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Gut-Brain Nutrient Sensing in Food Reward

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Abstract

For the past several decades, vagal and hormonal gut-brain negative feedback signaling mechanisms that promote satiety and the subsequent suppression of food intake have been explored. In addition, a separate positive feedback process termed “appetition”, involving postoral signaling from the gut to the brain, has been shown to promote food intake and produce flavor-nutrient preference conditioning. Afferent fibers emerging from the vagus nerve are the main pathway by which information is relayed from the abdominal viscera to the hindbrain and eventually other higher brain regions involved in food intake. Utilizing a specialized subdiaphragmatic vagal deafferentation technique, it was observed that gut vagal and splanchnic afferents play a role in the negative feedback control of satiety after nutrient intake, but are not required for nutrient reinforcement or flavor-nutrient preference conditioning, thereby highlighting the distinction between the processes of satiation and appetition. Linking these physiological and behavioral processes to a neurochemical mechanism, it was found that striatal dopamine release induced by intragastric glucose infusion is involved in sweet appetite conditioning. The mechanisms underlying appetition are still being investigated, but may involve other non-dopaminergic neurochemical systems and/or as yet undiscovered hormonal mediators. Future work to delineate the biological mechanisms whereby appetition drives increased intake and conditioned food preference in response to ingestion should take a multifaceted approach by integrating hormonal, neurophysiological, and behavioral techniques.

Keywords

Appetite; Flavor conditioning; Food intake; Satiety; Sugar; Vagus nerve

Introduction

This review is a summary of a presentation given by Gary J. Schwartz, Ph.D. at a special symposium of the Columbia University Seminar on Appetitive Behavior which was held on May 5, 2016 to honor the work of Anthony Sclafani, Ph.D. and Karen Ackroff, Ph.D.

Over the past several decades, as both a topic of work in the field, as well as an area of interest and discussion for the Appetitive Seminar, much attention and effort has focused on

describing vagal and hormonal gut-brain signaling mechanisms that promote satiety and limit food intake (1). The ingestion of nutrients is known to stimulate satiety signals, among them the release of hormones such as cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1), as well as gastric distension, which are relayed first to the hindbrain and ultimately to the hypothalamus and other brain reward regions involved in food intake regulation (2). In contrast to this homeostatic control, palatable sugar- and fat-rich foods, in a manner indicative of a hedonic drive, can override these aforementioned satiation signals to promote increases in food intake (3). Indeed, it is not just the palatable flavor of sugar- and fat-rich foods which can promote increases in food intake, but also a positive feedback signal from the gut to the brain provided by these nutrients that can condition food preferences and stimulate appetite (4). This process, termed “appetition” by Sclafani, is distinct from the satiety system, and represents a postoral signal to enhance food intake (4).

This brief review will include a description of the physiology underlying the gut-vagal signaling that influences food intake and its role in food preference learning, recent evidence on how the dopaminergic systems in the brain interact with factors from the gastrointestinal tract to influence sweet appetite, and a discussion of new experimental paradigms and future directions which can advance the study of appetition.

Gut vagal afferent signaling and the control of food intake

Afferent fibers emerging from the vagus nerve are the main pathway by which information is relayed from the abdominal viscera to the hindbrain, thereby representing the major linkage between the gut and the brain (5). Chemoreceptor and mechanoreceptor responses are among the signals detected by vagal afferents, representing the transmission of nutrients/nutrient-related compounds and gastric distension, respectively (5). Indeed, the satiety-inducing hormones CCK and leptin activate vagal afferents (6), whereas the feeding-stimulatory peptide ghrelin suppressed vagal afferent firing (7). Experimentally induced gastric distension was found to activate satiety circuit-related brain regions (8), and reduce consumption of a test meal (9) further indicating a role of vagal signaling in neural and behavioral control of food intake.

Support for the negative feedback role of gut vagal afferent signaling in the regulation of satiety and reducing food intake has come from studies which interrupted transmission between the gut and brain via surgical transection of the vagus nerve (10). However, since the vagus is a mixed nerve, a total subdiaphragmatic vagotomy will result in a disruption of efferent transmission, involved in gastric regulation and motor control, as well as the afferent traffic from the gut to the brain. Therefore, in order to appropriately investigate the role of vagal afferent signaling in the control of food intake without a concomitant interruption of efferent gastrointestinal control, Norgren and Smith developed a method to selectively section either the afferent or efferent axons of the vagus nerve in the rat (11). In this technique, one set of afferent dorsal rootlets are selectively severed unilaterally, and the contralateral vagal subdiaphragmatic trunk is transected (11). The result is a total subdiaphragmatic vagal deafferentation (SDA).

