Peptides 31 (2010) 357–369

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Review

Ghrelin, des-acyl ghrelin and nesfatin-1 in gastric X/A-like cells: Role as regulators of food intake and body weight

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ARTICLE INFO

Article history:
Received 18 September 2009
Received in revised form 12 November 2009
Accepted 16 November 2009
Available online 26 November 2009

Keywords:
Body weight
Endocrine cell
Food intake
Ghrelin
Nesfatin-1
NUCB2
Obesity
Stomach

ABSTRACT

Numerous peptides released from endocrine cells in the intestinal mucosa were established early on to be involved in the physiological regulation of food intake with a prominent role in termination of food ingestion when nutrients pass along the intestinal tract. Recently, peptides released from X/A-like endocrine cells of the gastric oxyntic mucosa were recognized as additional key players in the regulation of feeding and energy expenditure. Gastric X/A-like cells release the octanoylated peptide, ghrelin, the only known peripherally produced hormone stimulating food intake through interaction with growth hormone secretagogue 1a receptor (GHS-R1a). Additionally, non-octanoylated (des-acyl) ghrelin present in the circulation at higher levels than ghrelin is currently discussed as potential modulator of food intake by opposing ghrelin's action independent from GHS-R1a although the functional significance remains to be established. Obestatin, a ghrelin-associated peptide was initially reported as anorexigenic modulator of ghrelin's orexigenic action. However, subsequent reports did not support this contention. Interesting is the recent identification of nesfatin-1, a peptide derived from the nucleobindin2 gene prominently expressed in gastric X/A-like cells in different vesicles than ghrelin. Circulating nesfatin-1 levels vary with metabolic state and peripheral or central injection inhibits dark phase feeding in rodents. Overall, these data point to an important role of gastric X/A-like cells in food intake regulation through the expression of the orexigenic peptide ghrelin along with des-acyl ghrelin and nesfatin-1 capable of reducing food intake upon exogenous injection although their mechanisms of action and functional significance remain to be established.

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0196-9781/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.peptides.2009.11.019

1. Introduction

Several enteroendocrine cells scattered within the intestinal mucosa [114] have been recognized early on to influence food intake by releasing peptide hormones in response to changes in nutritional status [57,77,101] while endocrine cells in the gastric mucosa were mainly implicated in the regulation of acid secretion [34]. The gastric endocrine cells encompass enterochromaffin-like cells releasing histamine (ECL, 30% in human and 65% in the rat), gastrin-producing cells (G cells), somatostatin-containing cells (D cells >20% of gastric oxyntic endocrine cells in humans and 5-10% in rats), and the less abundant serotonin-containing enterochromaffin (EC) cells (Fig. 1) [113,114]. In addition, there is a distinct 5th endocrine cell type without connection to the lumen (closed-type) distributed throughout the gastric oxyntic glands that was labeled as P/D_1 cell in humans and X/A-like cell in rats due to similarity with the rat pancreatic A-cell [21]. This cell type accounts for up to 20–30% of the oxyntic endocrine cell population and represents the second most frequent type among the gastric endocrine cells [21,114]. Their content and function remained largely unknown until ghrelin was identified in rat X/A-like and human P/D_1 cells as the only peripherally produced and centrally acting peptide hormone known so far to increase food intake [84,115]. This seminal discovery revealed that the gastric mucosa contains endocrine cells able to influence food consumption by the release of a specific peptide as previously identified in the intestinal mucosa. Of functional relevance was the subsequent demonstration of interaction between ghrelin and anorexigenic peptides produced by intestinal endocrine cells such as cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide 1 (GLP-1) (for review see [77,101]).

Furthermore, the last years witnessed the identification and characterization of additional gene products within the X/A-like cells also able to influence food intake. These include peptides resulting from differential post-translational modifications of proghrelin (non-octanoylated ghrelin or des-acyl ghrelin and *n*-decanoyl ghrelin) [59,63], distinct potential processing of the ghrelin gene (obestatin) [164] or the processing of a distinct gene such as nucleobindin2 (nesfatin-1) [137]. Recent functional reports indicate the reduction of food intake induced by exogenous administration of des-acyl ghrelin [9,31] and nesfatin-1 [132] whereas the action of obestatin remains largely equivocal [49]. In the present review we will highlight gastric X/A-like cells and the actions of peptides processed in these cells on food intake and modalities pursued targeting these peptides for potential novel therapeutic venues in the treatment of obesity with emphasis on recent developments.

2. Ghrelin

Ghrelin (also known as acyl ghrelin or octanoylated ghrelin) was discovered in 1999 by Kojima and colleagues as the

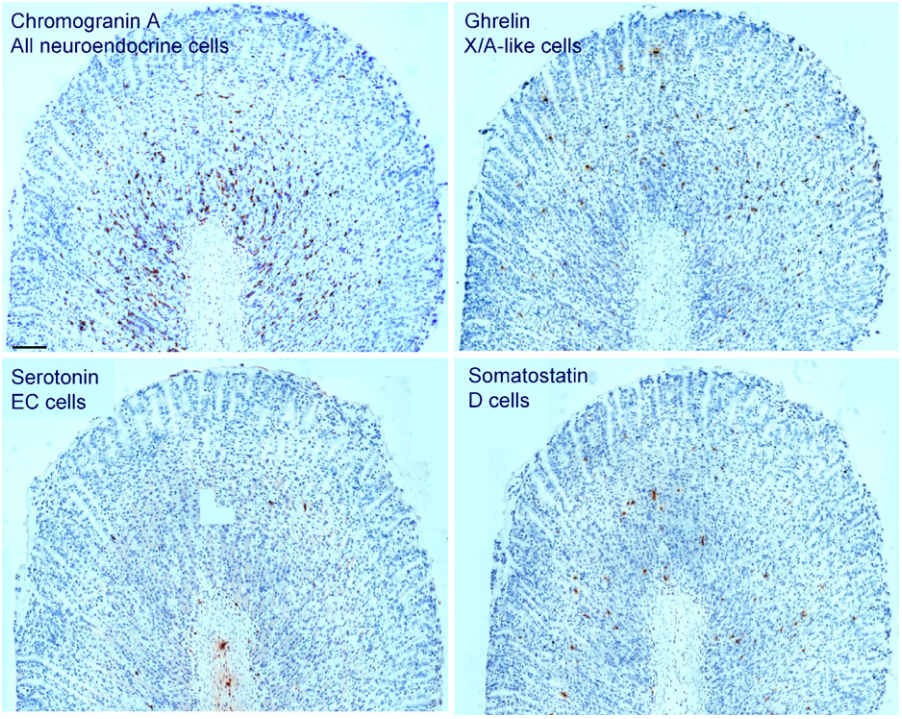

Fig. 1. Immunohistochemical picture of neuroendocrine cells in the rat gastric oxyntic mucosa of *ad libitum* fed male rats. While the majority of neuroendocrine cells reside in the lower part of gastric glands, ghrelin positive X/A-like cells are evenly distributed throughout the entire length of the glands. Somatostatin-positive D cells are mostly localized in the lower half of the oxyntic glands. Serotonin-positive EC cells are rare. Scale bar represents 100 μm.

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