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News and Reviews

Vagal afferents sense meal-associated gastrointestinal and pancreatic hormones: Mechanism and physiological role

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ABSTRACT

Some gastrointestinal and pancreatic hormones are potently secreted by meal intake and reduce food intake, therefore these hormones play a role in the meal-evoked satiety peptides. Previous reports have demonstrated that peripheral administration of these gastrointestinal or pancreatic hormones decrease feeding and the anorectic effects are abolished by lesions of vagal afferent nerves using surgical or chemical protocols, indicative of the involvement of the vagal afferents. Vagal afferent nerves link between several peripheral organs and the nucleus tractus solitarius of the brainstem. The present review focuses on cholecystokinin, peptide YY_{3-36}, pancreatic polypeptide, and nesfatin-1 released from endocrine cells of the gut and pancreas. These hormonal peptides directly act on and increase cytosolic Ca^{2+} in vagal afferent nodose ganglion neurons and finally suppress food intake via vagal afferents. Therefore, peripheral terminals of vagal afferents could sense gastrointestinal and pancreatic hormones and regulate food intake. Here, we review how the vagal afferent neurons sense a variety of gastrointestinal and pancreatic hormones and discuss its physiological significance in regulation of feeding.

Contents

1. Introduction

The effects of gastrointestinal and pancreatic hormones on the brain are crucial for biological homeostasis, especially regulation of food intake and energy homeostasis (Woods et al., 2006; Cummings and Overduin, 2007). Secretion of gastrointestinal and pancreatic hormones is either stimulated or inhibited by meal intake, and this change is linked to induction of satiety and hunger feeling.

The hypothalamus is the center for feeding and energy metabolism and regulated by various hormones, neurotransmitters, metabolic factors, many of which originate from the periphery. The peripheral factors send their information to the brain via two distinct routes, the blood–brain barrier and the vagal afferent fiber. Firstly, the access of the peripheral factors to the brain is generally prevented by the blood–brain barrier, but selected sets of molecules such as glucose and insulin can enter the brain through blood–brain barrier. Secondly, peripheral factors are sensed by vagal afferent fibers, a special machinery that conveys the peripheral information to the brain via neural transmission. The vagal afferent fibers are composed of the neurons whose cell bodies are located in the nodose ganglion (NG) and whose projections are bipolar, one terminating at various organs and the other at the nucleus tractus solitarius (NTS) of the brainstem (Hamilton and Norgren, 1984). The branch terminals of vagal afferents sense the peripheral factors including gastrointestinal and pancreatic hormones that regulate feeding and metabolism.

Here, we review how the vagal afferent neurons sense a variety of gastrointestinal and pancreatic hormones and discuss its physiological significance in regulation of feeding. In this review,

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we focus on cholecystokinin and peptide YY_{3-36} as gastrointestinal hormones, pancreatic polypeptide as pancreatic hormone, and nesfatin-1 as pancreatic and gastric hormone.

2. Cholecystokinin (CCK)

CCK is produced by enteroendocrine I cells in the duodenal and jejunal mucosa, enteric nervous system, and brain. Intestinal CCK is secreted in response to fatty acids and proteins in the intestinal lumen. CCK is present as a variety of different length peptides from 83 to 8 that are processed from prepro-cholecystokinin, in which the C-terminal peptide sequence is common. The CCK peptides sulfated at the 7th tyrosine from the C terminal are bioactive and have high affinity to CCK receptor. Two types of G protein-coupled receptors have been identified; CCK 1 receptor (CCK1R, formerly known as CCK A receptor) is predominantly located in the alimentary canal and CCK 2 receptor (CCK2R, formerly known as CCK B receptor) is predominantly located in the brain.

Peripheral injection of CCK decreases food intake in rats (Gibbs et al., 1973) and humans (Kissileff et al., 1981). The selective CCK1R agonist (A-71623), but not selective CCK2R agonist (A-63387), suppresses food intake (Asin et al., 1992). The anorectic effect of exogenous CCK was blocked by CCK1R antagonist (Devazepide) but not CCK2R antagonist (L365260) (Moran et al., 1992), Furthermore, CCK failed to decrease food intake in CCK1R knockout mice but not CCK2R knockout mice (Kopin et al., 1999), indicative of the involvement of CCK1R in the anorectic action of CCK. CCK is reportedly unable to penetrate the blood–brain barrier (Passaro et al., 1982; Zhu et al., 1986), and centrally administration of CCK1R antagonist does not attenuate the effect of peripherally injected CCK (Corp et al., 1997), therefore it is likely that peripherally administered CCK acts at a peripheral site to inhibit feeding. Bilateral section of the subdiaphragmatic vagus or gastric vagal branches, but not celiac, hepatic vagal branches, abolished or reduced the satiety effect of CCK (Smith et al., 1981). CCK intravenous injection increased gastric vagal afferent activity in anesthetized rats (Date et al., 2002). Subpopulation of vagal afferent NG neurons express CCK1R (Broberger et al., 2001; Burdyga et al., 2004), and CCK directly increases cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) (Simasko et al., 2002) and induces depolarization via interacting with CCK1R (Lankisch et al., 2002) in primary cultured rat NG neurons. We have confirmed that CCK-8 increases $[Ca^{2+}]_i$ in mice NG neurons in a dose-dependent manner (Fig. 1A–C). The majority of NG neurons that responded to CCK-8 also responded to capsaicin (Figs. 2F and 3B). This result is consistent with previous report that the ability of exogenous CCK to decrease food intake is attenuated in the rat pretreated with capsaicin that selectively destroys small unmyelinated sensory neurons expressing capsaicin receptor (TRPV1) including the vagus nerve (Ritter and Ladenheim, 1985). We have observed that peripheral injection of CCK did not alter food intake in ICR mice pretreated with capsaicin (Fig. 1E and F) in which number of eye-wiping (pain-related aversive behavior (Iwasaki et al., 2009b)) evoked by capsaicin administration to the eye was attenuated markedly (Fig. 1D). Take together, peripheral CCK directly acts on the vagal afferents via CCK1R, being linked to decreases in food intake.

