Regulation of intraocular pressure: structural analysis of dopaminergic and serotonergic systems

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Elevated intraocular pressure (IOP) is the main recognized risk factor of glaucoma, a progressive optic neuropathy, which is the leading cause of blindness in industrialized countries. Several systems are involved in the IOP regulation such as adrenergic, cholinergic, purinergic, serotonergic, and dopaminergic (1,2). However the role of the serotonergic and dopaminergic systems in regulation of IOP is still unclear. To investigate the role of dopaminergic and serotonergic systems on IOP regulation we used cabergoline as pharmacological tool in WT and KO $D_3R^{-/-}$ mice. Further, the structural basis on the cabergoline-mediated activation of the dopaminergic and serotonergic systems, were studied by molecular modeling. Cabergoline is a potent dopamine receptor agonist on D_2 and D_3, and it also possesses high affinity for serotonin receptors such as $5HT_{1A}$, $5HT_{2A\text{-}B\text{-}C}$ (3). Topical application of cabergoline significantly decreased, in a dose-dependent manner, the IOP in WT mice both in an ocular normotensive group and an ocular hypertensive group. No change of intraocular pressure was observed after topical application of cabergoline in KO $D_3R^{-/-}$ mice. The structural basis on the cabergoline-mediated activation of the dopaminergic and serotonergic systems have been studied by molecular modeling of D_3 (4) and $5HT_{1A}$, $5HT_{2A\text{-}B\text{-}C}$ receptors: optimizing receptor models by molecular dynamics in a water-membrane environment. Than molecular docking of cabergoline was carried out. High correlation (R^2=0.92, Pearson=0.94 p=0.02) of *in-silico* binding energies compared to experimental K_i was obtained. Cabergoline binds better to the D_3 receptor than to the analyzed serotonergic receptors both in computational and experimental studies. In conclusion, the present study support the hypothesis that dopaminergic system is pivotal to regulate IOP and that D_3R is the key receptor subtype in this system. Based on the data generated in our study we concluded that D_3R represents an intriguing target in the treatment of glaucoma.

1. Bucolo et al. *Curr Opinion Pharmacol* 2013, 13.
2. Bucolo et al. *Biochem Pharmacol* 2012, 83.
3. Sharif et al. *Exp Eye Res* 2009, 88.
4. Platania et al. *PlosOne* 2012, 7.