Utilizing this SDA technique, Schwartz et al. aimed to investigate the role of vagal afferents in food intake regulation (12). In a spontaneous feeding experiment, sham-operated rats and SDA rats had 12-h ad libitum access to a 1kcal/ml palatable liquid diet supplement (Ensure Nutritional Shake, Abbott Laboratories). Intake of the test liquid (rate, pattern, and total number of licks) was quantified during the first 6 h of the dark cycle before surgery and 3 wk after surgery in sham-operated and SDA rats. It was observed that SDA rats had increased spontaneous meal size, longer inter-meal interval, reduced meal frequency and satiety ratio, and maintained initial high rates of licking longer during meals (12). These alterations in intake are indicative of a reduction in meal-related satiety and support a role of gut vagal afferent signaling in the negative feedback control of spontaneous meal size (12).

Subsequently, Sclafani, Ackroff, and Schwartz further investigated the role of vagal afferents as well as splanchnic fibers in the regulation of the feeding inhibitory effects of nutrient intraduodenal (ID) infusion and nutrient-induced flavor conditioning via carbohydrate and lipid ID infusion (13). In the first set of experiments, rats had SDA surgery or sham surgery and underwent a satiation test in which they could drink a maltodextrin + saccharin (M + S) solution paired with ID infusions of water, maltodextrin (carbohydrate) and corn oil (lipid) on separate sessions. In the sham-operated rats, M + S intake was reduced after ID infusions, but not in the SDA rats, who did not suppress intake of the M + S solution after ID infusions of maltodextrin and corn oil compared to water (13). Next, rats were conditioned to drink non-nutritive sweet flavored saccharin solutions (either cherry or grape flavored) paired with a concurrent ID infusion of water, maltodextrin, or corn oil. Grape flavor was paired with maltodextrin or corn oil in half of the rats (CS+) whereas cherry flavor was paired with water (CS-), and the reverse was done for the other half of the group (13). In a two-bottle choice test, both the sham-operated and SDA rats consumed higher amounts of the CS+ vs. CS- sweet beverage in both the maltodextrin and corn oil conditions.

In the second set of experiments, in addition to the subdiaphragmatic vagal afferents already discussed, the role of nonvagal visceral afferents that pass through the celiac-superior mesenteric ganglion and transmit sensory information from the gut to the brain was investigated (13). To explore this, splanchnic nerves were transected by celiac-superior mesenteric ganglionectomy (CGX) and rats were studied either after CGX alone, CGX combined with SDA (COM) or sham surgery (13). In a satiation test, M + S intake was reduced after ID maltodextrin infusions in the sham-operated rats but not in CGX or COM rats (13). Following ID infusions of corn oil, the CGX and sham-operated rats, but not the COM rats, reduced M + S intake. In the two-bottle choice test, all groups consumed higher amounts of the CS+ vs. CS- sweet beverage, in both the maltodextrin and corn oil conditions.

Together, these findings indicate that gut vagal and splanchnic afferents play a role in the negative feedback control of satiety after nutrient intake, but are not required for nutrient reinforcement or flavor-nutrient preference conditioning, thereby highlighting the distinction between the processes of satiation and appetite (13).

Intestinal sugar sensing, striatal dopamine and sweet appetite

The prior work demonstrated that vagal deafferentation did not block sweet flavor conditioning. However, a decrease in post-bariatric surgery appetite for sweet food has been reported in mice (14, 15), suggesting that a rerouting of the gastrointestinal tract can impact postoral nutrient sensing, flavor conditioning, and subsequent sweet flavor preference.

Han et al. aimed to investigate how gut-nutrient-induced dopamine release in the striatum is affected by gastrointestinal rerouting and the effects of this rerouting on sweet preference in a mouse model of bariatric surgery (16). In their study, mice were trained to drink a non-nutritive sucralose solution which was paired with intragastric (IG) infusions of either sucralose or glucose. In a finding reinforcing the expected appetite-stimulating effect of sugar in the gut, in a satiation test, IG glucose exposed mice self-administered more glucose and sucralose than IG sucralose exposed mice, after a satiating preload of nutritive sweetener (16). Authors then tested whether a duodenal-jejunal bypass surgery (DJB), which results in ingested food being diverted to the mid-jejunum while bypassing the duodenum, has an effect on sweet appetite flavor conditioning. Interestingly, the previously observed “appetition” effect was reduced in the DJB mice, which self-administered significantly less glucose and sucrose than sham-operated mice after a satiating preload of IG glucose. It was concluded that the sugar sensing at the duodenum is necessary for sweet appetite conditioning (16).

