Influence of mTOR and ERK 1/2 pathways on the IGF-1 negative feedback in GH secreting pituitary adenoma cell line

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**Background:** Gigantism and Acromegaly are the main consequences of GH excess, mainly due to a pituitary adenoma. Surgery is the first therapeutic option, but also medical therapy is employed, being mostly represented by somatostatin analogues (SSA), that reduce both tumor mass and GH hypersecretion. However about 10% of patients is resistant to SSA. P13K/Akt/mTOR pathway, activated by growth-factors such as IGF-1, is important in regulating many cellular processes.

**Aim:** To understand whether PI3K/Akt/mTOR and ERK 1/2 pathways can influence IGF-1 feed-back in GH secreting pituitary adenoma cell line, we employed three inhibitors: Everolimus (mTOR inhibitor), NVP-BEZ235 (mTOR and PI3K inhibitor) and SCH772984 (ERK 1/2 inhibitor), evaluating their effects in presence or in absence of IGF-1.

**Material and methods:** Cell viability and GH secretion assays have been performed in the GH3 cell line (rat GH-secreting pituitary adenoma cell line).

**Results:**

- **CELL VIABILITY**
  - IGF-1 induced cell viability by 30%, Everolimus reduced viability up to 30% and this effect was not counteracted by IGF-1. NVP-BEZ235 reduced cell viability and IGF-1 counteracted this effect.
  - SCH772984 did not influence viability and not counteracted the effect of IGF-1.
  - Everolimus and NVP-BEZ235 reduced viability up to 30%, and this effect was not counteracted by SCH772984.

- **GH SECRETION**
  - GH secretion was reduced by IGF-1 (40%); Everolimus and NVP-BEZ235 did not affect GH secretion and these compounds did not enhance the negative feedback of IGF-1.
  - SCH772984 reduced GH secretion up to 20% without enhancing IGF-1 negative feed-back.
  - Everolimus and NVP-BEZ235 did not influence SCH772984 effects on GH secretion.

**Conclusions:** These data indicate that IGF-1 is important in regulating proliferation and GH secretion in GH3 cells. mTOR blockade reduces viability without affecting GH secretion. ERK 1/2 affects secretion but not IGF-1 negative feed-back. In conclusion, our data suggest that mTOR and ERK 1/2 pathways are not involved in IGF-1 feed-back on GH secretion.