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Gut fat sensing in the negative feedback control of energy balance - recent advances

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Abstract

Infusions of lipids into the small intestine potently suppress ongoing feeding. Prior work has identified potential roles for gut extrinsic vagal and non -vagal sensory innervation in mediating the ability of gut lipid infusions to reduce food intake, but the local biochemical processes underlying gut lipid sensing at the level of the small intestine remain unclear. This manuscript will summarize recent progress in the identification and characterization of several candidate gut lipid sensing molecules important in the negative feedback control of ingestion, including the fatty acid translocase CD36, peroxisome proliferator-activated receptor alpha (PPAR-alpha), and the fatty acid ethanolamide oleylethanolamide (OEA). In addition, this manuscript addresses a larger role for gut lipid sensing in the overall control of energy availability by modulating not only food intake but also hepatic glucose production.

Keywords

gut-brain axis; vagal afferent; food intake; glucose homeostasis; nutrient sensing

1. Introduction

The infusion of lipid emulsions into the small intestine has been demonstrated to rapidly and potently suppress food intake in multiple mammalian species, including man (1). A role for sensory gut innervation in this phenomenon was suggested by studies showing that local infusion of the anesthetic tetracaine blocked the ability of duodenal lipid infusions to suppress sham feeding, where ingested food drains from the stomach during a meal without impinging on the duodenum (2). Subsequent work supported a role for luminal sensory innervation in transmitting gut lipid negative feedback signals, in that local luminal application of the neurotoxin capsaicin, which selectively affects a subpopulation of unmyelinated afferent fibers, blocked the ability of intestinal infusions the fatty acid sodium oleate to inhibit sham feeding (3). Extrinsic afferent innervation of the gut from both vagal and non vagal sources has been implicated in the ability of duodenal lipid infusions to inhibit food intake in rodent models, as gut vagal deafferentation, as well as surgical transection of gut splanchnic nerves and removal of the celiac superior mesenteric ganglion,

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each blocked the ability of duodenal corn oil infusions to reduce food intake during a meal (4). Intestinal lipid infusions at feeding inhibitory doses also stimulate c-fos expression, a marker of neuronal activation, in the caudal brainstem nucleus of the solitary tract (NTS), the central nervous system terminus of gut vagal afferents (5). Vagal capsaicin treatment blocks the ability of gut lipids to activate brainstem NTS c-fos, further supporting a role for gut vagal afferents in determining the feeding inhibitory effects of duodenal fat infusions. Furthermore, vagal afferents supplying the jejunum have been reported to be directly activated by local infusion of lipids and fatty acids [Randich, 2000 #272]. Taken together, these data suggest that the proximal gut senses lipids, and communicates information regarding gut lipid availability to the central nervous system sites important in the control of feeding behavior via extrinsic gut sensory nerves.

Recent advances in understanding the molecular and systems biology of the gut-brain axis have suggested novel candidate gut lipid sensors, and have revealed roles for lipid sensing in the control of nutrient availability by modulating hepatic glucose production. These advances are outlined below.

2. Molecular mediators of gut lipid sensing

While the precise biochemical bases for gut lipid sensing remain elusive, several studies have begun to identify locally released or expressed factors potentially important in the gut-brain feedback control of ingestion. One target is duodenal serotonin (5-HT) release acting via vagal serotonin 3 (5-HT₃) ionotropic receptors. The ability of intestinal lipid infusions to inhibit food intake and activate brainstem NTS c-fos is blocked by administration of the selective 5-HT₃ receptor antagonist ondansetron (6, 7). Gut nutrient infusions rapidly increase serotonin release from intestinal endocrine cells, and intestinal serotonin acts in a paracrine fashion to increase gut vagal afferent neurophysiological activity (8). This activation is predominantly mediated by gut vagal 5-HT₃ receptors, as vagal afferent neurophysiological responses to luminal serotonin are blocked by local application of selective 5-HT₃ antagonists (8). A significant remaining question is whether duodenal lipid per se is sufficient to elicit local 5-HT release, and thereby increase gut vagal afferent negative feedback. One possibility is that serotonin is released secondarily to the local mechanical effects of CCK on gut motility. Gut CCK release from duodenal enteroendocrine cells is potently stimulated by duodenal fat infusions, and CCK increases duodenal motility near the pyloric junction. As mechanical gut stimulation promotes serotonin release (9), CCK-induced small intestinal motility may provide an indirect link between fat induced CCK release and activation of duodenal 5-HT₃ receptors secondary to increased local 5-HT. Functional evidence for an interaction between gut CCK and 5-HT in the control of feeding is supported by findings demonstrating that combinations of CCK and 5HT synergistically reduce food intake through 5-HT₃ receptors (10). Importantly, the feeding inhibitory effects of CCK are blocked by gut afferent vagotomy (11), suggesting that CCK and 5-HT₃ may share a common vagal afferent pathway in the negative feedback control of ingestion.

