Abstract form

Title: Functional role of AIP in pituitary adenoma predisposition.
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Abstract

Context: Mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene have been linked to predisposition to pituitary adenomas, however, the mechanism through which this occurs remains unknown. AIP interacts with a number of interesting proteins, including members of the cAMP signalling pathway which has been shown to be consistently altered in pituitary tumours.

Objectives: We investigated the functional role of wild type (WT) and mutant AIP on cAMP signalling and its downstream effectors, including growth hormone (GH) secretion.

Methods: A mutation identified in a local acromegalic patient was functionally analyzed and, together with wild-type and non-functional AIP variants, transfected into GH3, Hela and COS-7 cells for functional assessment. cAMP signalling was analyzed using cAMP assays, cAMP response element (CRE)-promoter luciferase reporter assays, real-time PCR and finally secreted growth hormone (GH) quantification.

Results: Wild-type AIP was able to reduce forskolin-induced cAMP signalling both at the total cAMP level, luciferase reporter activity and target gene expression when compared to empty vector and R304X mutant and generally also when compared to the R9Q variant. Additionally, GH secretion was also slightly but significantly reduced in wild-type AIP over-expressing GH3 cells treated with forskolin. IBMX, a PDE inhibitor, did not completely inhibit the effect of AIP on cAMP signalling.

Conclusions: We have provided a mechanism by which AIP acts as a tumour suppressor, by maintaining a low cAMP threshold and thereby also influencing GH secretion. Mutations of AIP render the protein incapable of such activity. However, this effect appears not to be mediated by the AIP-PDE interaction, suggesting the involvement of other interacting partners in mediating this outcome.