several years ROCK inhibitors have been under development as a novel IOP lowering strategy. Some clinical trials have already been discontinued due to undesirable ocular complications. Indeed, hyperemia is considered as the main dose limiting side effect. The ability to dose sufficiently high without causing clinically significant hyperemia is critical for ROCK inhibitors to be accepted as a novel IOP lowering strategy. Therefore, soft ROCK inhibitors might improve the side effect profile of this class of compounds, and consequently broaden their therapeutic window for future treatment of glaucoma.

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References


What is the potential of Rho kinase inhibitors in the treatment of glaucoma?

Editorial


