Effects of Growth Hormone-Releasing Hormone (GHRH) Gene Targeted Ablation on Ghrelin-Induced Feeding in Mice

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Impairment of the growth hormone (GH) signaling has been associated with increased feeding and adipose tissue mass. The gastric hormone ghrelin, besides its GH-stimulating effects, also stimulates food intake and body weight gain upon both central and peripheral administration (Tschöp et al., 2000; Wren et al., 2000; Nakazato et al., 2001). On the other hand, feeding induced by ghrelin is blunted in GH receptor deficient mice (Egecioglu et al., 2006). The aim of the present study was to further investigate the role of the ghrelin-GH axis in feeding in a mouse model of autosomal recessive isolated GH deficiency (GHD) due to targeted ablation of the GH-releasing hormone (GHRH) gene [GHRH knockout (GHRHKO)]. In this context, we evaluated the effects of intracerebroventricular ghrelin administration on feeding behavior and gene expression of orexigenic [agouti-related peptide (AgRP), neuropeptide Y (NPY) and orexin A] and anorexigenic [cocaine and amphetamine-regulated transcript (CART), proopiomelanocortin (POMC) and corticotropin-releasing hormone (CRH)] peptides in homozygous for GHRHKO allele (-/-) and heterozygous (+/-) control mice. Furthermore, we evaluated the effects of ghrelin on hypothalamic dopamine (DA), norepinephrine (NE) and serotonin (5-hydroxytriptamine, 5-HT) steady-state concentrations. Animals were also analyzed with respect to ghrelin circulating levels. -/- (n=12) and +/- (n=12) mice were intracerebroventricularly injected with either vehicle (saline) or ghrelin (3 nmol). Food intake was recorded 24 hours after the injection, thereafter animals were euthanized for blood collection for measurement of ghrelin and for hypothalamus dissection. Gene expression of AgRP, NPY, orexin A, CART, POMC and CRH in the hypothalamus was evaluated by real-time reverse transcription polymerase chain reaction. Hypothalamic DA, NE and 5-HT steady state concentrations were evaluated by high performance liquid chromatography (HPLC) coupled to electrochemical detection. After vehicle treatment, GHRHKO -/- mice showed increased food intake with respect to +/-animals, associated with elevated NPY and AgRP, and decreased mRNA levels, in the hypothalamus. Compared to heterozygous, -/- mice also had increased norepinephrine and circulating ghrelin levels. Ghrelin treatment significantly augmented food intake in both genotypes, and the relative increase with respect to vehicle was higher in -/- mice, possibly related to a significant reduction in POMC mRNA levels.

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Wren et al. (2000). Endocrinology. 141, 4325-28.

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