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Review

Role of the ghrelin/obestatin balance in the regulation of neuroendocrine circuits controlling body composition and energy homeostasis

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ABSTRACT

Ghrelin and obestatin are two peptides isolated from the gastrointestinal tract and encoded by the same preproghrelin gene. They convey to the central nervous system informations concerning the nutritional status and/or the energy stores. Ghrelin, mostly acting through the GH secretagogue receptor GHS-R, is a potent GH secretagogue, an orexigenic peptide and a long-term regulator of energy homeostasis. Obestatin was initially described for its anorexigenic effects and its binding to the G protein-coupled receptor 39 (GPR39). However, the role of obestatin is still controversial and the nature of the obestatin receptor remains an open question. This review is focussed on the possible implication of the ghrelin/obestatin system in psychiatric diseases with particular emphasis on eating disorders.

Ghrelin (Kojima et al., 1999) and obestatin (Zhang et al., 2005) are two peptides isolated from the gastrointestinal tract and encoded by the same preproghrelin gene. They convey to the central nervous system informations concerning the nutritional status and/or the energy stores. Ghrelin is a 28 amino-acid peptide which is acylated on the third amino-acid serine by the enzyme GOAT (Ghrelin-*O*-AcylTransferase) (Yang et al., 2008). It was initially characterized as the endogenous ligand for the growth hormone (GH) secretagogue receptor (GHS-R) (Howard et al., 1996). However, ghrelin also regulates other neuroendocrine and metabolic functions in rodents and humans: it is a potent GH secretagogue, an orexigenic peptide and a long-term regulator of energy homeostasis (Bluet-Pajot et al., 2005). Obestatin is a 23 amino-acid peptide initially described for its anorexigenic effects and its binding to G protein-coupled receptor 39 (GPR39) (Zhang et al., 2005). However, the role of obestatin is still controversial and the nature of the obestatin receptor remains an open question (Fig. 1).

GPR39 was originally cloned in 1997 (McKee et al., 1997) along with GPR38, later on identified as the motilin receptor (Feighner et al., 1999), as two novel orphan seven-transmembrane G protein-coupled receptors showing high structural similarity to the GH secretagogue receptor. After the claim that obestatin was an endogenous ligand for GPR39, at least four different groups reported that they could not elicit any binding of obestatin to GPR39 or any stimulatory function of the obestatin peptide on GPR39 (Chartrel et al., 2007; Holst et al., 2007; Lauwers et al., 2006; Tremblay et al., 2007). Thus, it was generally agreed that GPR39 is a receptor for Zn^{2+} (Holst et al., 2007; Yasuda et al., 2007) but not the receptor for obestatin (Zhang et al., 2007). Moreover, it was reported that if full length GPR39-1a is expressed selectively throughout the gastrointestinal tract, it is not expressed in the CNS, in contrast to a truncated splice variant five-transmembrane form, GPR39-1b, and an antisense gene called LYPD1 (Ly-6/PLAUR domain containing 1) which may encode a secreted protein product (Egerod et al., 2007). On the other hand, immunofluorescent labeling of GPR39 was recently observed as punctuate staining near dendrites and at the periphery of cells expressing the neuronal nuclear marker (NeuN) in the CA3 region of the rat hippocampus (Besser et al., 2009) and obestatin induces the association of GPR39/β-arrestin 1/Src signalling complex resulting in the transactivation of the epidermal growth factor receptor (EGFR) and downstream Akt signalling (Alvarez et al., 2009).

Even if GPR39 is not its *bona fide* receptor moiety, radiolabeled obestatin can bind in a specific and saturable manner with a subnanomolar affinity on HIT-T15 and INS-1E β-cell membranes (Granata et al., 2008). At higher doses (10–100 M), it can also inhibit ^{125}I–glucagon-like peptide-1 and ^{125}I-Tyr4–acylated ghrelin binding to β-cell membranes. In the same cellular models, obestatin exerts proliferative, survival, and antiapoptotic effects under serum-deprived conditions and interferon-γ/tumor necrosis factor-α/interleukin-1β treatment, particularly at pharmacologi-

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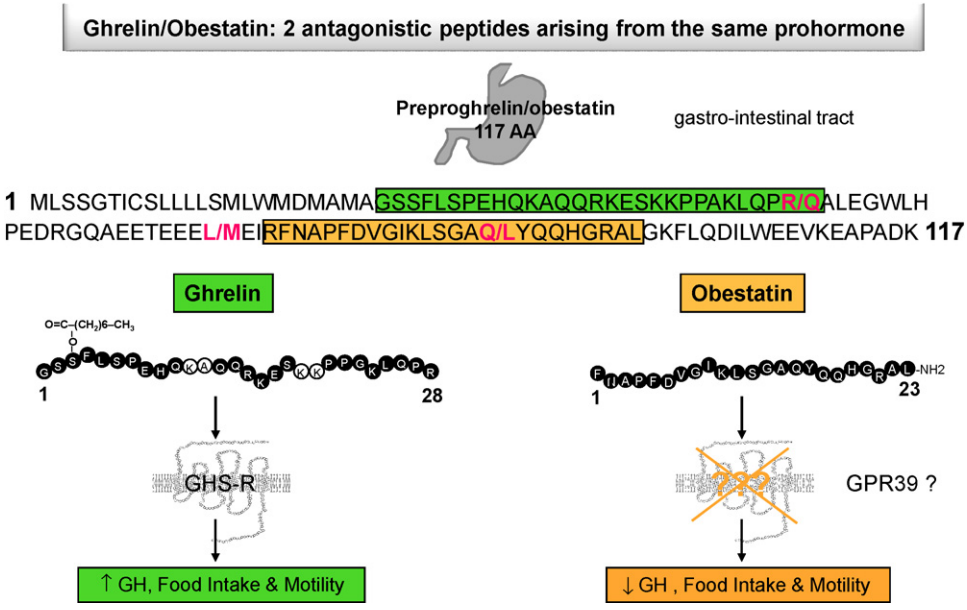

