Título: Ghrelin receptor signaling in dopamine neurons mediates high fat intake in a binge eating model

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Lugar y fecha: 10th International Brain Research Organization World Congress; 2019Daegu, Korea

Ghrelin is a peptide hormone secreted by endocrine cells located in the stomach fundus. It regulates a variety of biological processes, including energy homeostasis. Ghrelin administration to humans and rodents induces food intake. The orexigenic effects of ghrelin are mainly due to its action in the brain, where different neuronal populations express ghrelin receptor, the growth hormone secretagogue receptor (GHSR). A key neuronal population expressing GHSR is the dopaminergic population. Here, we investigated the role of dopaminergic GHSR-expressing neurons in the regulation of ghrelin's biological effects. We employed a genetically modified mouse model in which Cre recombinase is expressed exclusively in dopaminergic neurons (DAT-Cre mice). We crossed DAT-Cre mice to mice in which GHSR expression is blocked by a LoxP-flanked transcription blocking cassette (GHSR-deficient mice) in order to generate mice expressing GHSR selectively in dopaminergic neurons (GHSR-deficient/DAT-Cre mice). We first validated that GHSR-deficient/DAT-Cre mice were a useful tool to study the effect of GHSR expression exclusively in dopaminergic neurons. Then, we studied the effect of peripheral ghrelin administration to GHSR-deficient/DAT-Cre mice. We also studied the effect of central ghrelin administration on locomotor activity and food intake of GHSR-deficient/DAT-Cre mice. Finally, we employed different behavioral tests, including a binge eating and a conditioned place preference protocol, in order to determine the role of dopaminergic GHSR-expressing neurons in the regulation of ingestivebehaviors. Our results indicate that GHSR signaling in dopaminergic neurons mediates complex feeding behaviors while the selective expression of GHSR in dopaminergic neurons is not sufficient to restore ghrelin-induced food intake and locomotor activity.