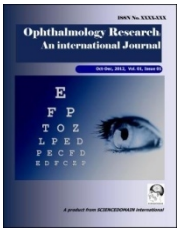

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Rock Inhibitors: Future of Anti-glaucoma Medication

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Authors' contributions

This work was carried out in collaboration between all authors. Author MG gave the concept to review this drug. Author VV studied the topic in detail and wrote the first draft of the manuscript. Author HC managed the literature searches and editing of the draft. All authors read and approved the final manuscript.

Mini-review Article

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ABSTRACT

Glaucoma constitutes the major burden of irreversible blindness worldwide as of today. All the modalities of treatment are focussed on lowering intraocular pressure (IOP), from medical to surgical. With the advent of new drugs, drug compliance has increased among the patients but still is the most worrisome problem for doctors. Current research is focussed to treat glaucoma by means other than just lowering IOP. Among the various molecules under trial, one group is Rho kinaseinhibitors (ROCK INHIBITORS). They modulate cellular motility of the trabecular meshwork, schlemm's canal, and ciliary muscle, thereby enhancing aqueous drainage. Being still under trials, hopes are on that these could revolutionise glaucoma therapy.

Keywords: Rho kinase inhibitors; ROCK inhibitors; glaucoma; trabecular meshwork remodeling.

1. INTRODUCTION

Glaucoma is a leading cause of blindness in the world, contributing significantly to disease burden [1]. Unlimited health resources are spent on glaucoma management. Therapeutic

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strategies vary widely from heavy duty drugs requiring life-long compliance to diverse surgical options with or without shunt devices/antifibrinolytic agents/laser. In the last decades, the therapy of glaucoma has largely shifted from surgery to medical treatment thanks to the introduction of strongly effective single and fixed combinations. This clinical scenario may dramatically change in the near future owing to the progresses in biochemistry, genetics and drug delivery technology. Market is huge and so is the niche for development of new agents. Newer agents are desired which can offer not only greater efficacy but also reduced intolerance, which is emerging as a leading cause of non-compliance, to topical anti glaucoma therapy [2].

2. CURRENT TRENDS

Abnormally high resistance to aqueous humor drainage through the trabecular meshwork and schlemm's canal is highly implicated as cause for development of primary open-angle glaucoma. Current anti glaucoma treatments are directed towards lowering intraocular pressure (IOP) which is the main modifiable risk factor for glaucoma. Currently, the five FDA established pharmacologic classes of IOP-lowering drugs are: α‑adrenergic agonists (e.g. brimonidine etc.), β‑adrenergic blockers (e.g. timolol etc.), carbonic anhydrase inhibitors (e.g. dorzolamide etc.), cholinergic agonists (e.g. pilocarpine etc.), and prostaglandin analogues (e.g. latanoprost etc.)[3]. Prostaglandins are currently the most prescribed IOP lowering drug worldwide. These reduce IOP by increasing aqueous outflow, and have not only good potency but also improved compliance. In recent times, focus of research has shifted beyond just lowering IOP, with an aim to protect or regenerate the optic nerve as well as novel targets to decrease inflow or increase outflow including small interfering RNA, cytoskeleton agents, cannabinoids, adenosine/serotonin/dopamine receptor ligands, nitric oxide/carbon monoxide system modulators, and hydroxysteroid dehydrogenase inhibitors [4]. The Rho kinase inhibitors (ROCK inhibitors), currently under clinical trials, are emerging as a new class of antiglaucoma drugs.

3. MECHANISM OF ACTION

Trabecular meshwork is the prime site of aqueous outflow resistance. Contractility of the actomyosin system in the trabecular cells or inner wall endothelium of Schlemm's canal is an important factor in the regulation of outflow resistance. Numerous studies indicate that dynamics of the trabecular meshwork cytoskeleton may be involved in the regulation of aqueous humor outflow. Reduction of outflow resistance induced by cytoskeletal agents acting directly on the trabecular meshwork and schlemm's canal of glaucomatous eyes may mimic the normal physiological function [5].

