



CONTRIBUTION OF ROCK IN CONTRACTION OF TRABECULAR MESHWORK: PROPOSED MECHANISM FOR REGULATING AQUEOUS OUTFLOW IN MONKEY AND HUMAN EYES

Emi Nakajima^{1,3}, Takeshi Nakajima^{1,3}, Yoko Minagawa², Chie Mito², Thomas R. Shearer³ and Mitsuyoshi Azuma^{1,3}

¹ Laboratory of Ocular Sciences (Beaverton OR)

² Kobe Creative Center (Kobe Japan)

³ Senju Pharmaceuticals Co. Ltd., and Oregon Health & Science University, Portland OR

Background: Aqueous outflow via conventional and uveoscleral pathways in humans is regulated by the contraction and relaxation of the ciliary muscle (CM) and trabecular meshwork (TM). An inhibitor of rho-associated coiled, coil-forming protein kinase (ROCK) causes relaxation of CM and TM and decreases intraocular pressure (IOP).

Design: Experimental animal and human tissue study

Materials/Methods: Genetic analysis (GeneChip) of ciliary muscle and trabecular meshwork in monkey and human

Main Outcome Measures: mRNA levels in CM and TM after application of ROCK inhibitor Y-39983 and resulting changes in Carbachol-induced contraction of target tissues

Results: The site of action of ROCK in monkey is unknown. Thus, the purpose of the first experiment was to compare expression of ROCK and ROCK substrate, and relaxation by ROCK inhibitor Y-39983, in monkey CM and TM. GeneChip analysis was used to compare levels of mRNA expression. Higher expression levels of mRNAs for ROCK and ROCK substrate were observed in TM compared to CM. This was confirmed by RT-PCR. To determine whether levels of mRNA expression for ROCK and ROCK substrate were reflected in contraction of CM and TM, relaxation of carbachol-induced contraction of CM and TM strips by Y-39983 was tested. Y-39983 led to relaxation of TM in a dose-dependent manner. In contrast, Y-39983 was only slightly effective in CM. GeneChip analysis of human tissues showed greater expression of mRNAs for ROCK and ROCK substrate in TM compared to CM.

Conclusions: These results suggested that TM is one of the major sites for regulating IOP by ROCK in monkey eyes. Y-39983 might be an ideal drug to lower IOP.

[Dr. Shearer has a significant financial interest (research contract and consulting fee) in Senju Pharmaceutical Co. Ltd.]

Updated: March 11, 2008 12:55 PM AST