Vázquez-Borrego, M.C., L-López, F., Gálvez-Moreno, M.A., Fuentes-Fayos, A.C., Venegas-Moreno, E., Herrera-Martínez, A.D., Blanco-Acevedo, C., Solivera, J., Landsman, T., Gahete, M.D., Soto-Moreno, A., Culler, M.D., Castaño, J.P., Luque, R.M., 2020. **A New Generation Somatostatin-Dopamine Analogue Exerts Potent Antitumoral Actions on Pituitary Neuroendocrine Tumor Cells. Neuroendocrinology** 110, 70–82. https://doi.org/10.1159/000500812

Abstract

Background

Pituitary neuroendocrine tumors (PitNETs) represent approximately 15% of all intracranial tumors and usually are associated with severe comorbidities. Unfortunately, a relevant number of patients do not respond to currently available pharmacological treatments, that is, somatostatin analogs (SSAs) or dopamine-agonists (DA). Thus, novel, chimeric somatostatin/dopamine compounds (dopastatins) that could improve medical treatment of PitNETs have been designed.

Objective

This study aims to determine the direct therapeutic effects of a new-generation dopastatin, BIM-065, on primary cell cultures from different PitNETs subtypes.

Methods

Thirty-one PitNET-derived cell cultures (9 corticotropinomas, 9 somatotropinomas, 11 nonfunctioning pituitary adenomas [NFPAs], and 2 prolactinomas), were treated with BIM-065, and key functional endpoints were assessed (cell viability, apoptosis, hormone secretion, expression levels of key genes, free cytosolic [Ca2+]i dynamics, etc.). AtT-20 cell line was used to evaluate signaling pathways in response to BIM-065.

Results

This chimeric compound decreased cell viability in all corticotropinomas and somatotropinomas tested, but not in

NFPAs. BIM-065 reduced ACTH, GH, chromogranin-A and PRL secretion, and increased apoptosis in corticotropinomas, somatotropinomas, and NFPAs. These effects were possibly mediated through modulation of pivotal signaling cascades like [Ca2+]i kinetic and Akt- or ERK1/2-phosphorylation.

Conclusions

Our results unveil a robust antitumoral effect in vitro of the novel chimeric compound BIM-065 on the main PitNET subtypes, inform on the mechanisms involved, and suggest that BIM-065 could be an efficacious therapeutic option to be considered in the treatment of PitNETs.

Keywords: Chimeric compound; Dopamine; Pituitary neuroendocrine tumors; Receptor; Somatostatin.