A second candidate is the fatty acid translocase CD36, present in rodent duodenojejunal enterocytes as well as in human duodenal epithelium (12). This translocase mediates cellular uptake of very long chain fatty acids and their intestinal absorption (13). Animals deficient in CD36 have significantly reduced chylomicron formation (14), as well as reduced fatty acid and cholesterol uptake from the proximal, but not distal intestine (15). Furthermore, CD36 protein expression is significantly higher in the proximal duodenum relative to more distal gut sites (16). CD36 gene deletion also reduces both preference for and intake of fat (17), but it remains unclear whether these reductions are related to the absence of CD36 specifically within the intestine. Taste cells in the oral cavity also express CD36, and it has been proposed to function as a taste receptor (18). CD36 is also expressed by neurons,

including ventromedial (VMH) hypothalamic neurons where it mediates oleic acid-induced signaling independently of fatty acid metabolism (19), suggesting that it may act centrally as a lipid sensor important in the control of energy balance.

Our recent findings support an important role for duodenal CD36 in lipid sensing in the negative feedback control of ingestion during a meal; CD36 null mice are insensitive to the feeding inhibitory effects of duodenal Intralipid infusions (20). Expression of CD36 is mediated by peroxisome proliferator-activated receptor alpha (PPAR-alpha), a ligand-activated transcription factor involved in lipid metabolism, and duodenal lipid infusions also fail to reduce food intake in PPAR-alpha deficient mice (20). The neural bases for these deficiencies are unknown. However, given the expression of CD36 in taste cells and VMH neurons, and increasing findings that orally expressed taste receptors are also expressed in the proximal small intestine in both rodents and humans (21, 22), it would not be surprising to identify CD36 expression in gut vagal afferents. This would provide another possible transduction pathway for gut lipid negative feedback signals.

CD36 expression in small intestinal enterocytes is also increased by exogenous administration of oleoylethanolamide (OEA), an endogenously produced fatty acid ethanolamide concentrated in duodenum and jejunum. Consistent with this increase, peripheral administration of OEA stimulates fatty acid uptake as well. The enzymes critical for biosynthesis of endogenous OEA are highly concentrated in the proximal small intestine, including the enzyme N-acylphosphatidylethanolamine (NAPE)-phospholipase D (PLD), which catalyzes the hydrolysis of NAPE to generate OEA. Adenovirally mediated small intestinal overexpression of NAPE PLD results in increased intestinal OEA and decreased food intake, as well as reduced intestinal PPAR alpha and CD36 expression (23). Together, these findings begin to link the control of putative gut lipid sensing and uptake by CD36 to two intestinal regulatory factors, PPAR alpha and OEA. Furthermore, endogenous OEA itself is nutritionally regulated specifically by intestinal lipid administration. Food deprivation reduces OEA biosynthesis in the small intestine, while intestinal lipid infusions, but not equicaloric carbohydrate or protein infusions, increase proximal small intestinal OEA levels (20). Interestingly, the biosynthetic pathway responsible for lipid stimulated endogenous OEA production also generates intraintestinal oleic acid, bringing full circle an extrinsic food-derived lipid signal (intestinal oleate infusion via intralipid) to a *de novo* intraintestinal oleate signal (20). Recall that jejunal vagal afferents are activated by infusions of lipid and fatty acids, including Intralipid and oleic acid (24). An intriguing possibility is that the feeding suppressive effects of small intestinal lipid infusions are mediated in part by a local regulatory network within upper small intestine: nutritional lipid is translocated into the luminal tissue, stimulating gut OEA and oleic acid biosynthesis, which individually and/or together downregulate gut CD36 and PPAR alpha expression.

Peripheral OEA administration reduces food intake by increasing the latency to feed and by prolonging the interval between two successive meals. These feeding inhibitory effects of OEA are not likely to be secondary to malaise, as exogenous OEA fails to support the formation of a conditioned taste aversion [Proulx, 2005 #275]. OEA's effects on food intake appear to be mediated in part by PPAR alpha, an OEA agonist. OEA fails to suppress feeding in PPAR-alpha deficient mice, while PPAR alpha agonists mimic the feeding inhibitory effects of exogenous OEA administration (25). Gut vagal afferents also contribute to the ability of OEA to reduce feeding, as vagal capsaicin application blocks OEA induced satiety [Rodriguez de Fonseca, 2001 #303]. Consistent with this finding, OEA also rapidly depolarizes capsaicin-sensitive cell bodies of vagal afferent neurons in the nodose ganglion. This activation is likely mediated by the transient receptor potential vanilloid type 1 (TRPV1) receptor, as it is blocked by TRPV1 antagonists and is absent in TRPV1 null mice [Wang, 2005 #309]. More recent data suggest that sympathetic outflow to the gut also

regulates small intestinal OEA synthesis, and may thereby affect feeding. Intestinal nutritional regulation of OEA upon refeeding is abolished by prior transection of the splanchnic nerves and removal of the sympathetic celiac-superior mesenteric ganglion, and this effect is mimicked by peripheral administration of beta 2 adrenergic receptor agonists that block gut sympathetic outflow. Combined splanchnectomy and ganglionectomy alone also increased meal frequency and reduced satiety ratio, and these consequences were reversed by exogenous OEA administration (J. Neurosci., in press 2011).

