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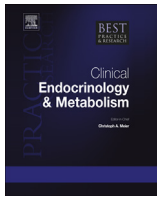

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Crosstalk between gastrointestinal neurons and the brain in the control of food intake

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Recent data have emphasized that the gastrointestinal nervous system is preponderant in the sensing of nutrients and hormones and its translation in terms of control of food intake by the central nervous system. More specifically, the gastrointestinal neural system participates in the control of hunger via the sensing of at least two major macronutrients, e.g. glucose and protein, which may control hunger sensations from the portal vein. Protein are first sensed by mu-opioid receptors present in the portal vein walls to induce intestinal gluconeogenesis-*via* a reflex arc and next portal glucose sensing. The gastrointestinal nervous system may also account for the rapid benefits of gastric bypass surgeries on energy homeostasis (hunger and body weight) and glucose homeostasis (insulin sensitivity). This knowledge provides novel mechanisms of control of body weight, which might be useful to envision future approaches of prevention or treatment of obesity.

Role of the extrinsic gastrointestinal neural system in the control of hunger

The worldwide increase in obesity and associated pathologies makes the efforts to better understand the mechanisms of control food intake and energy homeostasis crucial. The sensations of hunger and fullness are key determinants in the control of food intake. In normal individuals, there is a balance between the sensation of hunger preceding the meal and the sensation of fullness occurring after nutrient assimilation. This balance is deregulated in obesity, which makes that the sensation of fullness is inappropriately delayed or blunted [1]. The mechanisms underlying the shift from the sensation of

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hunger to the sensation of fullness after meal encompass the modulation of gastric distension, changes in gut motility and the secretion of gastrointestinal hormones as ghrelin, cholecystokinin (CCK), peptide YY_{3-36} (PYY_{3-36}) and glucagon-like peptide 1 (GLP1) [2]. It is obvious that the gastro-intestinal neural system plays a key role in the transmission of gastric distension and gut motility signals to the brain [2]. However, there is also a role for the gastrointestinal nervous system in the central or systemic effects of the hormones. It is noteworthy that the effect of the hormones is blunted after surgical ablation of the vagal-brain stem neural communication [3–6]. Indeed, the increase in food intake and secretion of growth hormone promoted by ghrelin are blunted by vagotomy [3], as is the food intake decrease initiated by CCK [4], PYY_{3-36} [5] or GLP1 [6]. Furthermore, the action of GLP1 is mediated least in part via GLP1 receptors located in the periportal neural system. Accordingly, the improvement of glucose control by GLP1 is attenuated upon antagonizing the GLP-1 receptor in the portal vein [6]. Recently, data have suggested that lipids deriving from food might modulate endogenous glucose production via the gastrointestinal nervous system [7]. The mechanisms by which macronutrients are sensed by the extrinsic gastrointestinal neural system to modulate food intake are reviewed herein.

Glucose portal sensing as a modulator of food intake

The rate of glucose appearance in the portal vein during the digestion of a carbohydrate-meal representative of current human nutrition (about 50% of calories as carbohydrates) is higher than the rate of total endogenous glucose production (EGP). Thus, it has long been hypothesized that glucose might induce satiation in the course of meal digestion. In line with this rationale, glucose infusions into the portal vein at a rate equivalent to EGP decrease food intake in previously fasting rats [8,9]. Glucose infusion into the portal vein at these rates also initiates a wide array of physiological and behavioral responses, including an acquisition of food preference and an alteration of the electrical activity of vagal and spinal afferents and of hypothalamic neurons (see 10 for a review). However, portal glucose infusion at lower rates (one sixth of EGP) is sufficient to initiate both a limitation of food intake and the activation of hypothalamic nuclei, as revealed by C-FOS labeling, in rats [10,11]. Whilst portal glucose infusion might represent what occurs during the postprandial period, various arguments have suggested that the portal delivery of glucose does not determine the termination of an ongoing meal but, instead, drives the size of the following meal [12]. This has suggested that portal glucose sensing might be related to satiety, rather than to satiation.

Recently, the molecular mechanism involved in the sensing of glucose appearance at low rates in the portal vein was deciphered. A putative role of taste receptors or of Glut 2 (the glucose transporter responsible for glucose sensing in the beta-cell) could be ruled out. Indeed, mice deficient for the transient receptor potential melastin 5 (Trmp5, a protein required for the transmission of the taste receptors signal) and mice deficient in Glut2 both retained the sensitivity to the satiety action of protein-enriched diets [13]. A body of arguments allowed us to suggest that the sodium-glucose co-transporter 3 (SGLT3) could be responsible for portal glucose sensing-initiated events. This includes: the inhibition of portal glucose sensing by phloridzin (a specific inhibitor of SGLTs); the activation of portal glucose sensing by α-methyl-glucose (a non-phosphorylable analog of glucose), which is transported by SGLT 1 and 2 and binds to SGLT3; and the absence of effect of 3-0-methylglucose, which is transported by SGLT1 and 2, but does not bind to SGLT3 [14]. It must be noted that afferents to the brain innervating the portal vein may travel via both the common hepatic branch and the celiac branch of the vagus nerve, but also via the dorsal root spinal way 15]. It is noteworthy that the portal glucose signal was not ablated by surgical vagotomy of the common hepatic branch 13], whereas it was suppressed by periportal capsaicin application that inactivates all the vagal and the spinal afferents to the brain [11]. This suggests that the portal glucose signal might also travel along the vagal celiac branch or the spinal way [13], whereas an accepted dogma is that it should be conveyed by the ventral vagus [15].

The portal glucose signal mediates protein-induced satiety

The mechanisms by which dietary proteins exert their satiety effect have long been unexplained. That the decreased food intake could be due to a conditioned taste aversion, malaise or low palatability of the diet could be excluded [11]. A role of the hypothalamic melanocortin system has also been ruled