Título: Constitutive ghrelin receptor signaling modulates the magnitude of the compensatory hyperphagia triggered by an event of fasting.

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Lugar y fecha: Reunión conjunta de sociedades de Biociencias. Noviembre de 2017, Buenos Aires.

Ghrelin is the only peptide hormone known to stimulate food intake. Ghrelin acts through the growth hormone secretagogue receptor (GHSR), which is a G protein coupled receptor highly expressed in the central nervous system. Notably, GHSR displays the highest known constitutive activity. The physiological relevance of the constitutive GHSR signaling is uncertain. Our goal here was to study if the ghrelin/GHSR system modulates the magnitude of the hyperphagia that follows an event of fasting. First, we characterized the food intake and body weight responses of wild-type (WT) mice that have been exposed to a 48-h fasting event and then refed. We found that refed WT mice display a robust hyperphagia after fasting that continues for 5 days after refeeding and changes its food intake daily pattern. Fasted WT mice show an increase of plasma ghrelin levels as well as the GHSR levels in the hypothalamic arcuate nucleus (ARC), indicated by both a ghrelin binding assay and gene expression analysis. Then, we compared the fast-refeeding response of WT, ghrelin-KO and GHSR-deficient mice in our protocol. In contrast to ghrelin-KO mice, only GHSR-deficient mice showed a significantly smaller compensatory hyperphagia than the observed in WT (14.4±3.5%, unpaired t test). Then, we tested the compensatory hyperphagia of WT mice intracerebroventricularly-treated during the fasting period with either a GHSR antagonist (D-Lys3-GHRP-6) or a GHSR inverse agonist (K-(D-1-Nal)-FwLL-NH2). The compensatory hyperphagia was significantly smaller only in the inverse agonist-treated group (14.8±3.8%, unpaired t test) as compared to vehicle- and antagonist-treated mice. Thus, the constitutive GHSR signaling modulates the magnitude of the compensatory hyperphagia triggered by an event of fasting.