Molecular and Cellular Endocrinology 418 (2015) 33–41

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

The role of pancreatic polypeptide in the regulation of energy homeostasis

Neeta Khandekar [a], Britt A. Berning [a], Amanda Sainsbury [b], Shu Lin [a, c, *]

[a] Neurological Diseases Division, Research Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia
[b] The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, Sydney Medical School, The University of Sydney, NSW 2006, Australia
[c] School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia

ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form
16 March 2015
Accepted 3 June 2015
Available online 27 June 2015

Keywords:
Pancreatic polypeptide (PP)
Neuropeptide Y (NPY)
Food intake
Neuronal pathway

ABSTRACT

Imbalances in normal regulation of food intake can cause obesity and related disorders. Inadequate therapies for such disorders necessitate better understanding of mechanisms that regulate energy homeostasis. Pancreatic polypeptide (PP), a robust anorexigenic hormone, effectively modulates food intake and energy homeostasis, thus potentially aiding anti-obesity therapeutics. Intra-gastric and intra-intestinal infusion of nutrients stimulate PP secretion from the gastrointestinal tract, leading to vagal stimulation that mediates complex actions via the neuropeptide Y4 receptor in arcuate nucleus of the hypothalamus, subsequently activating key hypothalamic nuclei and dorsal vagal complex of the brainstem to influence energy homeostasis and body composition. Novel studies indicate affinity of PP for the relatively underexplored neuropeptide y6 receptor, mediating actions via the suprachiasmatic nucleus and pathways involving vasoactive intestinal polypeptide and insulin like growth factor 1. This review highlights detailed mechanisms by which PP mediates its actions on energy balance through various areas in the brain.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

The increasing threat of obesity has gripped the world as an important health issue. Present studies have estimated that the number of overweight and obese individuals in the world have increased to 2.1 billion in 2013 as against 857 million in 1980 (Ng et al., 2014). Obesity is considered to be a consequence of excessive food intake and/or decreased physical activity and reduced energy expenditure, leading to excessive fat accumulation that often impairs wellbeing. Thus, understanding the regulation of appetite and energy intake or energy expenditure is seen as a potential avenue for the prevention and management of the global obesity epidemic.

Knowledge about appetite regulation has greatly advanced over the last few decades. Studies conducted in this area have unraveled complex pathways involving bidirectional neurohumoral communication systems that allow communication between the gut and the brain. Signals relating to nutritional and energy status are continually relayed between the gut and the central nervous systems to regulate appetite (hunger and satiety). Continued investigations and research into the modulation of appetite have uncovered the complex endocrine and neurological systems that comprise the gut–brain axis. As physiological regulators of appetite, gut hormones offer an attractive therapeutic target for the treatment of obesity. Meal size and overall energy intake are controlled by a series of short- and long-term hormonal and neural signals that are derived from the gastrointestinal tract (Cummings and Overduin, 2007; Perry and Wang, 2012). Besides regulating energy intake, these hormonal and neural signals function together to optimize the processes of digestion and absorption of nutrients from the gut. The most studied gut hormones in this regard are cholecystokinin (CCK), polypeptide YY (PYY), glucagon-like peptide-1 (GLP-1), oxyntomodulin and ghrelin (Chaudhri et al., 2006). With the exception of ghrelin, which functions as a 'hunger hormone' (Inui et al., 2004; Castaneda et al., 2010; Sakata and Sakai, 2010; Al Massadi, Lear et al., 2014), these gut-derived hormones act to suppress hunger, induce satiety and decrease food intake (Malaisse-Lagae et al., 1977; Lieverse et al., 1995; Gutzwiller et al., 1999; Naslund et al., 1999; Keire et al., 2000; Batterham et al.,

* Corresponding author. Neuroscience Research Program, Garvan Institute of Medical Research, St Vincent Hospital, 384 Victoria Street, Darlinghurst, NSW 2010, Australia.
E-mail address: s.lin@garvan.org.au (S. Lin).

http://dx.doi.org/10.1016/j.mce.2015.06.028
0303-7207/© 2015 Elsevier Ireland Ltd. All rights reserved.

2003; Dakin et al., 2004; Little et al., 2005; Wynne et al., 2005; Lumb et al., 2007).

The mechanisms by which gut hormones modify feeding have been areas of great interest. Local effects such as the inhibition of gastric emptying are thought to contribute to the decrease in energy intake in response to gut satiety factors (Sturm et al., 2004; Xu et al., 2005; Chaudhri et al., 2006). Activation of mechanoreceptors as a result of gastric distension may further inhibit food intake via neural reflex mechanisms that work in conjunction with gut hormones (Valenzuela and Defilippi, 1981; MacIntosh et al., 2001). However, in more recent years our understanding of central neuronal pathways has changed the view that gut hormones mediate effects on satiety predominantly via local effects on the gut, and research efforts in the past decade have focused on the role of the brain in mediating effects of gut hormones on energy intake and energy homeostasis. The importance of the brain–gut axis in the modulation of food intake is suggested by the dual role exhibited by gut peptides, which act as both hormone and neurotransmitter (Chaudhri et al., 2006). Indeed, certain circulating gut hormones have been shown to not only act as endocrine hormones exerting effects over distant target organs via classic hormone pathways, but to also be secreted locally and act directly on neurons in hypothalamic and brainstem centers to control satiety (Lin et al., 2009). Gut hormones have been shown to act on the extensive reciprocal connections that exist between hypothalamic and brainstem areas and the hypothalamic paraventricular nucleus and other centers in the central nervous system that control energy homeostasis (Ter Horst, Luiten et al., 1984; Ter Horst, de Boer et al., 1989). While there is a reasonable level of knowledge about the mechanisms via which CCK, PYY, GLP-1, oxyntomodulin and ghrelin induce their effects, there has been relatively little work on pancreatic polypeptide (PP), another gut-derived hormone that is known to reduce food intake and influence energy balance and body composition. Thus, this review will focus specifically on how PP interacts with central pathways to mediate effects on food intake. Before looking into these mechanisms, it is important to first provide an overview of the biology of PP, from where is it secreted to what effects it mediates.