Several research groups have reported that systemic administration of CCK1R selective antagonist including devazepide increases food intake (Reidelberger et al., 1991; Moran et al., 1992), suggesting that endogenous CCK participates in the control of feeding. However, the calculated plasma CCK concentration after intraperitoneal injection of 1 μg/kg CCK that can decrease food intake is at least 100 fold higher than circulating CCK concentration (fasting: 0.31 ± 0.5 pM, after meal: 6.2 ± 1.9 pM) in rat (Liddle et al., 1984). Considering from our data, minimum concentration of CCK for increasing $[Ca^{2+}]_i$ in cultured NG neurons is around 100 pM (Fig. 1A–C). Therefore, the anorectic effect of endogenous CCK is likely to be mediated via a paracrine mechanism rather than a hormonal manner. In fact, Peters et al. (Peters et al., 2006) have reported that CCK-responsive vagal afferent neurons project to the duodenum with high frequency which is the tissue producing and secreting CCK, suggesting the vagal afferent neurons innervating the duodenum might sense locally released CCK at high concentration in a paracrine fashion. It is suggested that the endogenous CCK acts on the vagal afferents in a paracrine manner thereby decreasing food intake. It is likely that vagal afferents sense CCK at the peripheral sites and that the converted neural signal triggers the release of corresponding neurotransmitter in NTS, thereby triggering the anorectic neural circuit.

Regarding the neurotransmitters in vagal afferents, cocaine- and amphetamine-regulated transcript (CART) is expressed in vagal afferent nerves and NG neurons and a large proportion of CART-containing neurons is colocalized with CCK1R (Broberger et al., 1999). The CART expression in NG is upregulated by peripheral injection of CCK (de Lartigue et al., 2007), and moreover, treatment with CCK to cultured NG neurons promotes CCK secretion (De Lartigue et al., 2010). On the other hand, local injection of CART into the medial NTS is less effective in suppressing food intake as compared with that of 4th ventricle injection (Zheng et al., 2001). Therefore, the functional role of CART in vagal afferents remains to be determined. Vagal afferent nerves produce glutamate (Zhuo et al., 1997). Recent reportedly, local injection of noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 or its competitive antagonist D-3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphoric acid blocked reduction of food intake following CCK intraperitoneal injection (Wright et al., 2011). In the NTS, proopiomelanocortin (POMC) neuron and prolactin-releasing peptide (PrRP) neuron might participate in CCK-induced anorexia. POMC is expressed in not only arcuate nucleus of the hypothalamus but also the NTS, and peripheral CCK injection-induced reduction of food intake was blunted in the mice lacking melanocortin 4 receptor (MC4R) and inhibited by injection of SHU9119, antagonist of MC3R and MC4R into 4th, but not 3rd ventricular (Fan et al., 2004). PrRP-expressing neurons are localized in the NTS, and peripheral injection of CCK fails to change food intake in PrRP knockout mice (Takayanagi et al., 2008).

3. Intestinal peptide YY_{3-36} (PYY_{3-36}) and pancreatic polypeptide (PP)

Neuropeptide Y (NPY), PP, and PYY, the neuropeptide Y family peptides, are 36-amino acids peptide with high homology. NPY is mainly distributed in central nerves system (Morton and Schwartz, 2001). PP is produced primarily in PP cells in the pancreatic islets and PYY in enteroendocrine L cells in ileum and colonic mucosa (Ekblad and Sundler, 2002). Meal intake stimulates PP and PYY release. PYY_{1-36} released to the circulation is cleaved at the N-terminal Tyr and Pro residues by dipeptidyl peptidase IV to yield PYY_{3-36} of (Eberlein et al., 1989). The ratio of PYY_{3-36} to total PYY in postprandial blood is around 60% (Grandt et al., 1994). At least five functional receptors, Y1, Y2, Y4, Y5 and Y6, have been identified. They are seven-transmembrane G protein-coupled receptors. NPY and PYY_{1-36} bind to all of these receptors with high affinity ($<10^{-9}$ M), while PP and PYY_{3-36} preferentially bind to Y4 and Y2 receptor, respectively (Michel et al., 1998).

PYY secretion strongly increases by ingestion of high protein diet (Batterham et al., 2006). Peripheral injection of PYY_{3-36} more effectively than PYY_{1-36} decreases food intake (Batterham et al., 2002; Chelikani et al., 2005), and this effect disappeared in Y2 deficient mice (Batterham et al., 2002). Therefore, Y2R is the functional target for anorectic effect of peripheral PYY_{3-36}. Y2R is widely distributed in the several organs such as the brain (hypothalamus, hippocampus, thalamus and brain cortex), peripheral nerves