In an effort to link these behavioral effects to neurochemical changes in the brain and further delineate the gut-brain signaling that underlies increased sweet appetite following sugar exposure, dopamine release at the dorsal and ventral striatum was monitored in real time in response to concomitant IG glucose or sucralose infusion in sham-operated and DJB mice (16). In the sham-operated mice, IG glucose infusions induced greater dopamine release in both the dorsal and ventral striatum compared to IG sucralose. In DJB mice, enhanced dopamine release in response to IG glucose vs. IG sucralose was seen in the ventral, but not dorsal, striatum (16). Next, the effects of infusions of glucose or sucralose in different intestinal locations on concomitant dopamine release in the dorsal striatum were investigated. In sham-operated mice, glucose infusions in the duodenum induced greater dopamine release in the dorsal striatum than jejunal glucose infusions (16). This effect was not seen in DJB mice, which had no difference in dorsal striatal dopamine release after glucose infusion in the duodenum vs. jejunum. The duodenum therefore appears to be the intestinal site most important for inducing dorsal striatal dopamine release in response to sugar ingestion. It was also observed that portal-mesenteric glucose infusion, but not a similar jugular infusion, induced increases in striatal dopamine release. This reinforces a role for glucose-absorption in the duodenum, as opposed to a systemic effect, in regulating sweet flavor conditioning (16).

Future directions: Novel approaches and ramifications for “appetition”

Sclafani and Ackroff have been jointly and actively investigating the systems governing the gut-brain regulation of nutrient sensing and food reward for close to 30 years. Their work over this time, along with others in the field, has been instrumental in our understanding of

how feedback from the gut produces an inhibitory satiety signal to reduce food intake (4). Moreover, it is now also clear that a separate and complimentary positive feedback system produces signals that can stimulate appetite via flavor conditioning in response to nutrients in the gut (17).

A better understanding of the appetition process which drives increased intake and conditioned food preference in response to ingestion should continue to be pursued from a physiological and neurochemical perspective, as this approach can help the development of therapeutic approaches to eating disorders. Similar to what was described in the mouse model of bariatric surgery above, a reversal or blockade of appetition may be possible via a pharmacological approach. Furthermore, a novel experimental paradigm was recently described wherein single-cell neural firing activity within the nucleus accumbens was shown to be predictive of behavioral responses to a reward-signaling cue (18). Such an experimental approach can be utilized within nutrient-flavor conditioning and food intake studies to enhance our understanding of the dopaminergic pathways related to appetition. Whereas much work has been done to demonstrate the important role of dopamine in the formation of flavor-nutrient conditioning, other neurotransmitter and neurochemical systems such as opioid, endocannabinoid, benzodiazepine, and orexin, should be further studied as well (19). Finally, it may also be possible to uncover an as yet unrecognized hormone involved in the stimulation of appetite, using the techniques described above (20). In pursuing these future research questions, it is important to integrate hormonal, neurophysiological, and behavioral approaches to determine mechanisms and potential treatment approaches.

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References

1. Amin T, Mercer JG. Hunger and Satiety Mechanisms and Their Potential Exploitation in the Regulation of Food Intake. *Current obesity reports*. 2016; 5:106–112. [PubMed: 26762623]
2. Woods SC. The control of food intake: behavioral versus molecular perspectives. *Cell metabolism*. 2009; 9:489–498. [PubMed: 19490904]
3. Egecioglu E, Skibicka KP, Hansson C, Alvarez-Crespo M, Friberg PA, Jerlhag E, Engel JA, Dickson SL. Hedonic and incentive signals for body weight control. *Reviews in Endocrine and Metabolic Disorders*. 2011; 12:141–151. [PubMed: 21340584]
4. Sclafani A, Ackroff K. Role of gut nutrient sensing in stimulating appetite and conditioning food preferences. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2012; 302:R1119–R1133.
5. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000; 404:661–671. [PubMed: 10766253]
6. Peters JH, Ritter RC, Simasko SM. Leptin and CCK modulate complementary background conductances to depolarize cultured nodose neurons. *American Journal of Physiology-Cell Physiology*. 2006; 290:C427–C432. [PubMed: 16192299]