3. Gut lipid sensing in the control of glucose homeostasis

In terms of the neurobiological controls of feeding, gut lipid detection has largely been construed as a sensory capability important in generating neuroendocrine negative feedback signals that limit food intake. From physiological and behavioral perspectives, the delivery of energy dense lipid into the gastrointestinal tract functions in part to limit further nutrient availability by terminating an ongoing meal. More broadly, new studies suggest that gut lipid sensing may play a significant role in regulating nutrient availability per se, be it from exogenous nutritional or endogenous biochemical sources. Work of Lam and colleagues has identified a novel gut-brain-liver pathway whereby intestinal lipid infusions potently suppress glucose production and plasma glucose levels, but not glucose uptake, during a basal pancreatic basal insulin clamp (26). Co-infusion of Intralipid with triacsin C, a potent pharmacological inhibitor of long fatty acyl CoA synthetase, blocked the conversion of Intralipid to long chain fatty acid-CoA, and prevented the ability of duodenal Intralipid infusions to suppress glucose production during the clamp. This suggests that LCFA-CoA themselves act as nutrient stimuli for gut lipid sensing. It is important to note that these lipid infusions increased upper intestinal LCFA-CoA levels, but did not alter plasma and portal free fatty acids acutely. This finding supports the idea the local intestinal fatty acid concentrations, not plasma levels, provide a critical negative feedback signal. Luminal application of the topical anesthetic tetracaine completely blocked the ability of duodenal lipid infusion to suppress hepatic glucose production, identifying a role for gut sensory innervation, likely vagal afferents, in this phenomenon. Consistent with this suggestion, both total subdiaphragmatic vagotomy as well as subdiaphragmatic gut deafferentation blocked the glucoregulatory effects of duodenal intralipid infusions.

As mentioned above, the central projections of gut vagal afferents synapse at neurons in the brainstem NTS, where presynaptic terminals and postsynaptic NTS neurons express glutamatergic NMDA receptors (27). Accordingly, fourth ventricular, as well as parenchymal NTS application of the NMDA channel blocker MK-801 each completely abolished the ability of duodenal Intralipid infusions to reduce glucose production, supporting the idea that brainstem glutamatergic neurotransmission is an important central mediator of gut lipid sensing in the control of endogenous glucose availability. Brainstem NTS neurons project mono and polysynaptically to adjacent dorsal motor vagal (DMX) neurons, and the DMX is a major source of parasympathetic vagal outflow to the liver via the hepatic vagal branch (28). Surgical transection of the hepatic vagus also blocked the ability of duodenal intralipid to affect glucose production. Taken together, these findings describe a gut-brainstem-liver neural pathway that links nutritional intestinal lipids to systemic glucose availability, as determined by endogenous glucose production and elevated plasma glucose.

Follow-up studies point to a role for CCK as a molecular mediator in this circuit, as duodenal CCK alone was able to recapitulate the effects of duodenal lipid infusions (29). Furthermore, luminal administration of the CCKA receptor antagonist devazepide blocked the ability of Intralipid to reduce glucose production, supporting a role for gut CCKA receptors in the gut lipid sensing control of endogenous glucose availability. As CCKA

receptors are localized to subdiaphragmatic vagal afferent neurons (30), local tetracaine infusions were applied to anesthetize luminal sensory nerves, including gut vagal afferents expressing CCKA receptors. This maneuver also blocked the ability of luminal CCK-8 to suppress glucose production. Finally, brainstem MK801 and hepatic vagotomy also abolished the effects of exogenous duodenal CCK infusion. Taken together, these findings suggest that duodenal fat-stimulated CCK acts at gut vagal CCKA receptors to drive brainstem NTS and hepatic vagal outflow in the negative feedback control of glucose production. A critical missing link in this chain of events is the molecular basis of the lipid sensing process whereby luminal lipid drives CCK release from gut enterocytes. It remains unclear from these studies whether the candidate lipid sensors described above, which also determine intestinal fatty acid availability, gut vagal afferent signaling, and the negative feedback control of food intake, also function to modulate glucose production during intestinal lipid infusions.

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Highlights

- Small intestinal fat infusions suppress feeding via extrinsic gut sensory innervation, identifying the gut as a primary site of lipid sensing.
- CD36, PPAR alpha, and oleoylethanolamide are candidate mediators of gut lipid sensing in the negative feedback control of ingestion.
- Duodenal fat infusions engage a gut-brain-liver circuit to affect nutrient availability by reducing endogenous glucose production.