The dopastatin BIM-23A760 distinctly influences key functional endpoints in different types of pituitary adenomas and normal pituitaries: role of somatostatin and dopaminergic receptor profile

Introduction

Chimeric somatostatin (SST)/dopamine (DA) compounds, termed dopastatins, such as BIM-23A760, an agonist of somatostatin (sst2, sst5) and dopamine (D2) receptors, are emerging as promising novel alternatives for the treatment of pituitary adenomas. However, their exact actions and precise mechanisms on the different types of pituitary tumors are still to be fully understood.

Thus, the aim of this study was to analyze a set of key functional parameters (signaling pathways, hormone expression and secretion, cell viability and apoptosis), in response to BIM-23A760 in a series of 74 human pituitary adenomas, 5 normal and 3 olive baboon pituitary samples (as a relevant non-human primate model).

Normal pituitary

We found that sst2, sst5 and D2 were highly expressed in both baboon and human pituitaries, and their expression was virtually identical in both species.

D2=D1+D3+D5+sst2.

We observed a decrease of GH and PRL release in response to BIM-23A760 in human and baboon normal pituitary primary cultures, as well as a significant decrease in LH and a slight inhibition in ACTH release in the case of baboon pituitary cell cultures.

Additionally, in primary cultures, we observed a decrease in GH and PRL at mRNA levels, which was supported by a significant repression of POUF1; but interestingly, we also observed an up-regulation of sst2, sst5, D2 and D3 expression.

Hormone release/expression

Cell viability

Molecular profile

Materials & Methods

Ca2+ signaling

Conclusion

Altogether, our results reinforce the notion that chimeric dopastatins (e.g., BIM-23A760) can affect multiple, clinically relevant parameters on most types of pituitary adenomas and may represent new therapeutic tools to treat pituitary tumors, wherein the relative SST/DA receptor expression profile might provide useful molecular markers to predict the ultimate response of these tumors to BIM-23A760.