Complex interactions between ghrelin and obestatin in the regulation of GH secretion and food intake

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Ghrelin and obestatin derive from the same precursor, preproghrelin, but appear to exert antagonistic effects on food intake and growth hormone (GH) secretion. Ghrelin is a 28 amino-acid peptide with a unique acylation on a serine in position 3 which was isolated from the stomach as an endogenous ligand of the GHS-R (GH secretagogue receptor). It potently stimulates GH secretion and food intake. Obestatin is a 23 amino-acid peptide, also initially isolated from stomach on its property to inhibit food intake and as a ligand of the GPR 39. However, this latter results have not been reproduced convincingly and the nature of the obestatin receptor remains unknown. Ghrelin/obestatin interactions were assessed by measuring plasma peptide levels during voluntary food intake periods in ad libitum-fed mice or 24 h fasted mice. Whereas fasting resulted in elevated ghrelin levels, obestatin levels were significantly reduced, suggesting that both hormones are differentially regulated. Obestatin administration per se did not modify food intake. However, it inhibited ghrelin orexigenic effect as observed in fed but not in fasted mice. The relationship between acylated ghrelin, obestatin, and GH secretions was evaluated by iterative blood sampling every 20 min during 6 h in freely moving adult male rats. Plasma obestatin levels exhibited an ultradian pulsatility with a frequency slightly lower than acylated ghrelin and GH ones but ghrelin and obestatin levels were not strictly correlated. Obestatin administration inhibited ghrelin stimulation of GH levels in freely moving rats. However, it was ineffective when GH release was monitored in superfused pituitary explants. It was therefore of interest to assess peptide interactions at the hypothalamic levels. Patch-clamp recordings in slices from mediobasal hypothalamus of GHRH-GFP transgenic mice indicated that ghrelin clearly decreased GABAergic transmission in 62% of recorded GHRH neurons (n = 85). Obestatin had no effect on glutamatergic or GABAergic synaptic transmission but it blocked ghrelin-induced decrease of GABA responses.

Interactions between ghrelin and obestatin may be relevant in term of eating disorders such as *anorexia nervosa*, a strongly familial with genetic factors disease, which affects 0.3% of young girls with a mortality of 6% per decade. Family trios study of the three preproghrelin sequence single nucleotide polymorphisms were performed in 114 *anorexia nervosa* probands and their two parents, recruited in two specialized French centres. A transmission disequilibrium was observed for the Leu72Met SNP of the preproghrelin gene. When stratified by clinical subtype, this polymorphism was preferentially transmitted for the trios with a bingeing/purging proband. An excess of transmission of the Gln90Leu72 preproghrelin/obestatin haplotype in patients with *anorexia nervosa* was also observed. Thus, preproghrelin/obestatin polymorphisms may confer susceptibility to *anorexia nervosa*. Further analysis of ghrelin/obestatin interactions which represent an interesting component of the biological determinants of energy metabolism and feeding behavior, should contribute to the understanding of pathophysiological patterns in a highly redundant and homeostatic system such as the neuroendocrine control of growth and energy metabolism.