Loss of $P2Y_1$ receptor causes ocular hypertension and glaucoma-like phenotype in mice

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Glaucoma is second leading cause of blindness worldwide which is characterized by progressive degeneration of retinal ganglion cells (RGCs). Elevated intraocular pressure (IOP) is one of the highest risk factors and IOP-lowering agents are used to prevent glaucoma. New molecular target is required because of the side effects, drug resistance, and insufficiency for IOP reduction by a part of pre-existing agents. Here, we report that $P2Y_1$ receptor ($P2Y_1R$) activation induces IOP reduction and knock out of $P2Y_1R$ ($P2Y_1KO$) causes sustained IOP elevation associated with age-dependent RGC degeneration. Topical application of MRS2365, selective agonist for $P2Y_1R$, caused significant reduction in IOP in wild-type (WT) mice but not in $P2Y_1KO$ mice. We also found that $P2Y_1KO$ mice showed significantly higher IOP level than that in WT mice. Because sustained IOP elevation is one feature of hypertensive glaucoma, we checked RCG damages and found that the number of RGCs in $P2Y_1KO$ mice was comparable at 3 months old but significantly smaller at 12 months old. Furthermore, optical coherence tomography (OCT) revealed that 12-month-old $P2Y_1KO$ mice showed thinner ganglion cell and inner plexiform layers, general diagnostic feature of glaucoma patients. Taken together, our results demonstrated that (1) $P2Y_1R$ activation reduces IOP; (2) loss-of-function of $P2Y_1R$ causes sustained elevation in IOP and (3) hypertensive glaucoma-like phenotypes in middle-aged mice.