The Rho kinase proteins are a family of small guanosine triphosphatases (GTPases) that have a key role in these cellular processes, particularly those involving actin cytoskeleton assembly, actin-myosin mediated cell contraction and motility [6,7]. These are serine/ threonine kinases which are present in two isoforms in mammals: ROCK 1 and ROCK 2. ROCK1 and ROCK2 are expressed in the majority of tissues, including human trabecular meshwork and ciliary muscle cells [8]. On binding to Rho, the catalytic activity of ROCKs is enhanced, which inhibit myosin light chain kinase (MLCK) by phosphorylating it, resulting in increased contractility of actin fibres and by phosphorylating LIM kinases (LIMK) they reduce cell migration (Fig. 1). ROCK inhibitors may lower resistance to aqueous outflow by activities that include decreasing myosin light-chain phosphorylation, which leads to cellular relaxation in human trabecular meshwork and schlemm's canal cells. Thus, specific inhibitors of

ROCK, that modulate changes in the actin cytoskeleton and cellular motility of the trabecular meshwork, schlemm's canal, and ciliary muscle may comprise a potential new class of ocularhypotensive drugs that enhance aqueous drainage [9-11].

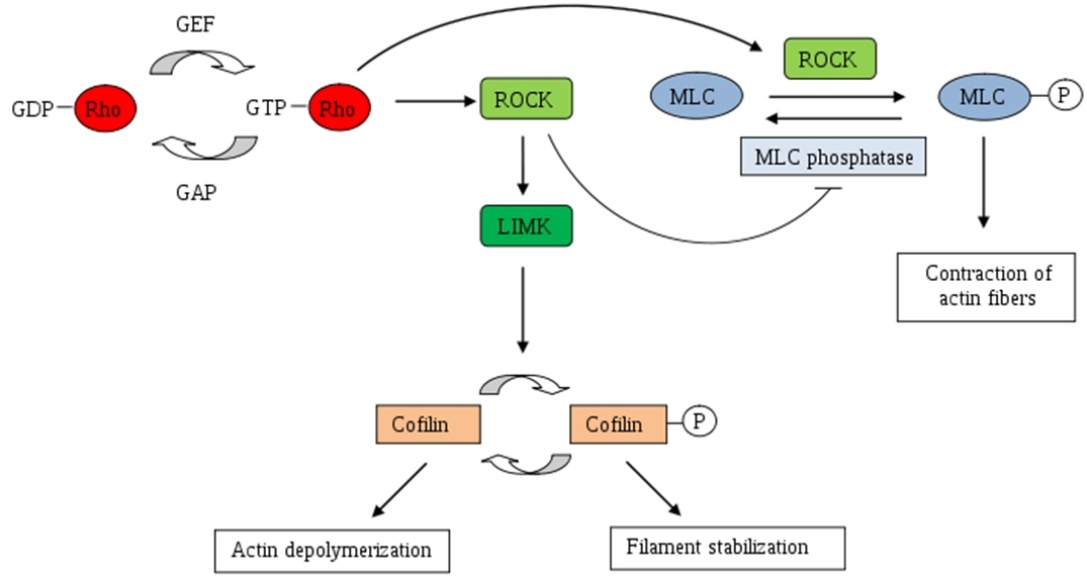

Fig. 1. ROCK protein action and regulation

Many studies state that alteration in the level of Rho-kinase plays a role in the pathophysiology of several age-related diseases, including pulmonary hypertension, diabetes and renal disorders as per many studies. Since glaucoma is also age-related, it is not surprising that clinical data supports a role for Rho-kinase in this disease. Zhang et al demonstrated that sustained activation of Rho-GTPase signalling in the aqueous humor outflow pathway increases resistance to outflow through the trabecular meshwork, by influencing the actomyosin assembly cell adhesive interaction and expression of extracellular matrix protein and cytokinase in trabecular meshwork cells [12]. In addition, levels of Rho-GTPase agonists, including endothelial 1 and TGF-β, have been reported to be elevated in the aqueous humor of glaucomatous patients [13,14].

4. ANIMAL STUDIES

To be able to explore the role of these Rho-kinase inhibitors for glaucoma treatment in humans, various trials are underway [15]. Animal model testing is showing vast potential. Five different mechanisms have been described [16-26].

Firstly, ROCK inhibitors may be able to increase aqueous outflow by relaxing trabecular meshwork tissue. Studies have demonstrated that selective ROCK inhibitors reduce IOP and increase outflow facility by altering the behaviour of trabecular meshwork cells and relaxing ciliary muscle in bovine and human tissue [16,17].

