Published in final edited form as:

Appetite. 2013 December ; 71: . doi:10.1016/j.appet.2012.05.024.

Gut-Brain Nutrient Signaling: Appetition vs. Satiation

Anthony Sclafani

Brooklyn College and the Graduate, School, City University of New York, Brooklyn, New York
11210 USA

Abstract

Multiple hormonal and neural signals are generated by ingested nutrients that limit meal size and suppress postmeal eating. However, the availability of sugar-rich and fat-rich foods can override these satiation/satiety signals and lead to overeating and obesity. The palatable flavor of these foods is one factor that promotes overeating, but sugar and fat also have postoral actions that can stimulate eating and increase food preferences. This is revealed in conditioning studies in which rodents consume flavored solutions paired with intragastric sugar or fat infusions. The significant flavor preferences and increased intake produced by the nutrient infusions appear to involve stimulatory gut-brain signals, referred to here as appetition signals, that are distinct from the satiation signals that suppress feeding. Newly developed rapid conditioning protocols may facilitate the study of postoral appetition processes.

Keywords

Flavor conditioning; Sugar; Fat; Gastric infusions

Introduction

During the last 40 years, the Columbia University Seminar in Appetitive Behavior has provided a valuable forum to discuss the latest developments in virtually all areas of ingestive behavior research. One of the many topics covered in the Seminar is the role of gut-brain nutrient signaling in limiting meal size and food intake. Our understanding of this process was greatly advanced by the use of gastric and intestinal infusions to study the influence of nutrients on the suppression of ongoing eating (satiation) and eating in the post-meal interval (satiety). The infusion procedure has been extensively used in experimental animals, including rats, mice, rabbits and pigs, as well as in humans to study the satiation/satiety processes (French & Cecil, 2001; Hout, 1982; Smith, 1998a). These and other studies led to the identification of several gut and pancreatic hormones that suppress feeding by activating vagal projections to the brain or by direct actions in the brain (Smith, 1998b). The first “satiation” hormone discovered was cholecystokinin (CCK) which is released by intestinal cells by ingested food (Smith, 1998c). Subsequent studies identified several other gut hormones including GLP-1 and PYY, and the pancreatic hormones amylin and glucagon (Woods, 2009). During the course of a meal, intestinal and absorbed nutrients stimulate the release of these hormones in increasing amounts until a “satiation” threshold is reached and

© 2012 Elsevier Ltd. All rights reserved.

Correspondence: Dr. Anthony Sclafani, Department of Psychology, Brooklyn College of CUNY, 2900 Bedford Avenue, Brooklyn, NY 11210 USA, Voice: 718-951-5606, Fax: 718-951-4824, asclafani@gc.cuny.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the meal is terminated (Woods, 2009). Gastric distention by ingested food is another satiation signal that limits meal size (Berthoud, 2008).

All of these gut satiation signals that suppress eating raise the question why overnutrition and obesity are such predominant health concerns in many modern societies. One simple potential explanation is the wide availability of palatable sugar- and fat-rich foods which tempt the palate and promote overeating (Berthoud, 2011; Eggecioglu *et al.*, 2011; Erlanson-Albertsson, 2005; Ryan *et al.*, 2012). Animal studies document the ability of sweet taste and fatty flavor to activate brain reward systems that promote food consumption (Hajnal & Norgren, 2008; Liang *et al.*, 2006). The obesity promoting effects of high-sugar or high-fat foods, or an assortment of such foods are well established in laboratory rodents (Sclafani, 1993; Speakman *et al.*, 2008). The effectiveness of intestinal and postabsorptive satiation signals to suppress feeding is reduced as the palatability of the food source is increased (Bédard & Weingarten, 1989; Campbell & Davis, 1974). In addition, chronic exposure to high-fat diets appear to raise the defended adiposity threshold such that higher levels of short-term satiation and long-term adiposity signals are required to suppress feeding (Ryan *et al.*, 2012).

While most attention has focused on the palatable flavor of high-sugar and high-fat foods in promoting overconsumption, research during the last 40 years has revealed that postoral actions of sugar and fat can also stimulate consumption and condition increased food preference (Sclafani & Ackroff, 2012). I propose the term “appetition” to refer to the postoral processes that increase food intake and food preference to distinguish them from the satiation processes that inhibit ingestion. This Seminar paper briefly reviews the evidence for postoral appetition.

