**Biguanides: A new potential therapeutic option for pituitary tumors?**


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**Introduction**

Pituitary adenomas (PA) comprise a commonly underestimated pathology in terms of incidence and associated morbimortality. Somatostatin analogs and dopamine antagonists constitute the main medical treatments for PA. However, an appreciable subset of patients are resistant or poorly responsive to these drugs, and hence, the search for new therapies to control tumor growth and/or hormone secretion is crucial. Biguanides such as metformin (MF; commonly used to treat type-2 diabetes), phenformin (PF) and buformin (BF) have been shown to exert antitumoral actions in different tumor types (brain tumors, prostate, breast and lung cancers) but their actions in PA cells have not been reported.

The aim of this study was to determine the effect of these biguanides on key functional parameters (hormone expression and secretion, gene expression of key modulators of pituitary cell function and signaling pathways) and on cell viability in normal and/or tumoral pituitary cell cultures and cell lines.

**Materials & Methods**

Primate pituitary cells

Human pituitary adenomas

Somatotropinomas - Corticotropinomas

Pituitary tumor cell lines: ACTH-20 & GHS

**mRNA expression**

Cell viability

[Ca²⁺]: signaling

**Results**

Treatment with different biguanides, especially with phenformin and buformin, was able to reduce cell viability in a dose-dependent manner in different pituitary adenomas subtypes, including corticotropinomas, somatotropinomas and non-functioning pituitary adenomas.

Similar results were obtained in pituitary ACTH- and GH-secreting tumors derived cell lines.

**Conclusions**

1. Different biguanides are able to significantly decrease cell viability in tumoral, but not normal, pituitary cells in a dose- and cell type-dependent manner, through a mechanism that could involve calcium mobilization.

2. Treatment with MF and PF directly decreases GH, ACTH and FSH expression and/or secretion in normal pituitary cell cultures from two primate species (Papio anubis and Macaca fascicularis) through common (mTOR, PI3K and intracellular calcium) and distinct (MAPK) intracellular signaling pathways.

3. The effects of MF and PF in the function of different pituitary cell types from primates also involved the regulation of the expression of key receptors essential in the normal function of these cell types (i.e. st2, st5, Ins-R and IGF1-R).

Therefore, given the demonstrated clinical safety of biguanides, our results suggest that these drugs could be used as a potential therapeutic option for the treatment of human pituitary adenomas.