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Review

The function of glucagon-like peptide-1 in the mouse peripheral taste system

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ABSTRACT

Background: Several studies have demonstrated that some gut peptides known to be important in energy metabolism are expressed in mouse taste bud cells. However, the functions of these peptides in taste cells are still largely unknown. In the gut, one of these peptides, glucagon-like peptide-1 (GLP-1), which is known as the insulinotropic gut peptide, is secreted from enteroendocrine L-cells, which express as many taste molecules as those on the tongue. These taste transduction molecules are suggested to be involved in GLP-1 secretion from L-cells in response to various nutrient stimuli. GLP-1 is reported to function as a neurotransmitter via activation of its receptors expressed on the vagus nerve, thereby regulating insulin secretion.

Highlight: Consistent with this evidence from the gastrointestinal tract, recent studies have demonstrated that GLP-1 is secreted from mouse taste cells in response to taste compounds such as sugars, artificial sweeteners, and long-chain fatty acids. GLP-1 secreted from taste cells may activate particular types of gustatory nerve fibers because they express GLP-1 receptors and respond to GLP-1 administered via the femoral vein.

Conclusion: GLP-1 released from taste cells may be involved in transmission of sweet and lipid signals, thereby impacting animals' feeding behavior in response to these important nutrient factors.

Contents

Abbreviations: CALHM1, calcium homeostasis modulator protein 1; CCK, cholecystokinin; CT, chorda tympani; CV, circumvallate papillae; FP, fungiform papillae; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; LCFA, long chain fatty acid; NTS, nucleus of the solitary tract; P2X2/3, purinergic receptor 2/3; TCs, taste cells; TRPM5, transient receptor potential cation channel subfamily M member 5; VIP, vasoactive intestinal peptide

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1. Introduction

Sweet, bitter, salty, sour, and umami are recognized as the five basic taste qualities. These different taste qualities are detected by taste cells (TCs) in taste buds located on the tongue and the palate. Mammalian taste buds contain at least four different cell types (type I, II, III, and IV TCs) and each of them has characteristic cytological and functional features [1–3]. Among them, type II TCs, which express T1R (sweet and umami) or T2R (bitter) G-protein-coupled taste receptors, are thought to be dedicated to sensing sweet, bitter, and umami tastes [3,4]. Activation of these G-protein-coupled taste receptors leads to cell-depolarization, generation of action potentials, and release of adenosine triphosphate (ATP) via hemichannels [5–7] or the newly reported voltage-gated ion channel calcium homeostasis modulator protein 1 (CALHM1) [8]. It is well established that ATP and its receptors, ionotropic purinergic receptor 2 and 3 (P2X2/3), play a crucial role in taste signaling pathways, because P2X2/3 double knockout mice show significantly diminished neural and behavioral responses to taste compounds [9]. Thus, ATP acts as a functional neurotransmitter between TCs and gustatory nerve fibers. However, it remains to be determined how the specificity of each taste quality is maintained through the signal transmission from TCs to nerve fibers. Sweet-, bitter-, and umami-sensitive type II TCs lack conventional synaptic connections [10] and use the same transmitter, ATP. Therefore, some mechanism may exist to specify taste quality during signal transmission from TCs to nerve fibers.

Recently, several studies have demonstrated that subsets of TCs express gut peptides, including glucagon-like peptide-1 (GLP-1) [11], neuropeptide Y [12], glucagon [13], ghrelin [14], vasoactive intestinal peptide (VIP) [15], and cholecystokinin (CCK) [16–18] in rodents. Furthermore, these peptides have characteristic expression patterns that are correlated with specific taste cell markers. For example, GLP-1 and glucagon are mainly coexpressed with T1R3 and α-gustducin [13,19,20] in mouse TCs, and 56% of the CCK-expressing TCs coexpress α-gustducin and also 60% of VIP-expressing TCs coexpress α-gustducin in rat TCs [18]. In the gut, GLP-1 is expressed in enteroendocrine L-cells, which express multiple taste transduction molecules including the sweet taste receptor T1R2/T1R3, the taste G-protein gustducin [21,22], and the lipid receptor GPR120 [23]. Such transduction molecules might be involved in GLP-1 release from L-cells in response to stimulation with sweet compounds or dietary lipids [23, 24]. GLP-1 promotes insulin release in a glucose-dependent manner via activation of its G protein-coupled receptors (GLP-1R) expressed on pancreatic islet β cells and suppresses glucagon release from α cells [21]. Additionally, in a rat study, infusion of GLP-1 into the portal vein facilitated hepatic vagal afferent activity via GLP-1R, and evoked a powerful neuroincretin effect through the central vagal pathway; thus, it may play an important role in energy homeostasis [21,25,26]. These findings raised the possibility that GLP-1 in TCs may also contribute to signal transmission from TCs to gustatory nerve fibers.

