Changes in corneal limbal stem cells after β-Blocker eye drops treatment.

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Description

Glaucoma is a group of optic neuropathies that lead to an increase in Intra Ocular Pressure (IOP), loss of the inner retinal nerve cells and the retinal ganglion cells. Nowadays, approximate 3.5% of the global population aged 40 to 80 years suffer from glaucoma, which making the second leading cause of blindness worldwide [1].

In clinic, the treatment of glaucoma is focused on lowing the IOP with medicines targeting β-blockers, α2 receptor agonists, the carbonic anhydrase inhibitor, parasympathomimetic pilocarpine, or sympathomimetics. In the human iris-ciliary body, β2-Adrenoceptor (β2AR) predominantly expresses in membrane homogenates and β1AR comprises approximately 10% of βAR in the entire iris-ciliary body [2]. Thus, selective β1-antagonists and nonselective β-antagonists have been used widely for ocular hypertension and glaucoma treatment. For open-angle glaucoma and ocular hypertension treatment, topical application of β-blocker eye drops levobunolol (0.5%) and timolol (0.5%) are first-choice agents which blocks the sympathetic nerve endings in the ciliary epithelium [3,4]. However, since anti-glaucoma treatment requires long-term medication, chronic side effects of β-blocker eye drops are a major concern in clinic.

Clinical trials have demonstrated that the contraindications for β-blocker including uncontrollable organic heart disease, bronchial asthma or bronchospasm, sinus bradycardia, atrioventricular block, cardiogenic shock and diabetes. Topical application of β-blocker eye drops induces damage to the goblet cell density and tear film, accumulation of inflammatory cells, and the human ocular surface. In the corneal epithelium, β2AR is the predominant βAR, while β1AR comprises approximately 17% of βAR, and minimal β3AR expression is found [5,6]. When instilled β-blocker eye drops topically, the drugs reach the highest concentration in corneal epithelium. β-blocker eye drops decreases the corneal epithelial barrier function, delays corneal epithelial wound healing and reduction in the corneal epithelial thickness. Moreover, the corneal limbal epithelial stem cells have the capacity for self-renewal, proliferation, and migration, which make them indispensable for corneal wound healing. In glaucoma patients with anti-glaucoma therapy, the morphologic alterations of the corneoscleral limbus presented a worse limbal transition epithelium regularity, which may play a role in the glaucoma-related ocular surface disease [7].

In the present study, β-blocker eye drops levobunolol has been found impaired corneal wound healing after limbal stem cells debridement [8]. Moreover, the corneal wound healing was inhibited by β2AR antagonist ICI 118, 551, whereas the β1AR antagonist atenolol showed no significant effects in mice. Levobunolol and ICI 118, 551 inhibited the migration and proliferation of mouse corneal epithelial progenitor cell line (TKE2) in vitro. It indicated that β-blocker eye drops delayed corneal wound healing mainly through inhibition the β2AR of limbal stem cells. Meanwhile, levobunolol and ICI 118, 551 decreased the expressions of the differentiation markers including cytokeratin 3, cytokeratin 14, and cytokeratin 19, as well as proliferation marker Ki67, and the phosphorylation of EGFR and ERK1/2 in the limbal and regenerated corneal epithelial cells.

Conclusion

Considering the side effects of β-blocker eye drops on the ocular surface and the expression of βAR in iris-ciliary body and corneal epithelial cells, non-selective β-blocker eye drops may not be the first choice for glaucoma treatment. The adverse effects of β1AR antagonist include itching, burning or shooting pain, which is commonly seen in clinic. Considering the therapeutic effect and damage to the fragile ocular surface of patients, the selective β1AR antagonist is recommended for glaucoma treatment when β-blocker eye drops are unavoidable.

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