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

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Introduction

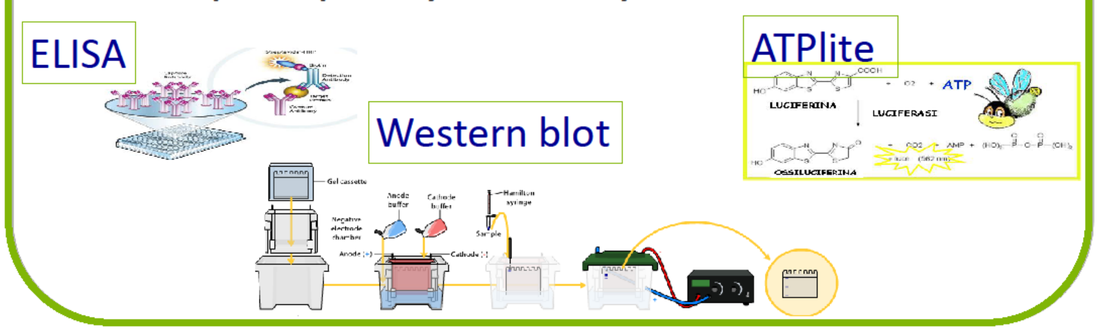
Acromegaly results from excess growth hormone (GH) secretion, due to a pituitary adenoma. Surgery is the first option recommended for treatment of GH secreting pituitary adenomas; medical therapy, mostly represented by somatostatin analogues (SSA), is most often used if surgery is not successful. Insulin-like 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

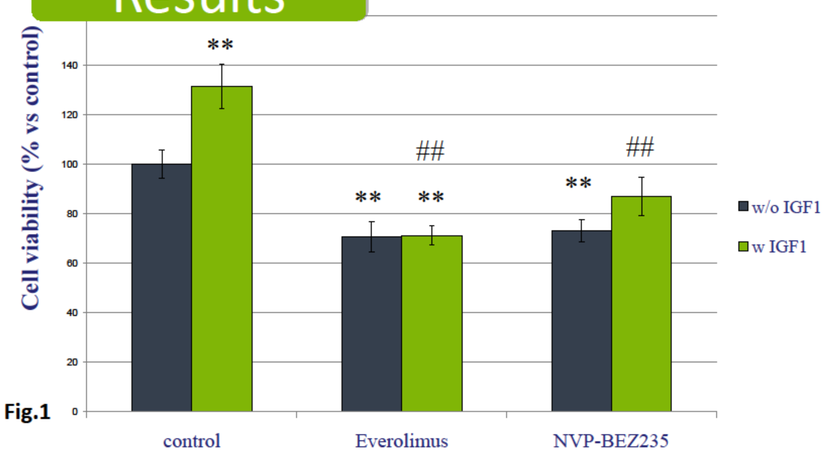


Fig.1

- ✓ 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

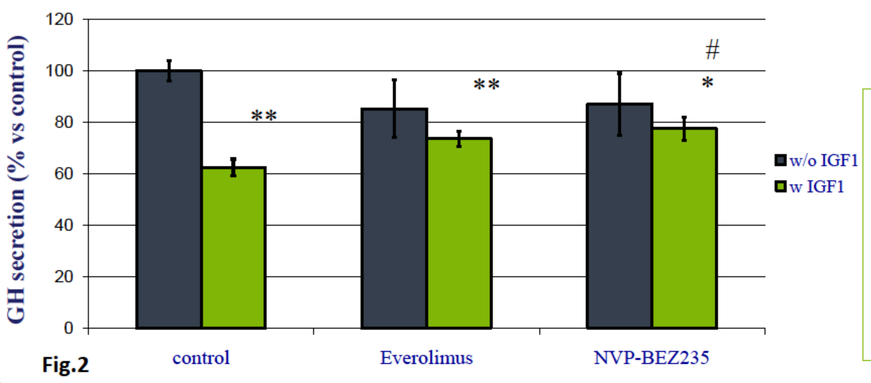
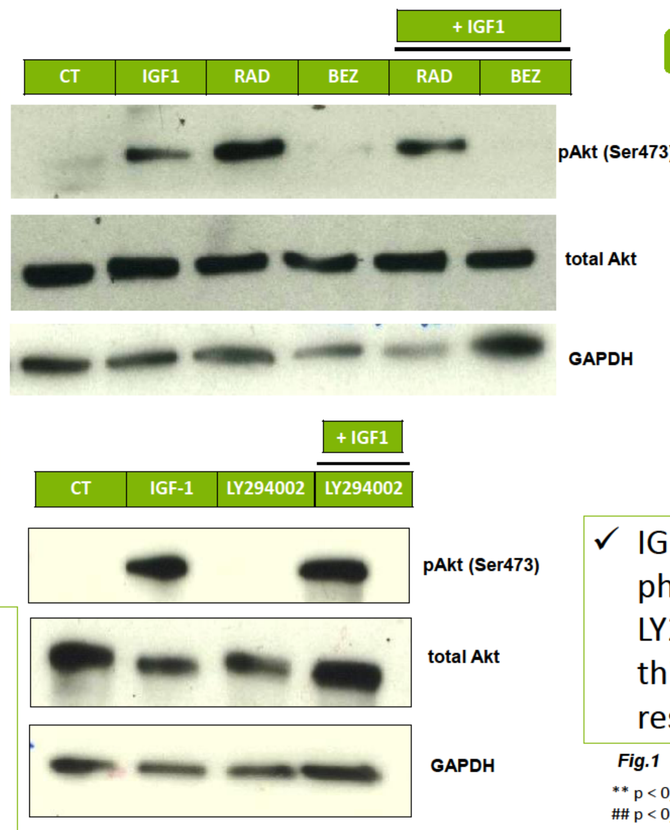


Fig.2

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

Western blot



- ✓ IGF-1 induced AKT phosphorylation, that was enhanced by Everolimus and completely abolished by NVP-BEZ235
- ✓ IGF1 increases Akt phosphorylation while LY294002, alone, arrest this effect but IGF-1 restored it

Fig.1

** p < 0,01 vs. control
p < 0,01 vs. IGF1

Fig.2

** p < 0,01 vs ct
# p < 0,05 vs IGF1

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

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- Gorshtein A, Rubinfeld H, Kendler E, Theodoropoulou M, Cerovac V, Stalla GK, Cohen ZR, Hadani M, Shimon I. ***Mammalian target of rapamycin inhibitors rapamycin and RAD001 (everolimus) induce anti-proliferative effects in GH-secreting pituitary tumor cells in vitro.*** Endocr Relat Cancer. 2009 Sep;16(3):1017-27.