mTOR PATHWAY: ITS ROLE IN REGULATING GH SECRETION IN A RAT PITUITARY ADENOMA CELL LINE

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Introduction
Acromegaly results from excess growth hormone (GH) secretion, due to a pituitary adenoma. Surgery is the first option recommended for treatment of GH secreting pituitary adenomas; medical therapy, mostly represented by somatostatin analogues (SSA), is most often used if surgery is not successful. Insulin-like Growth Factor-1 (IGF-1) physiologically reduces GH levels through an endocrine negative feedback loop. IGF-1 exerts its effects also through PI3K/Akt/mTOR pathway activation and regulates different cellular processes.

Objectives
The aim of this study is understand whether PI3K/Akt/mTOR pathway can influence IGF-1 feed-back in a rat pituitary adenoma cell line (GH3 cells). We used three inhibitors: Everolimus (mTOR inhibitor), NVP-BEZ235 (mTOR and PI3K inhibitor) and LY294002 (PI3K inhibitor) in the presence or in the absence of IGF-1.

Methods
- Cell viability by ATPlite assay
- GH secretion by ELISA
- Akt phosphorylation by Western blot

Results
- **Cell viability was induced by IGF-1 (+30%)**
- Everolimus reduced cell viability (-30%), this effect was not counteracted by IGF-1
- NVP-BEZ235 reduced cell viability and IGF-1 counteracted this effect

- **GH secretion was reduced by IGF-1 (-40%)**
- Everolimus not influenced GH secretion
- GH secretion was blocked by NVP-BEZ235

Conclusions
These results show that IGF-1 is an important regulator of cell proliferation and GH secretion in pituitary cells and that PI3K/Akt/mTOR inhibitors may modulate IGF-1 signaling. This pathway has a role in IGF-1 negative feedback on GH secretion, probably through Akt inhibition. Therefore, mTOR pathway may represent a possible target for treatment of GH-secreting pituitary adenomas.

References