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Over-expression of AIP protein in GH3 cells reduces cAMP signalling and Growth hormone secretion

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Mutations in the AIP gene have been linked to familial cases of pituitary adenomas (Vierimaa et al, 2006). Analysis of the protein support its role as a tumour suppressor since mutations cause a loss-of-function with reduced protein interactions and over-expression of wild-type (WT) AIP reduces cell proliferation (Leontiou et al, 2008). AIP interacts with a number of interesting proteins, among them are the phosphodiesterases, PDE4A5 and PDE2A, the G proteins, Gαq and Gα13, survivin, RET, nuclear receptors and others (Trivellin & Korbonits, 2011). However, the mechanism by which AIP dysfunction causes increased susceptibility to pituitary adenomas remains unknown. Owing to AIP's interaction with the phosphodiesterases and G proteins, we investigated the effect of WT and mutant AIP proteins on cAMP signalling and its downstream effectors in cell cultures.

WT AIP, R304X-AIP mutant and empty vector (EV) were transfected into GH3 cells. Basal and forskolin – induced cAMP signalling was analyzed using cAMP assays, CRE-promoter luciferase assays, real-time PCR and finally growth hormone (GH) assays.

WT AIP was able to reduce forskolin-induced, but not basal, cAMP signaling. Total cAMP, the luciferase activity of cAMP-driven promoter and target gene expression were reduced when compared to EV and R304X mutant. Additionally, analysis of GH secretion which occurs after cAMP cascade activation, was slightly but significantly reduced in WT over-expressing GH3 cells treated with forskolin. Addition of IBMX, a phosphodiesterase inhibitor, did not reverse the effect of AIP on cAMP signalling or GH secretion, indicating that this effect occurs independently of AIP-phosphodiesterase interaction.

AIP protein appears inhibit pituitary cells from proliferation by suppressing cAMP production, activation of which is known to cause tumour formation (Lania et al, 2003) and thereby also influencing GH secretion. However, this effect appears not to be mediated by the AIP-phosphodiesterase interaction, suggesting G protein involvement in mediating this outcome.

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