Appetition

The first definitive study showing that postoral nutrient actions can enhance food preferences was reported by Holman using a conditioned flavor preference paradigm (Holman, 1968). Food-restricted rats were trained to drink a flavored saccharin solution (the conditioned stimulus or CS+, e.g., lemon) paired with intragastric (IG) infusions (7–10 ml) of an egg-nog diet (the unconditioned stimulus or US) in 5 min/day sessions alternating with another flavored solution (the CS–, e.g., anise) paired with IG water infusions. After six training sessions a two-bottle test (140 min) was conducted with the CS+ vs. CS– solutions without IG infusions. The rats showed a significant CS+ preference (~66%) preference during the first 20 min of the test although the preference dissipated in the remaining 120 min of testing. While the preference was rather modest and temporary, perhaps due to the short training sessions and complex diet used, Holman’s findings established that food preferences can be influenced by the postoral actions of nutrients.

Over the next 20 years several more studies reported that IG nutrient infusions (milk, glucose, casein) conditioned flavor preferences in food-restricted rats (Puerto *et al.*, 1976; Deutsch & Wang, 1977; Sherman *et al.*, 1983; Baker *et al.*, 1987). Given the nutritional needs of the animals, it was proposed that caloric or nutrient restoration served as the effective “reinforcer” for the conditioned flavor preference (Sherman *et al.*, 1983; Baker *et al.*, 1987). However, in 1988 we reported that rats with unlimited access to a chow diet developed a very strong (96%) preference for a flavored solution (e.g., cherry) that was paired with IG infusions of 16% maltodextrin (Polycose) over a differed flavored solution (e.g., grape) paired with IG water infusions during 24 h/day conditioning sessions (Sclafani & Nissenbaum, 1988). Furthermore, this preference persisted over four days of “extinction” testing during which both the CS+ and CS– were paired with IG water infusions. In this and many subsequent studies an automated “IG self-infusion” procedure was used in which the

animal controlled the infusion by its licking of the CS+ and CS- sipper tubes and the volume infused matched the CS volume consumed (Elizalde & Sclafani, 1990). These subsequent studies reported that non-deprived rats and mice acquired strong preferences for CS+ solutions paired with IG self-infusions of sugars (glucose, sucrose, maltose), fat (corn oil, Intralipid) or milk diets in 24-h tests (Lucas & Sclafani, 1989; Sclafani *et al.*, 1993; Azzara & Sclafani, 1998; Lucas *et al.*, 1998a; Sclafani & Glendinning, 2005; Ackroff & Sclafani, 1994; Lucas *et al.*, 1998a). Preferences were conditioned by IG self-infusions of calorically dense (2.1 kcal/ml) as well as very dilute (0.04 kcal/ml) nutrient sources (Ackroff & Sclafani, 1994; Lucas *et al.*, 1998a). IG nutrient self-infusions also conditioned flavor preferences in food-deprived and non-deprived rats given 30 min/day training sessions (Yiin *et al.*, 2005). Taken together, these findings demonstrate that animals need not be in an energy depleted state in order to acquire nutrient-based flavor preferences. Furthermore, energy repletion may not be sufficient to reinforce a flavor preference. In particular, IG fructose infusions, unlike glucose infusions, do not condition flavor preferences in hungry rats trained 30 min/day (Sclafani *et al.*, 1999). Nevertheless, nutrient restoration may be critical for some types of flavor conditioning as in the case of amino acid or calcium deficient animals (Gietzen *et al.*, 1992; Tordoff, 2002).

In addition to conditioning preferences, IG carbohydrate or fat self-infusions can substantially increase the intake of a flavored solution in some test situations. For example, chow-fed rats drank 2–3 times more saccharin solution when intake was paired with IG self-infusion of 6% glucose rather than with water (Ramirez, 1994). Chow-fed mice (C57BL/6, B6) also consumed substantially (~95%) more of a saccharin-sweetened CS+ solution paired with IG self-infusions of sugar (16% sucrose) or fat (5.6% Intralipid) than of the CS- solution paired with IG water during 24 h/day training sessions (Sclafani & Glendinning, 2005). Note, however, that the intake-stimulating effect of IG nutrient infusions is dependent upon the palatability of the CS+ flavor: the intake of a sweet CS+ is stimulated much more than the intake of a non-sweet CS+ solution (Ackroff & Sclafani, 1994; Ramirez, 1994; Sclafani & Glendinning, 2005). In one study rats given unlimited access to chow and a palatable sweet solution paired with IG self-infusions of 32% maltodextrin for 28 days, consumed more solution, total calories, and gained more weight than did rats given a mildly unpalatable bitter solution (Sclafani *et al.*, 1996). These findings indicate that the overeating and obesity promoting effects of sugar- and fat-rich foods are due to both their palatable (“appetizing”) flavor and their postoral stimulatory (“appetition”) actions.

