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Editorial

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Rho-associated Kinase Inhibitors for the Treatment of Ocular Diseases

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The Rho family consists of a series of small G-proteins, including RhoA, RhoB, and RhoC. When bounded to guanosine triphosphate, Rho molecules activate their effectormolecule,Rho-associated kinase (ROCK). A Rho-ROCK signal is a regulator of factors such calcium-independent smooth muscle contraction, cell adhesion and motility, as well as of actin cytoskeleton [1]. In September 2014, a ROCK inhibitor, ripasudil,was approved in Japan for the treatment of glaucoma and ocular hypertension as the first anti-glaucoma agent of this category in the world.In this Editorial, I describe the unique mechanisms by which ROCK inhibitors lower intraocular pressure (IOP), as well as their other actions.

It was found in Japan that several kinds of ROCK inhibitors, including Y-27632 and HA1077 (fasudil), reduce IOP by increasing conventional outflow through the Schlemm canal. Honjo., *et al*. Reported that administration of the ROCK inhibitors caused a reduction in IOP and an increase in the outflow facility in rabbits. Their *in vitro* experiments suggested that the IOP-lowering effects of the ROCK inhibitors might be related to the altered cellular behavior of trabecular meshwork cells and relaxation of ciliary muscle contraction [2,3]. Ripasudil, a selective ROCK inhibitor, has recently been approved for human use after undergoing a series of clinical trials, and was found to have additive effect when combined with timolol or latanoprost [4-6]. It is noteworthy that ripasudil is now the only anti-glaucoma agent in clinical use that lowers IOP by modulating the conventional aqueous outflow pathway [7].

Fasudil was clinically verified to be effective in reducing cerebral vasospasm after aneurysmal subarachnoid hemorrhage [8]. It was also reported that intravenous administration of fasudil increased cerebral blood flow in patients with chronic cerebral infarction [9]. There have been several reports describing the vasodilator effects of ROCK inhibitors in the eye. Topical administration of Y-39983, another ROCK inhibitor, or ripasudil increased ocular blood flow (optic nerve head (ONH) or retina) in normal animals [10,11]. However, the vasodilator effects of fasudil on the retinal arteriole in spontaneously hypertensive rats were reported to be greater than those in age-matched normotensive rats [12]. We also reported that intravenous or topical application of fasudil prevented or improved the ONH blood flow impairment, although it had no significant effects on normal ONH blood flow in rabbits [13]. It seems that ROCK inhibitors have more effects on ocular blood flow in pathological conditions than in normal states.

It was suggested that RhoA and ROCK II may be upregulated and might be involved in N-methyl-D-aspartate (NMDA)-induced retinal neurotoxicity and that fasudil might be neuroprotective against glutamate-related excitotoxicity [14]. Another study suggested that inhibition of Rho/ROCK signaling by Y-27632 is neuroprotective against postischemic neural damage via regulation of leukocyte infiltration in the neural tissue [15]. Other studies indicated that Y-39983 promoted axonal regeneration of retinal ganglion cells (RGCs) and that oral ripasudil administration delayed RGC death, probably mediated through Nox1 downregulation [10,16]. Although further investigations are needed, ROCK inhibitors might be beneficial for optic neuropathy including glaucoma.

Rho-ROCK signaling may play an important role in wound healing. Therefore, ROCK inhibitors mediate transforming growth factor (TGF) -β-induced contraction in human tenon fibroblasts, block subsequent my ofibroblasttrans differentiation, and may modulate postoperative scarring after glaucoma filtering surgery [17]. Topical application of Y-27632 was effective in preventing fibroproliferation and scar formation in a rabbit model of glaucoma surgery [18]. Moreover, we reported that topical application of ripasudil maintained bleb formation and IOP reduction by suppressing cell proliferation in a canine model of glaucoma surgery [19]. ROCK inhibitors seem promising for bringing about an improvement in the outcomes of glaucoma surgeries.

Rho/ROCK signaling is thought to promote cell-cycle progression in various cell typesincluding corneal endothelial cells (CECs) [20]. The inhibition of Rho/ROCK signaling by Y-27632 promoted the adhesion of monkey CECs, inhibited apoptosis, and increased cell proliferation [21]. Topical application of Y-27632 reduced wound area in a rabbit model of corneal endothelial damage [22]. Moreover, Y-27632 eye drops were effective in monkey models of corneal endothelial dysfunction, and improved corneal edema in patients with corneal endothelial dysfunction [23]. Ripasudil also promoted corneal endothelial wound healing [24]. These reports suggest that ROCK inhibitors might be candidates for treating acute corneal endothelial damage due to eye surgeries, especially cataract surgery.

Traction retinal detachment occurs through potent contraction of proliferative tissues, leading to blindness, in vitreoretinal diseases including proliferative diabetic retinopathy and proliferative vitreoretinopathy. Rho-ROCK signaling is involved in such contraction in ocular proliferative tissues. Previous reports describe the involvement of the rho-kinase pathway and its regulation in TGF-β2-induced collagen gel contraction by hyalocytes or retinal pigment epithelial cells [25,26]. In addition, TGF-β2-dependent Smad4 translocation and connective tissue growth factor gene expression were mediated through Rho kinase [27]. As the results indicate, ROCK inhibitors prevented the progression of experimental proliferative vitreous retinopathy [28]. Furthermore, the Rho/ROCK pathway plays a critical role in diabetic retinal microvasculopathy. A ROCK inhibitor protected the vascular endothelium by inhibiting neutrophil adhesion and reducing neutrophil-induced endothelial injury in diabetic rats [29]. ROCK inhibition may develop into a new strategy in the management of diabetic retinopathy, in its early as well as advanced stages. Ripasudil eye drops also have therapeutic potential in the treatment of retinal hypoxic neovascular diseases via anti-angiogenetic effects as well as vascular normalization [30].

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