Biochemical properties and biological actions of obestatin and its relevance in type 2 diabetes

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ABSTRACT
Obestatin was initially discovered in rat stomach extract, and although it is principally produced in the gastric mucosa, it can be found throughout the gastrointestinal tract. This 23-amino acid C-terminally amidated peptide is derived from preproghrelin and has been ascribed a wide range of metabolic effects relevant to type 2 diabetes. Obestatin reportedly inhibits gastrointestinal motility, reduces food intake and lowers body weight and improves lipid metabolism. Furthermore, it appears to exert actions on the pancreatic β-cell, most notably increasing β-cell mass and upregulating genes associated with insulin production and β-cell regeneration, with relevance to type 2 diabetes. It is becoming evident that obestatin also exerts pleiotropic effects on the cardiovascular system, possibly modulating blood pressure, endothelial function and triggering cardioprotective mechanisms, which may be important in determining cardiovascular outcomes in type 2 diabetes. Furthermore, it seems that like other gut peptides obestatin has neuroprotective properties. This review examines the biochemical properties of the obestatin peptide (its structure, sequence, stability and distribution) and the candidate receptors through which it may act. It provides a balanced examination of the reported pancreatic and extra-pancreatic actions of obestatin and evaluates its potential relevance with respect to diabetes therapy, together with discussion of direct evidence linking alterations in obestatin signalling with obesity/diabetes and other diseases.

1. Introduction
Globally more than 400 million people are affected by type 2 diabetes mellitus (T2DM) but the rising incidence and decreasing age of onset has led to the prediction that there will be 642 million T2DM patients by 2040 [1]. Despite the range of available treatment options, diabetes is still a leading cause of global mortality, with cardiovascular complications e.g. atherosclerosis, nephropathy, stroke, the most common underlying factor, increasing risk of death by approximately 4-fold [2].

Human peptide hormones have played a key role in advancing the available pharmacological agents for treatment of T2DM and its complications. Perhaps the most significant example of this in the clinic has been the exploitation the incretin hormone system. Diabetic patients routinely receive either drugs which are agonists of the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) or drugs which inhibit the primary incretin inactivating enzyme (called dipeptidylpeptidase-4 (DPP-4)) [3]. Remarkably, the global market for incretin-based therapeutics was valued at nearly $12.7 billion in 2014.

The incretin hormones were discovered in the 1970s (in the case of glucose-dependent insulinotropic peptide, GIP) and the 1990s (in the case of GLP-1) and represent an important example of how investing resources in the discovery and investigation of peptide hormones can impact greatly on the treatment of human disease. In this regard, it has been more than 10 years since the discovery of a gastrointestinal peptide called obestatin, and this review article will evaluate what is currently known about this peptide with an emphasis on its actions in relation to T2DM.

References
2. An overview of the peptide obestatin

2.1. Biochemical properties

Obestatin is a 23-amino acid peptide which is post-translationally modified with a C terminal amide group on Leu$^{23}$. The peptide is derived from the same 117-residue prepropeptide as ghrelin [4]. As with many regulatory peptides, the presence of a C-terminal amide group is thought to have functional significance. In the case of obestatin, it was initially suggested to be essential for receptor binding [4], although it has since been demonstrated to be important for stabilising the peptide’s overall conformation [5]. Using nuclear magnetic resonance and circular dichroism spectroscopy, Subasinghage et al. [6] found that in pure water solution human obestatin peptides do not possess secondary structural features. However, in a 2,2,2-trifluoroethanol:water mixture, obestatin (1–23) forms an α-helix followed by a single turn helix conformation between residues Pro$^{4}$ and Gln$^{15}$ and His$^{19}$ and Ala$^{22}$, respectively (Fig. 1). Obestatin (1–10) had no structural components whereas obestatin (11–23) formed an α-helix between residues Val$^{14}$ and Ser$^{20}$ (Fig. 1). Similar structural studies confirmed that both human and mouse obestatin adopt α-helical conformations [7]. In fact, various fragments of human obestatin: (6–23), (11–23) and (16–23)), adopted an α-helical conformation despite not sharing contiguous amino acid sequences [7].

2.2. Conservation of the obestatin amino acid sequence

A close examination of obestatin amino acid sequences across species finds it to be relatively well conserved (Table 1) suggesting that this peptide is functionally important. Human and primate sequences are identical, and those from rodents, dogs and cats share 87% sequence similarity, whilst pig, goat and sheep sequences are 70–74% similar to human. Sequence similarities for bovine (65%) and avian species (emu, chicken, goose and duck (48–57%)) are significantly lower. Even among the non-conserved amino acids there are in fact several which are structurally or biochemically similar to one another (e.g. alanine$^3$/valine$^6$; leucine$^1$/isoleucine$^1$; serine$^2$/thereonine$^2$ and glutamine$^8$/glutamic acid$^{18}$) further underlining the conserved nature of this peptide.

2.3. Stability of obestatin

Obestatin is proteolytically degraded by the action of a number of proteases, particularly aminopeptidases and post-prolyl endopeptidases, and evidently occurs in blood plasma, and in tissue preparations from liver and kidney [8]. Degradation is apparently very rapid although the reported half-lives in the published literature vary markedly. For example, the half-life of native mouse obestatin in mouse plasma is reported to be 42.2 min, compared with 12.6 min in liver and 138 min in kidney membranes [8], whilst the half-life of rodent obestatin in rat liver homogenate was found to be 21.7 min [9]. With particular regard to potential therapeutic application, it is possible to markedly extend the half-life of obestatin by chemically modification. For example, the addition of a polyethylene glycol (PEG) group to the N-terminus of obestatin increased half-life by more than 3-fold [9], whilst combination of N-terminal PEG modification with amino acid substitutions further extended half-life by as much as 17-fold [10].

2.4. Physiological distribution of obestatin

The physiological production of obestatin is principally confined to the gastrointestinal tract [11] but it is also known to be produced in the brain [12], testis [13] and mammary glands [14]. Whilst obestatin is found in the gastrointestinal tract of rodents in pancreas and duodenum, expression predominates in the gastric mucosa with specific localisation in A-like cells and oxyntic glands [11]. Studies in human tissue have reported similar expression profiles with the majority of obestatin production in the gastrointestinal tract, mainly in the stomach, but also in the duodenum, jejunum and ileum, with notable absence from the colon [14]. Within the human intestine, obestatin is specifically found in the crypts of Lieberkuhn and Brunner’s glands, but interestingly it was also detected on the periphery of the pancreatic islets and the exocrine pancreatic ducts [14]. Its presence here lends some support to reports that obestatin has positive effects on β-cells and islets, which are discussed later in this review article.

2.5. Possible receptors for obestatin-mediated effects

A number of potential receptors have been proposed as the cognate receptor for obestatin, however, at the present time there is no consensus among researchers as to its identity. Nonetheless, there is good evidence that obestatin signalling is mediated via G protein-coupled receptors (GPCRs). Detailed studies employing a range of intracellular pathway inhibitors demonstrate that obestatin-mediated effects (within
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