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Minireview Article

ROCK INHIBITORS: FUTURE OF ANTI-GLAUCOMA MEDICATION???

Abstract:

Glaucoma constitutes the major burden of irreversible blindness worldwide as of today. All the modalities of treatment are focussed on lowering intra ocular pressure, 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. Rho kinase inhibitors (ROCK Inhibitors) 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 ocular hypotensive drugs that enhance aqueous drainage. Being still under trials, hopes are on that these could revolutionise Glaucoma therapy.

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 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 future thanks 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 improved efficacy but

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also reduced intolerance, which is emerging as a leading cause of poor adherence, or non-compliance as is often referred, to topical anti glaucoma therapy (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 (3) pharmacologic classes of IOP-lowering drugs are A‑adrenergic agonists (e.g. brimonidine); β‑adrenergic blockers (e.g. timolol); carbonic anhydrase inhibitors (e.g. dorzolamide); cholinergic agonists (e.g. pilocarpine, carbachol); and prostaglandin analogues (e.g. latanoprost, travoprost, bimatoprost). Prostaglandins are currently the most prescribed glaucoma treatment world. These reduce IOP by increased aqueous outflow, and have not only good potency but also improved adherence profile. The Rho kinase (ROCK) inhibitors, currently under Phase II trials, are emerging as the new class of antiglaucoma drugs.

MECHANISM OF ACTION

These act specifically at the trabecular meshwork which has been identified as the prime site of aqueous outflow resistance. These target cells in the trabecular meshwork to enhance aqueous humor outflow. 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(4) .The Rho family

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of small guanosine triphosphatases (GTPases) has a central role in these cellular processes, particularly those involving actin cytoskeleton assembly, actin-myosin mediated cell contraction and motility (5)(6). ROCK (Rho-associated coiled coil-forming protein kinase) is a downstream effector of Rho factor in the Rho-dependent signal transduction pathway (7). 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 ocular hypotensive drugs that enhance aqueous drainage (8)(9)(10). 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.

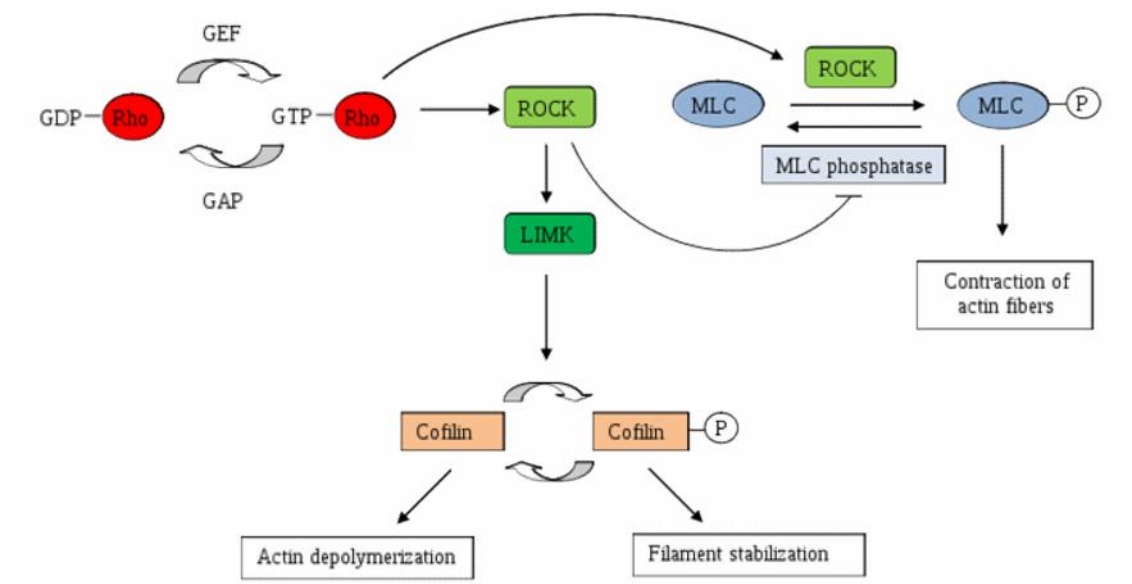

Fig 1. ROCK protein function.

Since glaucoma is also age-related, it's 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

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meshwork cells. (11) In addition, levels of Rho-GTPase agonists, including endothelial 1 and TGF-beta, have been reported to be elevated in the aqueous humor of glaucomatous patients. (12)(13)

ANIMAL STUDIES

To be able to explore the role of these Rho-kinase inhibitors for glaucoma treatment in humans, various trials are underway (14). Animal model testing is showing vast potential. Four different mechanisms have been described. (15-24)

Firstly, Rho-kinase inhibitors may be able to increase aqueous outflow by relaxing trabecular meshwork tissue. Studies have demonstrated that selective Rho-kinase inhibitors reduce IOP and increase outflow facility by altering the behaviour of trabecular meshwork cells and relaxing ciliary muscle in bovine and human tissue. (15)(16).

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. (17)(18)These agents not only improve optic nerve perfusion but also improve cerebral and coronary perfusion. (19)(20)

Thirdly, Rho-kinase 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 at the cell body is neuroprotective and overcomes growth inhibition.(21)(22) In addition, animal studies have shown an increase in retinal ganglion cell survival with Rho-kinase inhibitors.(23)

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Fourthly, Rho-kinase inhibitors may aid us in treating glaucoma is as an antifibrotic agent in glaucoma surgery. One of the main reasons for failure of glaucoma surgery is scarring. Although the use of antimetabolites (5FU 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 Rho-kinase inhibitor) is associated with reduced subconjunctival scarring in rabbits after filtration surgery and that it was safe and well-tolerated. (24)

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. (15) . 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. (25)

DRUG	ORGANIZATION	CLINICAL TRIAL PHASE	NOTES
AR-12286	Aerie	PII	Rho kinase inhibitor
INS-117548	INSPIRE	P I	Rho kinase inhibitor
K-115	Kowa	PII	Rho kinase inhibitor
Y-39983; SNJ-1656; RKI-983	Senju/Novartis	PII	Rho kinase inhibitor

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TABLE 1- RHO KINASE INHIBITORS UNDER CLINICAL TRIALS

ONGOING CLINICAL TRIALS

ROCK inhibitors that are currently in clinical trials for glaucoma or ocular hypertension include AR‑12286 (Phase II, Aerie Pharmaceuticals) and K‑115 (Phase II, Kowa Pharmaceutical). Other ROCK inhibitors Y‑39983/SNJ‑1656/ RKI‑983 (Phase II, Senju and Novartis Pharmaceuticals) and INS‑117548 (Phase I, Inspire Pharmaceuticals) are still under development, but have encountered efficacy and tolerability.

CHALLENGES??

DE‑104 (Phase I/II, Santen Pharmaceuticals and Ube Industries) development was discontinued in late 2010 after its trial failed to meet the primary endpoint. (5)

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 (26) 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. (27). For example, such drugs could potentially prevent cancer from spreading by blocking cell migration, stopping cancer cells from spreading into neighbouring tissue. (28)

PIT FALLS

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Rho kinase inhibitors seem to have a promising role in glaucoma management. The one notable problem with using Rho-kinase 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 Rho-kinase 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 Rho-kinase inhibitors might be, but a molecule designed to affect only trabecular meshwork tissue would be a safer alternative.

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.

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