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Gastrointestinal satiety signals in humans — Physiologic roles for GLP-1 and PYY ?

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Abstract

The present review summarizes the appetite suppressing effects of PYY and GLP-1 in the regulation of food intake in humans. Current evidence supports a role for gastrointestinal peptides as regulators of satiety. The regulation of satiety is, however, complex and it is not surprising that multiple control systems exist. It is interesting to note that nutrients in the small intestine such as hydrolysis products of fat stimulate the release of satiety peptides such as GLP-1 or PYY that serve as satiety signals. Both peptides, released from L-cells from the gastrointestinal tract by the local action of digested food, exert various regulatory functions: stimulation of insulin secretion and inhibition of glucagon secretion as typical actions of GLP-1, inhibition of gastric emptying, and inhibition of appetite for both GLP-1 and PYY. The review focuses on the question, whether the two peptides are true endocrine factors that act as physiologic, hormonal regulators of appetite.

Keywords: PYY; GLP-1; Appetite control; Human studies

1. Control circuits in appetite and satiety

Food intake is a tightly regulated, complex system. Afferent signals provide information to the central nervous system, which is the centre for the control of satiety [1–3]. Many factors are involved in this central nervous system's regulation of appetite [3]. To rationalize all of the putative factors found to play a role, several approaches have been used to better understand the mechanisms controlling appetite and food intake.

The gastrointestinal (GI) tract processes ingested food, both mechanically and chemically, into small, absorbable units. Thus carbohydrates are processed in the stomach and small intestine into fatty acids and monosaccharides; lipids are transformed into glycerol and fatty acids; and finally, proteins are cleaved to amino acids [4]. All these digestive end products become absorbed by the body. The entire process of digestion is coordinated by interactions of the enteric nervous system that innervates the walls of the GI tract. Many gastrointestinal factors are released from specialised endocrine cells into the circulation or serve as neurotransmitters mediating signals from the enteric nervous system. These signals are transmitted from the gut to the brain and become integrated at various centres in the hypothalamus, reflecting the load of nutrients ingested [1–4]. As a group, these peptides are called satiety signals because most create a sensation of fullness in humans and reduce food intake when administered to humans or animals.

By applying classical algorithms from endocrinology to evaluate satiety signals, several criteria must be fulfilled before a hormone or neurotransmitter can be considered a satiety signal [5,6]. First, the signal must exert a reducing effect on the meal size. Second, it should evoke the opposite effect when blocked by a specific receptor antagonist, or when the respective signal is knocked-out. Third, the reduction in food intake caused by administration of such a "satiety" signal should not be the consequence of illness or malaise. Finally, the secretion of an endogenous satiety signal must be induced by ingested food, and the pharmacological profile must be related to the ingestion of meals. This last condition can only be applied to hormonal factors [5].

In humans, most meals are initiated at times that are convenient or habitual and are therefore based more on social or learned factors rather than on adjustments of energy levels within the body. This type of control allows considerable

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flexibility and individuals can adapt their meal patterns to their environment and lifestyle while still maintaining control over the amount of food eaten. The satiety system, as its name implies, determines meal size, which is equated with the phenomenon of satiety or fullness. In the following review we have attempted to apply the criteria of classical endocrinology on potential satiety signals in humans in order to provide a basis for classifying these signals as physiological satiety factors.

2. Gastrointestinal hormones as regulators of food intake

Powerful signals arise from the upper gastrointestinal tract during the course of meals. These signals include a variety of gut peptides [1–4]. The initial sites of action of these peptides are peripheral, within the gastrointestinal tract. The peptide-induced satiety messages are then transmitted to the central nervous system by afferent neurons and received in visceral sensory fields of the dorsal hindbrain. The central neural processing required transforming ascending satiety messages into appropriate behaviour (the cessation of eating) and the appropriate sensation (satisfaction) is almost entirely unknown.

