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Title : CELLULAR MECHANISMS OF ACTION OF RESVERATROL IN REGULATION OF AQUEOUS HUMOUR DYNAMICS

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Glaucoma, a common cause of optic neuropathy, is associated with elevated intraocular pressure (IOP) and is the leading cause of irreversible visual disability. Steroid-induced glaucoma, a common type of secondary glaucoma, is also associated with elevated IOP (steroid-induced ocular hypertension (SIOH)). SIOH and glaucoma are currently treated with antiglaucoma agents, which often have suboptimal efficacy and are associated with adverse effects. The objective of this study was to determine if topical application of *trans*-resveratrol reduces IOP in rats with SIOH and to investigate its mechanisms of action. This study was divided into *in vivo* and *in vitro* studies. In the *in vivo* study, we evaluated the oculohypotensive effects of topical *trans*-resveratrol in normal and SIOH rats and investigated the role of adenosine receptors (ARs) and transforming growth factor-β (TGF-β) signalling in the IOP lowering effect of *trans*-resveratrol. Involvement of AR was studied by observing the IOP changes in response to *trans*-resveratrol after pre-treating SIOH animals with AR subtype-specific antagonists. The study also investigated phospholipase C (PLC) activation, extracellular regulated kinase 1/2 (ERK1/2) phosphorylation and increased matrix metalloproteinases (MMPs) secretion in the aqueous humour (AH) as mechanism of resveratrol-induced oculohypotension in SIOH rats. *In vitro* studies evaluated the effect of *trans*-resveratrol on cellular signalling pathways of ARs and TGF-β in primary human trabecular meshwork cells (HTMCs). Single drop of all concentrations of *trans*-resveratrol produced significant oculohypotension in normotensive rats and 0.2% concentration produced maximum IOP reduction. Twice-daily topical application of *trans*-resveratrol 0.2% for 21-day in SIOH rats resulted in significant and sustained IOP reduction. This was associated with significantly higher AH MMP-2 level; significantly reduced trabecular meshwork (TM) thickness and increased number of TM cells. Treatment with *trans*-resveratrol also significantly increased the ganglion cell survival and reduced retinal oxidative stress. Pretreatment with adenosine A_1 receptor antagonist inhibited the oculohypotensive effect of resveratrol. The use of A_1 AR, PLC and ERK 1/2 inhibitors also reduced resveratrol-induced MMP-2 secretion. These results were further supported by *in vitro* study that demonstrated that ERK1/2, PLC and MMP-2 secretion by HTMC is stimulated after resveratrol treatment and these effects are associated with upregulation of A1AR gene expression. Topical *trans*-resveratrol also produced significantly raised plasminogen activator levels and combined TGF-β2+resveratrol treatment caused significant upregulation of inhibitory SMAD7 when compared to TGF-β2-only treated group. Hence, it could be concluded that *trans*-resveratrol-induced oculohypotension in SIOH rats involves its agonistic activity at the A_1AR leading to PLC activation, ERK 1/2 phosphorylation and increased MMP-2 secretion. Increased MMP-2 secretion seems to cause changes in TM favourable for AH outflow leading to reduced IOP. *Trans*-resveratrol-induced oculohypotension could also be attributed to increased level of plasminogen activators, which seems to result from increased expression of inhibitory SMAD7, a TGF-β2 signalling molecule. Although current study, for the first time, has clearly demonstrated the significant effects of topical *trans*-resveratrol on IOP in rats with SIOH and some of the underlying mechanisms; further investigations are needed to fully understand the mechanisms of action of *trans*-resveratrol and to explore its potential as a future antiglaucoma agent.