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Peripheral Glucagon-like Peptide-1 (GLP-1) and Satiation

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ABSTRACT

Peripheral GLP-1 is produced by post-translational processing of pro-glucagon in enteroendocrine L-cells and is released in response to luminal nutrient (primarily carbohydrate and fat) stimulation. GLP-1 is well known for its potent insulinotropic and gluco-regulatory effects. GLP-1 receptors (GLP-1R) are expressed in the periphery and in several brain areas that are implicated in the control of eating. Both central and peripheral administration of GLP-1 have been shown to reduce food intake. Unresolved, however, is whether these effects reflect functions of endogenous GLP-1. Data collected in our laboratory indicate that in chow-fed rats: 1) Remotely controlled, intra-meal intravenous (IV) or intraperitoneal (IP) GLP-1 infusions selectively reduce meal size; 2) hindbrain GLP-1R activation is involved in the eating-inhibitory effect of IV infused GLP-1, whereas intact abdominal vagal afferents are necessary for the eating-inhibitory effect of IP, but not IV, infused GLP-1; 3) GLP-1 degradation in the liver prevents a systemic increase in endogenous GLP-1 during normal chow meals in rats; and 4) peripheral or hindbrain GLP-1R antagonism by exendin-9 does not affect spontaneous eating. Also, although our data indicate that peripheral GLP-1 can act in two different sites to inhibit eating, they argue against a role of systemic increases in endogenous GLP-1 in satiation in chow-fed rats. Therefore, further studies should examine whether a local paracrine action of GLP-1 in the intestine or and endocrine action in the hepatic-portal area is physiologically relevant for satiation.

1. Introduction

Glucagon-like-peptide (7–36) amide (GLP-1) is the product of post-translational processing of pro-glucagon in the gut and the brain [1]. In the brain, GLP-1 is expressed in some neurons of the nucleus tractus solittarii (NTS) [2,3]. In the gut, GLP-1 is released primarily from enteroendocrine L-cells located in the distal jejunum and ileum [1]. Luminal carbohydrates and fats are potent stimuli for GLP-1 secretion, and these effects appear to be mediated in part by taste receptors expressed on enteroendocrine cells [4] (Fig. 1). Recently GLP-1 has also been identified in sweet- and umami-taste receptor cells in the oral cavity [5], suggesting that GLP-1 signaling is involved in taste. GLP-1 receptors (GLP-1R) are widely distributed in the brain and in peripheral organs such as the pancreatic islets and the whole gastrointestinal (GI) tract [6,7]. In the brain, GLP-1R are found in several hindbrain and forebrain areas [8], including areas that are implicated in the control of food intake and energy balance, such as the area postrema (AP), NTS, hypothalamus and amygdala [3]. GLP-1 has several physiological effects: it acts as a strong incretin, i.e., stimulates glucose-induced insulin release [9], it inhibits glucagon release [1], and it inhibits gastric emptying, i.e., contributes to the ileal brake mechanism [10]. Further potential physiological effects of GLP-1 include an influence on learning and memory [11], neuroprotection [12,13], and the inhibition of eating and drinking [14,15]. Administration of GLP-1 or of potent, long-acting natural or synthetic GLP-1 analogs, such as exendin-4 (Ex-4) or liraglutide, inhibits eating in many species, including humans [16–22]. Ex-4 is a naturally occurring peptide resistant to rapid enzymatic degradation by dipeptidyl peptidase 4 (DPP-4) [23]. The synthetic GLP-1 analog liraglutide also resists enzymatic degradation and, because it binds to albumin in the plasma, delays renal excretion [23]. Chronic administrations of GLP-1 or its analogs have effectively reduced weight and improved glucose metabolism in overweight individuals [18,24], suggesting GLP-1 may offer an effective therapeutic option for overweight and type II diabetes [25].