The small intestine is a crucial source of satiety signals. In humans, infusion of nutrients (lipids, carbohydrates) into the small intestine is associated with suppression of food intake to a much greater extent than when the same nutrients are given intravenously [7–10]. The interaction of nutrients with specific receptors in the small intestine stimulates the release of satiety hormones such as CCK, peptide YY (PYY) or glucagon-like peptide-1 (GLP-1) [11–17]. The physiological status of these hormones as satiety factors is, however, not fully established for all of them. The criteria for a physiological endocrine role of CCK as a satiety factor have been recently reviewed by Geary [5]: 1) CCK is released during meals, mainly by digestion products of fat [18]; 2) infusion of CCK at physiological doses reduces food intake and stimulates satiety, both in animals and humans [19]; 3) a tight temporal link is present between nutrient-stimulated CCK secretion and inhibition of food intake [5]; 4) CCK1 receptor blockade antagonizes the satiating effects of exogenous CCK and reverses fat-induced inhibition of food intake (blockade of endogenous CCK) and finally, increases meal size [20]. With this information available, CCK is a physiological satiety factor. In the next sections of this short review, the same criteria will be applied to PYY and GLP-1.

3. PYY

Peptide tyrosine-tyrosine (PYY) is a gut-derived hormones. Like proglucagon-derived peptides, PYY is synthesized and released from endocrine L-cells from the distal gut in response to food consumption [21]. Fat is a strong stimulus for PYY release, whereas intravenously applied lipids have no effect on circulating PYY concentrations. PYY is converted into PYY3-36 by the enzyme dipeptidyl peptidase IV [22]. Receptors that mediate the effects of PYY belong to the NPY receptor family and include Y1, Y2, Y3, Y4, and Y5 [23,24]. Once PYY3-36 is formed, it binds with high affinity to the Y2 receptor. The hypothesis that hormonal PYY3-36 acts as a satiety factor is based on the observation that the peptide can inhibit sensations of appetite and inhibit food intake when administered into animals or humans [15,16]. The animal results were recently questioned, as several groups were unable to reproduce the satiety inducing effects [25]. In the following we discuss the PYY satiation hypothesis for humans only, because research has led to different conclusions for rodents and humans.

3.1. Secretion

In the mid-eighties, the first sensitive and specific radioimmunoassay for PYY was developed [21]; using this assay it was shown that PYY is released by meals; the prandial release is dependent on the caloric load with progressively larger increases in plasma PYY concentrations measured after ingestion of larger meals; relevant amounts in circulating PYY are measured after caloric loads of more than 1500 kcal [17,21]. At that time, the different molecular forms of PYY were unknown; the results therefore represent total PYY. When nutrients are administered separately, double cream (fat) caused a large increase, steamed cod (protein) caused a moderate increase, and glucose solution caused only a transient and minor response [21]. Long-chain fatty acids in the form of sodium oleate perfused to the small intestine into healthy males are potent secretagogues for PYY release, whereas medium-chain fatty acids are ineffective (Fig. 1, Degen and Beglinger, unpublished data). Initial results suggest that after meal intake 60–70% of circulating PYY is in the form of PYY3-36 (which is the biologically active form of the peptide in satiation) and the rest is PYY1-36 [10,11,22]. It should be noted that individual circulating forms of PYY (PYY1-36 or PYY3-36) have been measured in very few studies; therefore very little solid information is available with respect to circulating molecular forms of PYY. Nevertheless we infer from this observation that PYY3-36 is only released to large calorie meals, but sufficiently rapid after meal ingestion to function as a satiation signal in humans.

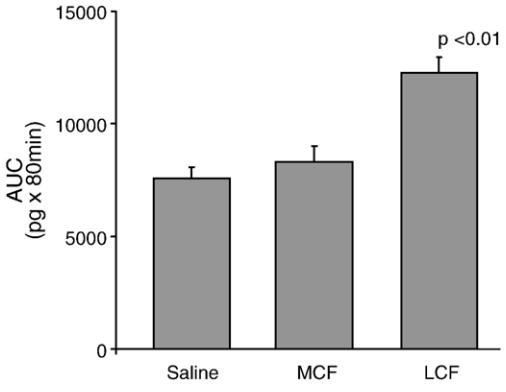

Fig. 1. Double-blind, randomized, three-way, crossover study on the effect of long-chain free fatty acids (LCF; sodium oleate, 8 mmol/h), medium-chain free fatty acid (MCF; sodium caprylate, 8 mmol/h) saline (control) perfused to the duodenum via a feeding tube on PYY release in 12 healthy male subjects. Data are presented as area under the curve (AUC) in the form of means (±SEM). LCF induced a marked and significant ($p<0.01$) increase in PYY release, whereas MCF and saline were ineffective.