

Rho-associated kinase inhibitors: A novel glaucoma therapy

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The rho-associated kinase (ROCK) signaling pathway is activated via secreted bioactive molecules or via integrin activation after extracellular matrix binding. These lead to polymerization of actin stress fibers and formation of focal adhesions. Accumulating evidence suggests that actin cytoskeleton-modulating signals are involved in aqueous outflow regulation. Aqueous humor contains various biologically active factors, some of which are elevated in glaucomatous eyes.

These factors affect aqueous outflow, in part, through ROCK signaling modulation. Various drugs acting on the cytoskeleton have also been shown to increase aqueous outflow by acting directly on outflow tissue. In vivo animal studies have shown that the trabecular meshwork (TM) actin cytoskeleton in glaucomatous eyes is more disorganized and more randomly oriented than in non-glaucomatous control eyes. In a previous study, we introduced ROCK inhibitors as a potential glaucoma therapy by showing that a selective ROCK inhibitor significantly lowered rabbit IOP. Rho-associated kinase inhibitors directly affect the TM and Schlemm's canal (SC), differing from the target sight of other glaucoma drugs. The TM is affected earlier and more strongly than ciliary muscle cells by ROCK inhibitors, largely because of pharmacological affinity differences stemming from regulatory mechanisms.

Additionally, ROCK inhibitors disrupt tight junctions, result in F-actin depolymerization, and modulate intracellular calcium level, effectively increasing SC-cell monolayer permeability. Perfusion of an enucleated eye with a ROCK inhibitor resulted in wider empty spaces in the juxtacanalicular (JCT) area and more giant vacuoles in the endothelial cells of SC, while the endothelial lining of SC was intact. Interestingly, ROCK inhibitors also increase retinal blood flow by relaxing vascular smooth muscle cells, directly protecting neurons against various stresses, while promoting wound healing.

These additional effects may help slow progressing visual field loss in glaucoma patients, making ROCK inhibitors an even more desirable anti-glaucoma agent. All evidence indicates that aqueous humor outflow is affected by cytoskeleton physiology and this information may provide valuable insight into understanding glaucoma pathology and treatment.

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