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Review

The expanding roles of the ghrelin-gene derived peptide obestatin in health and disease

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ABSTRACT

Obestatin is a 23 amino acid, ghrelin gene-derived peptide hormone produced in the stomach and a range of other tissues throughout the body. While it was initially reported that obestatin opposed the actions of ghrelin with regards to appetite and food intake, it is now clear that obestatin is not an endogenous ghrelin antagonist, but it is a multi-functional peptide hormone in its own right. In this review we will discuss the controversies associated with the discovery of obestatin and explore emerging central and peripheral roles of obestatin, which includes adipogenesis, pancreatic homeostasis and cancer.

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Contents

1. Introduction

A little more than a decade ago, Kojima et al. (1999) successfully isolated the 28 amino acid growth hormone releasing peptide, ghrelin, from the stomach. As reviewed in this special issue of *Molecular and Cellular Endocrinology*, the discovery of ghrelin sparked a large number of studies investigating the role of ghrelin and its receptor in disease. In this review article, we will highlight what is known about the recently discovered ghrelin gene-derived peptide, obestatin.

2. The controversial discovery of obestatin

Using comparative genomics analysis, Zhang et al. (2005) revealed that the ghrelin gene region that encodes the 66 amino acid, C-terminal region of preproghrelin contained a conserved region flanked by convertase cleavage sites, hinting that it may harbour a peptide hormone. Indeed, they found that a 23 amino acid peptide, obestatin, was derived from this region (Fig. 1) and it was named obestatin (derived from obese and statin) to indicate that it was anorexigenic, opposing the function of ghrelin on food intake (Zhang et al., 2005). Obestatin is thought to arise through the post-translational cleavage of the ghrelin preprohormone (Zhang et al., 2005). It is also possible that novel, specific obestatin-coding transcripts may be translated (Seim et al., 2007), although the

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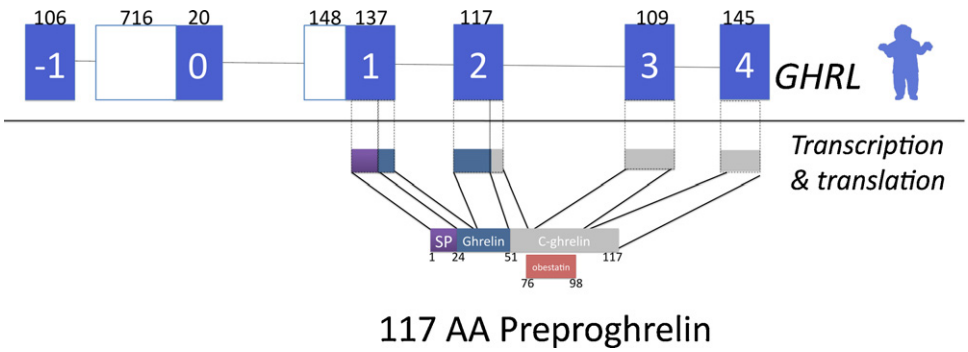

Fig. 1. Schematic genomic organisation of the human ghrelin gene and the preproghrelin coding exons. The exons shaded in white indicate extended exons. Exon sizes (bp) are shown above each exon. The regions of preproghrelin are indicated by different colours.

contribution of these transcripts to obestatin peptide expression may be negligible (Volante et al., 2009). Like ghrelin, the stomach is the primary site of obestatin expression (Zhang et al., 2005), and obestatin is produced in the same endocrine cell type as ghrelin (Granata et al., 2008; Gronberg et al., 2008, 2010; Guo et al., 2008; Zhao et al., 2008; Tsolakis et al., 2009; Volante et al., 2009; Morash et al., 2010). This finding suggested that obestatin was an endocrine gut hormone, primarily acting on the brain (Fig. 2).

While the initial discovery of obestatin was an exciting finding in the ghrelin field, it has since met with some controversy, particularly regarding its effect on food intake. The original study reporting the discovery and function of obestatin demonstrated that intraperitoneal or intracerebroventricular injection of obestatin inhibited food intake and reduced body weight in mice (Zhang et al., 2005). The effects of obestatin on feeding have been confirmed by independent investigators (Bresciani et al., 2006; Green et al., 2007; Nagaraj et al., 2008, 2009; Zhang et al., 2008a; Brunetti et al., 2009, 2010), however, the majority of studies suggest that obestatin does not have anorexigenic effects, regardless