Endogenous intestinal GLP-1 has been implicated in meal termination (satiation) because: 1) exogenous GLP-1 inhibited eating primarily by reducing meal size [26,27] and 2) intraperitoneal (IP) injection of the specific GLP-1R antagonist exendin (9–39)(Ex-9) stimulated eating under some conditions [26], indicating that satiation can be delayed when endogenous GLP-1 signaling is blocked. In other studies, however, Ex-9 administration failed to stimulate eating, suggesting that endogenous GLP-1 is not required for the control of meal size under all conditions. Thus, further research is warranted to identify the situations under which endogenous GLP-1 is physiologically relevant for satiation. Furthermore, the site and mechanism of GLP-1's eating-inhibitory action, including the intracellular signaling cascades involved, are still largely unknown.

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After secretion, GLP-1 is rapidly degraded into GLP-1 (9–36) by DPP-IV [28]. As a result, the biological half-life of GLP-1 is less than 5 min [29]. If prandial secretion is maintained and exceeds degradation, endogenous GLP-1 may still have an endocrine satiating effect by direct central nervous system action. In addition, such a route of action may be particularly relevant for pharmacological interventions that lead to sustained, and substantial increases in circulating levels of native GLP-1 or GLP-1R agonists. It is also relevant to mention that paracrine effects of GLP-1 in rats may be endocrine effects in humans, as is the case for the satiating effect of cholecystokinin (CCK). Finally, gut hormones can also signal the brain through an endocrine or paracrine effect on afferent nerves, with the vagus being the prominent neural route of gut-brain signaling [30,31]. Whether or not endogenous peripheral GLP-1 induces satiation through such an endocrine or paracrine action is still unresolved. This review briefly summarizes what is known about these open questions, capitalizing on some experiments that we recently did to address them.

2. Endocrine effects of GLP-1

The insulinotropic effect of GLP-1 is mediated in part by GLP-1R on hepatic branch vagal afferents terminating in the wall of the hepatic portal vein close to the liver [32]. Activation of these receptors triggers a vago-vagal reflex that increases pancreatic vagal-efferent activity and stimulates insulin release [33]. Therefore, it appeared logical to test whether a similar mechanism is involved in the eating-inhibitory effect of peripheral GLP-1. In an attempt to mimic the meal-induced release of endogenous GLP-1 from the small intestinal L-cells into the hepatic portal vein as closely as possible, we equipped rats with chronic hepatic portal vein catheters and infused various doses of GLP-1 during the first spontaneous nocturnal meal. The animals were continuously monitored via infra-red video cameras, and the infusions were triggered by remote control from an adjoining room to prevent disturbing them. Under these conditions, hepatic portal vein infusions of GLP-1 reduced the size and duration of the ongoing meal but did not affect the subsequent inter-meal interval or the size or duration of the second meal [27]. Furthermore, intra-meal hepatic portal vein and vena cava (i.e., systemic) infusions of GLP-1 (1 nmol/kg body weight [BW]) produced similar effects on eating, suggesting that the satiating effect of circulating GLP-1 is not mediated by GLP-1R located in the hepatic portal system or liver. Interestingly, although hepatic portal vein infusion of Ex-4 under the same conditions reduced the sizes of both the first and the second meals, it did not affect the duration of the intervening inter-meal interval, suggesting that GLP-1R activation has a selective effect on satiation. Whether the briefer and smaller increases in plasma GLP-1 levels produced by GLP-1 infusions and the more prolonged and greater increases in GLP-1R activation produced by Ex-4 reduce food intake by acting at the same site(s) or whether Ex-4 recruits additional receptors for its extended effect remains to be investigated. In addition, while all these findings are consistent with a possible physiological endocrine satiating effect of endogenous GLP-1, our data to date do not support a role of GLP-1 in the graded satiating effect of food because we have not found a clearly dose-related satiating effect of exogenous GLP-1 [27].

We also examined whether the eating-inhibitory effect of circulating GLP-1 is mediated by abdominal vagal afferents. Rats underwent subdiaphragmatic vagal deafferentation (SDA) [34] or sham surgery and were equipped with hepatic portal vein catheters. SDA produces the most specific and complete lesion of abdominal vagal afferents. That is, it lesions both vagal A- and C-fibers, whereas capsaicin lesions only unmyelinated vagal C-fibers and lesions non-vagal as well as vagal fibers [35]. In addition, SDA leaves about 50% of the vagal efferents intact [34,36], which reduces the adverse side effects related to impaired GI motility and secretion that are produced by complete subdiaphragmatic vagotomy. Intra-meal hepatic portal vein infusions of GLP-1 reduced meal size and duration similarly in SDA and sham-operated rats [27]. In addition, Ex-4 reduced first (Fig. 2) and second meal size (data not shown) without a significant effect on other meal parameters. Ex-4 also produced similar 2 and 4 h decreases in cumulative food intake in SDA and sham-operated rats (Fig. 3). Overall, these data indicate that abdominal vagal afferents are not necessary for the eating-inhibitory effect of circulating GLP-1 or Ex-4.