7. Date Y, Murakami N, Toshinai K, Matsukura S, Nijima A, Matsuo H, Kangawa K, Nakazato M. The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology*. 2002; 123:1120–1128. [PubMed: 12360474]
8. Wang G-J, Tomasi D, Backus W, Wang R, Telang F, Geliebter A, Korner J, Bauman A, Fowler JS, Thanos PK. Gastric distention activates satiety circuitry in the human brain. *Neuroimage*. 2008; 39:1824–1831. [PubMed: 18155924]
9. Geliebter A, Westreich S, Gage D. Gastric distention by balloon and test-meal intake in obese and lean subjects. *The American journal of clinical nutrition*. 1988; 48:592–594. [PubMed: 3414573]
10. Schwartz GJ. The role of gastrointestinal vagal afferents in the control of food intake: current prospects. *Nutrition*. 2000; 16:866–873. [PubMed: 11054591]
11. Norgren R, Smith GP. A method for selective section of vagal afferent or efferent axons in the rat. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 1994; 267:R1136–R1141.
12. Schwartz GJ, Salorio CF, Skoglund C, Moran TH. Gut vagal afferent lesions increase meal size but do not block gastric preload-induced feeding suppression. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 1999; 276:R1623–R1629.
13. Sclafani A, Ackroff K, Schwartz GJ. Selective effects of vagal deafferentation and celiac–superior mesenteric ganglionectomy on the reinforcing and satiating action of intestinal nutrients. *Physiology & behavior*. 2003; 78:285–294. [PubMed: 12576127]
14. Mathes CM, Bohnenkamp RA, Blonde GD, Letourneau C, Corteville C, Bueter M, Lutz TA, le Roux CW, Spector AC. Gastric bypass in rats does not decrease appetitive behavior towards sweet or fatty fluids despite blunting preferential intake of sugar and fat. *Physiology & behavior*. 2015; 142:179–188. [PubMed: 25660341]
15. Bueter M, Miras A, Chichger H, Fenske W, Ghatei M, Bloom S, Unwin R, Lutz T, Spector A, Le Roux C. Alterations of sucrose preference after Roux-en-Y gastric bypass. *Physiology & behavior*. 2011; 104:709–721. [PubMed: 21827777]
16. Han W, Tellez LA, Niu J, Medina S, Ferreira TL, Zhang X, Su J, Tong J, Schwartz GJ, Van Den Pol A. Striatal dopamine links gastrointestinal rerouting to altered sweet appetite. *Cell metabolism*. 2016; 23:103–112. [PubMed: 26698915]
17. Sclafani A. Gut–brain nutrient signaling. Appetition vs. satiation. *Appetite*. 2013; 71:454–458. [PubMed: 22664300]
18. McGinty VB, Lardeux S, Taha SA, Kim JJ, Nicola SM. Invigoration of reward seeking by cue and proximity encoding in the nucleus accumbens. *Neuron*. 2013; 78:910–922. [PubMed: 23764290]
19. Sclafani A, Touzani K, Bodnar RJ. Dopamine and learned food preferences. *Physiology & behavior*. 2011; 104:64–68. [PubMed: 21549727]
20. Ackroff K, Sclafani A. Post-oral fat stimulation of intake and conditioned flavor preference in C57BL/6J mice: a concentration-response study. *Physiology & behavior*. 2014; 129:64–72. [PubMed: 24582671]

Comment: On Collaborating with Tony Sclafani

“Tony’s long-standing interest in identifying and characterizing the sensorineural sources of gut feedback critical to the establishment and maintenance of food preferences were no secret to the field. Based on my presentations of the results of gut neural transections at the Columbia Appetitive Seminar, Tony took advantage of my less-than-regular attendance at the Seminar to approach (and reproach!) me, point-blank, saying, “I have a collaboration for you.” He proposed we work together to explore the then novel idea of vagal vs. non-vagal visceral afferent gut innervation in the development and expression of food preferences. I happily agreed, and thus began a “subway series” between my home in the Bronx and his in Brooklyn, surgical kit in hand, to work with Tony and Karen to perform these studies over the following year. Early findings suggested an important role of gut vagal afferents in the expression of food preferences. Never one to leave well enough alone, Tony nonetheless asked whether non-vagal afferents also contributed to fat and carbohydrate preference. To my surprise, we found that they did. Tony gracefully suggested I draft the findings, and he and Karen then brought the results to fruition in our manuscript, which appeared in this journal in 2003 (*Physiol Behav.* 2003 Feb;78(2):285–94).”

Gary Schwartz