2. Distribution of PP in the gastrointestinal system

Before describing the role that PP plays in the regulation of energy homeostasis, it is important to note the distribution of PP in the gastrointestinal system. It is also important to provide insight into the group of peptides to which PP belongs, how it interacts with other peptides in that family, and the structural features that contribute to its function.

2.1. The NPY family and the structural significance of PP

PP is a member of the neuropeptide Y (NPY) family that is characterized by three peptides (PP, PYY and NPY) with an amidated carboxyl terminus that results in a hairpin fold referred to as the 'PP-fold' (Cabrele and Beck-Sickinger, 2000; Ekblad and Sundler, 2002). Electromagnetic resonance, X-ray crystallography and other studies have shown that this 'PP-fold' is a tightly organized tertiary structure that is crucial to the physiological functioning and maintenance of biological activities of members of the NPY family (Germain et al., 2013). PP was the first member of this family to be isolated (Kimmel et al., 1975), and is the least evolutionarily conserved of all three members of the NPY family (Blomqvist et al., 1992; Conlon, 2002).

2.2. Relevance of PP and other peptides of NPY family in the gastrointestinal system

The NPY-ergic system has been one of the key targets for research into the prevention and treatment of obesity and related feeding disorders. Studies have shown that while NPY stimulates appetite and reduces energy expenditure, PYY and PP are produced in response to food intake and have opposite effects on appetite or energy expenditure to those induced by NPY. NPY is known as one of the most powerful orexigenic neuropeptides, while PYY and PP act in an antagonistic manner to NPY and are amongst the most effective endogenously-produced satiety hormones known (McLaughlin and Baile, 1981; Taylor and Garcia, 1985; Katsuura et al., 2002; Batterham et al., 2006; le Roux et al., 2006). The peptides in this family induce their effects on energy homeostasis by binding to G-protein coupled receptors, with mammals possessing the subtypes Y1, Y2, Y4, Y5 and y6, as will be outlined in more detail in a subsequent section. While members of the NPY family interact with each other and a common receptor system, these interactions are not limited to the NPY family, as their interactions with other gut hormones (Briggs et al., 2010; Kohno and Yada, 2012; Wang et al., 2013; Chandler-Laney et al., 2014; Schmidt et al., 2014), not discussed in this review, also contribute towards appetite regulation and energy homeostasis.

3. Expression and release of PP from the gastrointestinal tract in response to food

3.1. Location of PP-expressing cells

PP is a 36-amino acid peptide produced by specialized pancreatic islet cells called F cells, which represent approximately 10% (Bommer et al., 1980) of the volume of the pancreatic islets of Langerhans (Larsson et al., 1975; Adrian et al., 1976). Studies have shown that some PP is also produced as an exocrine hormone in the distal gut (Larsson et al., 1975; Adrian et al., 1976; Ekblad and Sundler, 2002). It has been noticed that in humans, the endocrine F cell mass is narrowly restricted to the uncinate process, along with a distinct presence in the duodenal part (the head region) of the pancreas (Orci et al., 1976; Malaisse-Lagae et al., 1977; Rahier et al., 1979; Wang et al., 2013). Observations in the bovine gut revealed relatively large numbers of F cells in the large intestine, while in rats, F cells were also observed in the colon and the rectum (Pyarokhil et al., 2012).

3.2. Release of PP in response to food intake

Evidence demonstrates that the most powerful stimulant for PP release is the intake of food (Simonian et al., 2005), particularly fat-rich food (Kojima et al., 2007; Guyenet and Schwartz, 2012). The post-prandial release of PP is proportional to energy intake, and circulating levels of PP remain elevated for up to 6 h after feeding (Adrian et al., 1976; Adrian et al., 1977). Various phases of PP release have been delineated, and it is known that PP is released into the circulatory system during both the pre-absorptive and the post-prandial phases of nutrient digestion (Schwartz et al., 1978). Thus, taken together it can be seen that the magnitude and time course of the release of PP greatly reflect both the content and size of the meal ingested. (see Fig. 1).

4. The biological effects of PP

In this section we briefly explain the role that PP plays in modulating food intake and energy homeostasis in mammals – namely rodents and humans.

Download English Version:

https://daneshyari.com/en/article/2195742

Download Persian Version:

https://daneshyari.com/article/2195742

Daneshyari.com