In order to identify the neural substrates that may be involved in mediating the satiating effect of circulating GLP-1, we assessed c-Fos expression in some hindbrain (area postrema [AP], NTS) and forebrain structures (central nucleus of the amygdala [CeA], hypothalamic paraventricular and arcuate nuclei [PVN and Arc]) implicated in the control of eating. We found that hepatic portal vein GLP-1 infusion, at a dose (1 nmol/kg BW) that reliably inhibited eating, activated the NTS, AP, and CeA, suggesting that these brain areas participate in the endocrine eating-inhibitory effect of GLP-1 [37]. One previous study using femoral vein infusion of a lower dose of native GLP-1 (1 μg = 0.24 nmol/kg BW) failed to detect a significant increase in c-Fos expression in the brainstem [38], whereas another study using femoral vein infusions of Ex-4 [39] found a wider-spread activation than we did. Because of the much longer biological half-life of Ex-4, however, these results cannot directly be compared to ours.

In addition to causing satiation, GLP-1 may inhibit eating non-specifically by inducing malaise. GLP-1 can trigger a conditioned taste aversion and pica (kaolin intake) in rodents [40,41]. On the other hand, behavioral observations in macaques did not reveal any overt signs of malaise, such as decreased alertness, drooling, or vomiting, in response to GLP-1 [16]. Under which conditions GLP-1 produces satiation or malaise remains unclear. GLP-1R in the CeA appear to mediate some of the response to peripheral illness [42]. This is because 1) intra-amygdala administration of GLP-1, but not of the inactive analog, GLP-1 (9–39), produced a strong conditioned taste aversion, similar to those produced by visceral malaise or food poisoning, and 2) intra-amygdala administration of Ex-9 prevented taste aversion learning in response to IP injections of the toxin lithium chloride [42]. Importantly, intra-amygdala injection of GLP-1 did not itself reduce food intake, suggesting that this mechanism is not a necessary component of the eating-inhibitory effect of endocrine GLP-1. Presumably, GLP-1 projections from the NTS are involved in this receptor activation. At the same time, however, our c-Fos data are consistent with the possibility that the CeA may also be involved in mediating the eating-inhibitory effect of circulating GLP-1. Whether or not this increase in CeA c-Fos occurred in GLP-1R-expressing neurons or was related to an aversive component of GLP-1's eating-inhibitory effect under our conditions requires further research.

We recently found that infusion of Ex-9 (10 μg/rat) into the 4th cerebral ventricle blocked the eating-inhibitory effect of hepatic portal vein GLP-1 infusion in rats, indicating that GLP-1R that are accessible from the 4th ventricle (e.g. NTS and AP) are involved in mediating this effect [43]. Also, preliminary findings of ours indicate that AP lesions block the eating-inhibitory effect of hepatic portal vein GLP-1 infusions, suggesting that the AP is involved as well (Punjabi et al., in preparation). IP injection of (2.0 μg/kg BW) Ex-4 was recently reported to reduce food intake in AP-lesioned rats after IP injection [44], which at first glance seems to contradict the idea that the AP mediates the eating-inhibitory effect of circulating GLP-1. It is possible, however, that the greater and more prolonged GLP-1R activation produced by Ex-4 may have recruited redundant neural circuits to inhibit eating. It may be relevant in this connection that it was not determined whether Ex-4 elicited a conditioned taste aversion after AP lesions.

3. GLP-1R mechanisms

GLP-1R are G-protein-coupled and activate diverse intracellular signaling pathways involving cyclic adenosine monophosphate, protein kinase A (PKA), phospholipase C, phosphatidylinositol-3