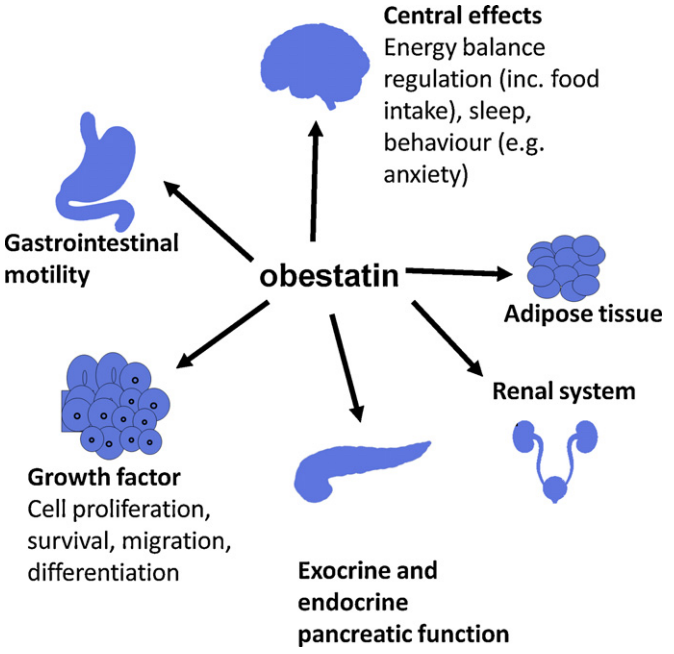

Fig. 2. Known and putative functions of obestatin. The effects of obestatin may be endocrine, paracrine, or autocrine. The biological effects may be direct, resulting from obestatin binding its receptor on target cells, or indirect. Indirect effects can results by obestatin conveying vagal afferent information by interacting with its cognate receptor on vagal neurons, or by secretion of other hormones that are able to reach the target tissue.

of injection site (Gourcerol et al., 2006; Lauwers et al., 2006; Sibilia et al., 2006; Bassil et al., 2007; Chartrel et al., 2007; De Smet et al., 2007; Holst et al., 2007; Nogueiras et al., 2007; Samson et al., 2007; Tremblay et al., 2007; Yamamoto et al., 2007; Zizzari et al., 2007; Kobelt et al., 2008; Mondal et al., 2008; Unniappan et al., 2008; Van Dijck et al., 2009). The initial description of obestatin also reported that it inhibited gastrointestinal motility (Zhang et al., 2005) (Fig. 2), however, a number of subsequent studies failed to replicate this effect (Gourcerol et al., 2006; Bassil et al., 2007; Yamamoto et al., 2007; Chen et al., 2008, 2010; Depoortere et al., 2008). Recent studies by Inui and colleagues, however, demonstrated that intravenously administered obestatin could inhibit gastrointestinal motility, acting via corticotropin-releasing factor (CRF) receptors in the hypothalamic nuclei of the brain (Ataka et al., 2008; Fujimiya et al., 2008). Studies into obestatin levels in obesity have reported inconsistent findings, with both elevations in obestatin levels and reductions in plasma obestatin being associated with obesity and overweight (Hassouna et al., 2010; Zhang et al., 2011). The large number of divergent observations regarding the actions of obestatin may have arisen as a result of major, or perhaps subtle, differences in the various *in vivo* and *in vitro* experimental models employed to date. Conflicting results in the obestatin field may also partly be due to the lack of stability of the obestatin peptide and its short half-life (Vergote et al., 2008). It is clear that much research is needed to clearly define the role of obestatin as a hormone involved in body weight regulation and gastrointestinal motility.

Obestatin may also have other effects unrelated to food intake, including emerging roles in memory improvement and the reduction of anxiety (Carlini et al., 2007) and regulation of metabolism and sleep during torpor (mediated centrally by acting on the brain) (Szentirmai and Krueger, 2006; Szentirmai et al., 2009). Obestatin may also inhibit thirst (Samson et al., 2007, 2008) (Fig. 2), although this effect was not observed in an independent study (Van Dijck et al., 2009). Like ghrelin, obestatin may play an immunomodulatory role and it protects against the development of pancreatitis in a curulein-induced rat model (Ceranowicz et al., 2009).

It was initially reported that GPR39 (G-protein coupled receptor 39), a member of the ghrelin receptor-family, was the obestatin receptor (Zhang et al., 2005, 2008a). Studies by other research groups have failed to reproduce these findings, however, and it is now appreciated that GPR39 is not a cognate receptor for obestatin (Lauwers et al., 2006; Chartrel et al., 2007; Holst et al., 2007; Yasuda et al., 2007). It was recently reported that obestatin binds the GLP-1R (glucagon-like peptide 1 receptor) in cultured β-cells (Granata et al., 2008). A subsequent study, however, showed that obestatin did not bind GLP-1R, nor displace the GLP-1 ligand, in GLP-1R overexpressing cells (Unniappan et al., 2008). Interestingly, it has recently been demonstrated that intravenously administered obestatin activates corticotropin-releasing factor (CRF) receptor 1

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