Regulation of hypothalamic GHRH neuronal activity by ghrelin and obestatin

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Ghrelin, a natural ligand of the Growth Hormone Secretagogue Receptor (GHS-R), is synthesized in the stomach but it may also be expressed in lesser quantity in the hypothalamus where the GHS-R is located on Growth Hormone Releasing Hormone (GHRH) neurons. Obestatin, a 23 amino acid peptide derived from the same precursor as ghrelin, antagonizes ghrelin-induced increase of Growth Hormone (GH) secretion *in vivo* but it is not active on pituitary explants *in vitro*. Thus, the blockade of ghrelin-induced GH release by obestatin is likely mediated at the hypothalamic level within the neuronal network which controls pituitary GH secretion. Ghrelin increased GHRH and decreased somatostatin (somatotropin releasing inhibitory factor, SRIF) release from hypothalamic explants while obestatin only reduced ghrelin-induced increase of GHRH release. Thus, the effect of ghrelin and obestatin is targeted to GHRH neurons. Patch-clamp recordings on mouse GHRH-eGFP neurons indicate that ghrelin and obestatin do not affect glutamatergic synaptic transmission. In sharp contast, ghrelin decreases GABAergic synaptic transmission, an effect which is blocked in the presence of the GHS-R antagonist BIM-28163. Ghrelin also stimulates the firing rate of GHRH neurons. Obestatin blocks the effects of ghrelin on GABAergic synaptic transmission. These data suggest that 1) ghrelin increases GHRH neurons excitability by increasing their action potential firing rate and decreasing the strength of GABA inhibitory inputs, thereby leading to an enhanced GHRH release and 2) obestatin can counteract ghrelin actions. Such interactions between metabolic regulatory neuropeptides on GHRH neurons are likely to participate in the control of GH secretion.