In this review, we will discuss the function of GLP-1 expressed in peripheral taste tissues in mice. Recent studies have suggested that GLP-1 signaling may contribute to at least oral sweet and lipid sensing in mice [19,20,27]. GLP-1R null mice exhibited diminished behavioral responses to sugars and artificial sweeteners and higher thresholds for long chain fatty acids (LCFAs) detection compared with wild type (WT) controls. GLP-1 is released from a subset of sweet-sensitive taste cells immediately after sweet stimulation. GLP-1 injected in the femoral vein directly activates a subset of sweet-sensitive nerve fibers, and these responses are blocked by pre-treatment with a GLP-1R antagonist. These data imply that peripheral GLP-1 signaling may affect dietary lipid and sugar intake.

2. GLP-1R$^{-/-}$ mice have reduced behavioral and neural responses to sweeteners

Mice genetically lacking GLP-1R (GLP-1R$^{-/-}$) [28] on a C57BL/6 background exhibit no significant differences in feeding behavior, body weight, lean mass, or fat mass, compared with WT littermates under normal chow feeding conditions, but they do show abnormal glycemic excursion following intraperitoneal/oral glucose infusion [29,30] and upregulation of gastric inhibitory polypeptide (GIP) synthesis and secretion [31]. GIP is an insulinotropic hormone that is released from enteroendocrine K-cells in the upper intestine. Morphologically, the size of the pancreatic islets in GLP-1R$^{-/-}$ mice is generally smaller than that of WT mice although total β-cell volume and number are not significantly different [29,32]. With regards to taste sensitivity, GLP-1R$^{-/-}$ mice exhibited reduced behavioral responses to sweet compounds (sucrose, saccharin, and sucralose) compared with those observed in WT mice (Fig. 1) [19,20,33]. Consistent with the reduction of sweet taste sensitivity in behavioral assays, chorda tympani (CT) nerve recordings revealed that the neural responses of GLP-1R$^{-/-}$ mice to various kinds of sweeteners (both sugars and artificial sweeteners) were smaller than those of WT controls, but this was not the case for sour, salty, bitter, and umami compounds (Fig. 1) [20]. Thus, GLP-1 may contribute to sweet taste signaling in mice.

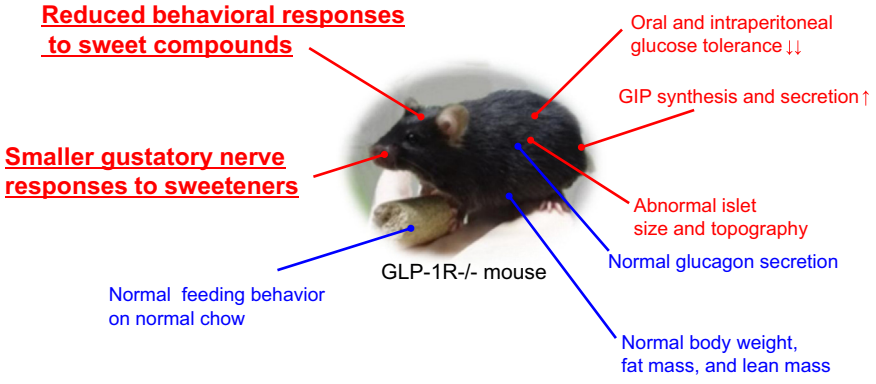

Fig. 1. GLP-1R$^{-/-}$ mice exhibit several differences in physiological state but normal feeding behavior, body weight, and body mass, compared with wild type mice under normal chow feeding conditions. However, they showed reduction of gustatory nerve responses and behavioral responses to sweet stimuli. It has also been reported that these mice showed diminished responses to sweeteners in some behavioral experiments. GLP-1R: glucagon-like peptide-1 receptor.

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