Fig. 1. The ghrelin/obestatin system. Ghrelin (green box) and obestatin (orange box) are cleaved from the same 117 amino-acid precursor. The three single nucleotide polymorphisms in the sequence of preproghrelin are indicated in red. Ghrelin stimulates GH secretion, appetite and gastric motility through the GHS-R receptor. Obestatin has been reported to decrease ghrelin-induced GH secretion, food intake and gut motility but these effects are not always observed and, despite initial claims that GPR39, an orphan GPCR closely related to GHS-R was involved, the receptor of obestatin remains to be determined. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

cal concentrations. Obestatin also mediates proliferation of human retinal pigment epithelial cells by MEK/ERK 1/2 phosphorylation in a dose-dependent manner (Camiña et al., 2007).

As for the demonstration of the nature of its receptors, obestatin physiological effects appear difficult to reproduce. Indeed, a very comprehensive study could not observe any effect of obestatin, injected either peripherally or centrally, on food intake, body weight, body composition, energy expenditure, locomotor activity, respiratory quotient, basal of ghrelin-stimulated GH secretion or the expression of hypothalamic neuropeptides involved in energy balance regulation (Nogueiras et al., 2007). Similarly, central obestatin administration did not modify either spontaneous or ghrelin-induced food intake in both ad libitum and food restricted rats (Seoane et al., 2006) and neither intravenous nor intracerebroventricular administration of obestatin affected the secretion of basal GH, PRL, TSH and ACTH secretion nor ghrelin- or GHRH-induced GH secretion in rats (Yamamoto et al., 2007).

On the other hand, obestatin effectively blunted the hunger caused by short-term starvation in young-adult male rats and it inhibited feeding but did not modulate basal or hexarelin-stimulated GH and spontaneous corticosterone secretion in 10-day-old rats (Bresciani et al., 2006). In mice, acute administration of obestatin (10–100 nmol/kg i.p.) inhibited feeding and similar effects were observed in lean and fatty Zucker rats (Lagaud et al., 2007). Interestingly, dose–response relationships were U-shaped such that both low and high doses were without effect in either species. A similar U-shaped dose-response was also observed on gut motility: at subnanomolar doses, obestatin (0.1–1 nM) reduced by half the ability of ghrelin (1 μM) to facilitate electrical field stimulation-evoked contractions of the stomach (Bassil et al., 2007). However, at higher concentrations (10–1000 nM), changes were not statistically significant. Such peculiar dose-responses may explain the difficulties in reproducing the effects of obestatin as reported in the literature.

We recently confirmed that obestatin inhibits exogenous ghrelin actions on food intake and demonstrated that it also antagonizes its actions on GH secretion (Zizzari et al., 2007). To determine how plasma ghrelin/obestatin ratio is correlated to GH secretion and food intake, we developed sensitive immunoassays to measure ghrelin and obestatin pulsatile secretions in freely behaving rats and mice. Whereas fasting resulted in elevated ghrelin levels, obestatin levels were significantly reduced, suggesting that both hormones may be differentially regulated. Obestatin administration per se did not modify food intake. However, it inhibited ghrelin orexigenic effect that were evident 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 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, taking advantage of a GHRH-GFP mouse model. Patch-clamp recordings in slices from mediobasal hypothalamus GFP transgenic mice indicated that ghrelin clearly decreased GABAergic transmission in 44% of recorded neurons ($n = 84$) but did not affect glutamatergic transmission. Obestatin had no effect on glutamatergic or GABAergic synaptic transmission but it blocked ghrelin-induced decrease of GABA responses. Therefore, the balance between endogenous ghrelin and obestatin appears essential to maintain a homeostatic state of these neuroendocrine systems.

Interactions between ghrelin and obestatin may be relevant in term of eating disorders such as anorexia nervosa (Table 1) which affects 0.3% of young girls with a mortality of 6% per decade and is strongly familial with genetic factors (Hoek, 2006; Sullivan, 1995). The peak age of onset is between 15- and 19-year-old and the course of the disease is often marked by crossover to bulimia nervosa, mainly occurring within the first 5 years (Tozzi et al., 2005). Most studies on genetic factors focussed on the serotonin system but genes involved in the regulation of feeding and energy metabolism, including the ghrelin/obestatin system, are also good candidates (Ramoz et al., 2007). Intravenous administration of ghrelin to healthy human subjects increases subjective appetite and energy intake (Wren et al., 2001). Circulating ghrelin levels are