Secondly, These also work by improving blood flow to the optic nerve. Altered optic nerve perfusion, due either to vasospasm or altered hemodynamics, is believed to play a role in the pathophysiology of certain types of glaucoma, especially normal tension glaucoma, and it is believed that some of these glaucoma patients may

have altered blood perfusion in the rest of the body as well [18,19]. These agents not only improve optic nerve perfusion but also improve cerebral and coronary perfusion [20,21].

Thirdly, ROCK inhibitors may provide neuroprotection of healthy ganglion cells. Animal studies have shown the involvement of Rho-kinase in induced neurotoxicity, and that Rho-kinase inhibition in the cell body is neuroprotective and overcomes growth inhibition [22,23]. In addition, animal studies have shown an increase in retinal ganglion cell survival with Rho-kinase inhibitors [24].

Fourthly, ROCK inhibitors may aid in treating glaucoma as an antifibrotic agent in glaucoma surgery. One of the main reasons for failure of glaucoma surgery is scarring. Although the use of antimetabolites (5 flourouracil or mitomycin C) has decreased the incidence of glaucoma surgery failure, it's associated with a higher incidence of bleb-related complications. In contrast, Honjo M et al. demonstrated that topical use of Y 27632 (a ROCK inhibitor) is associated with reduced subconjunctival scarring in rabbits after filtration surgery and that it was safe and well-tolerated [25].

Fifthly, ROCK inhibitors may be a potential therapeutic treatment for certain forms of corneal endothelial cell dysfunction in humans. Y-27632 has been shown to promote wound healing in primates with partially injured corneal endothelia. Y-27632 increased corneal endothelial cell density and restored function in these animals [26].

5. ROUTES OF ADMINISTRATION

Various routes of administration have been studied in rabbits and IOP was seen to fall within 30 minutes, with the effect lasting upto 12 hours in topical, intravitreal as well as intracameral injections [16]. Safety and efficacy of topical route in humans has also been demonstrated by a Phase I clinical trial with SNJ-1656, a selective Rho-kinase inhibitor, used at different concentrations [27].

6. ONGOING CLINICAL TRIALS

ROCK inhibitors that are currently in clinical trials for glaucoma or ocular hypertension include AMA0076, AR-13324, K115, PG324, Y39983 and RKI-983 (Table 1).

Table 1. ROCK inhibitors under clinical trials

Compound	Organization	Current status
AMA0076	Amakem	Phase II
AR-13324	Aerie	Phase III
K-115	Kowa	Phase III
PG324	Aerie	Phase II
AR-12286	Aerie	Discontinued after phase II
Y-39983; RKI-983; SNJ-1656	Senju and Novartis	SNJ1656-discontinued
ATS907	Altheos	Discontinued after phase II
DE-104	Santen-Ube	Discontinued after phase II
INS-115644	Merck	Discontinued after phase I
INS-117548	Merck	Discontinued after phase I

7. POTENTIAL ADVERSE EFFECTS

ROCK inhibitors when administered topically induce conjunctivalhyperemia and subconjunctival hemorrhages as these are vasodilators. The effect of concomitantly administered topical drugs may decrease by rapidly increasing extraocular clearancedue to dilation of the conjunctival vessels [28].

8. ROLE OF ROCK INHIBITORS OUTSIDE THE EYE

Recent research has shown that ROCK signalling plays an important role in many diseases including diabetes, neurodegenerative diseases, pulmonary hypertension [29] and cancer. It has been shown to be involved in causing tissue thickening and stiffening around tumours in a mouse model of skin cancer, principally by increasing the amount of collagen in the tissue around the tumour [30]. For example, such drugs could potentially prevent cancer from spreading by blocking cell migration, stopping cancer cells from spreading into neighbouring tissue [31].

9. PIT FALLS

ROCK inhibitors seem to have a promising role in glaucoma management. The one notable problem with using ROCK inhibitors to treat glaucoma at this point is that selective Rho-kinase inhibitors are not available. Being able to target only the desired cells may be crucial, as increasing the concentration of a non-specific ROCK inhibitor could have undesirable consequences. Given our limited knowledge about the multitude of biochemical systems and interactions taking place inside the eye, it's impossible to know what the exact effect of increasing the level of non-specific ROCK inhibitors might be, but a molecule designed to affect only trabecular meshwork tissue would be a safer alternative.

10. CONCLUSION

ROCK inhibitors, though still in their research phase, may emerge as a new therapeutic option for glaucoma management and revolutionise both medical and surgical therapy.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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