The flavor preference and intake stimulating actions of nutrients described above were produced by IG infusions. An early study proposed that flavor conditioning is mediated by nutrient sensors in the stomach (Deutsch & Wang, 1977), but subsequent work challenged this idea (Baker & Booth, 1989; Drucker & Sclafani, 1997). In the case of glucose, the upper intestinal tract appears to be a critical site of action for flavor conditioning. This is indicated by the findings that preferences for a CS+ saccharin solution were conditioned by IG glucose infusions only if the sugar was allowed to empty into the intestine, and by direct glucose infusions into the duodenum or jejunum but not into the ileum or hepatic-portal vein (Ackroff *et al.*, 2010; Drucker & Sclafani, 1997). However, hepatic-portal glucose infusions conditioned a preference when the CS+ flavor was presented in a nutritive chow rather than a non-nutritive saccharin solution (Tordoff & Friedman, 1986). These and other results (Gowans, 1992) suggest that intravascular glucose can reinforce a flavor preference when it is associated with a CS+ that provides preabsorptive nutrient stimulation (Ackroff *et al.*, 2010).

While it is now well established that gastrointestinal nutrient infusions can condition flavor preferences and stimulate intake in laboratory rodents and as well as sheep (Villalba & Provenza, 1997), the time course of this appetition effect has been uncertain. In most

conditioning studies animals are given multiple training sessions with the CS+ and CS– paired with nutritive and non-nutritive infusions, respectively, before the flavor preference test is conducted. Multiple training trials are not always necessary, and two studies have reported one-trial flavor conditioning in rats given IG glucose infusions (Ackroff *et al.*, 2009; Myers, 2007). However, the critical flavor choice test was not conducted until a day or more after the CS+ conditioning trial so these studies did not reveal how rapidly the IG glucose conditioned the CS+ preference, i.e., within or after the training session.

Using a new mouse conditioning model, we observed that IG nutrient infusions can rapidly stimulate on-going ingestion within the first CS+ conditioning session (Zukerman *et al.*, 2011). Food-restricted B6 mice were trained to drink a flavored saccharin CS– solution paired with IG self-infusions of water during daily 1-h sessions (days 1–3) followed by sessions with a CS+ solution paired with IG self-infusions of 16% glucose (days 4–6); licks were recorded every minute throughout the sessions. Lick rates at the start of the first CS+ training session were at or below that of the preceding CS– sessions but by 12–15 min the mice increased their rate of licking such that their total 1 h CS+ licks were 44% greater than their CS– baseline. In the subsequent two CS+ training sessions, the mice licked the CS+ at a high rate from the very first minutes although their lick rate rapidly declined later in the sessions as the animals experienced the satiating action of the self-infused glucose. Nevertheless, total 1-h licks and intakes increased by 90% above the CS– baseline. Similar findings were obtained in a second group of mice that self-infused a fat emulsion (6.4% Intralipid) as they consumed the CS+ solution. The Intralipid infusion stimulated licking 10–12 min into the first session and increased total 1 h licks by 60% to 120% in CS+ sessions 1 to 3. In both experiments the mice significantly preferred the CS+ to the CS– in a two-bottle choice test (without IG infusions) conducted after training.

The rapid increase in licking observed in the first CS+ session suggests an unconditioned response to the glucose and Intralipid infusions, although rapid learning of a CS+ preference may have contributed to the appetition response. The elevated lick rates observed at the very start of the subsequent sessions is indicative of a conditioned response to the CS+ flavor. This is confirmed by the elevated lick rates observed in an extinction test with the CS+ paired with IG water self-infusions (Sclafani, unpublished observations). In the case of the Intralipid infusion, the early stimulation of drinking was presumably triggered by intestinal sensors since prior research indicates that Intralipid is not absorbed into the circulation within the first 30-min of an intestinal infusion (Greenberg *et al.*, 1995; Yoder *et al.*, 2009). The glucose infusion may have acted at pre- and/or post-absorptive sites to stimulate licking, but additional findings suggest an intestinal site of action. That is, unlike IG infusions, intraperitoneal self-infusions of 8% glucose failed to stimulate CS+ licking in the first or subsequent sessions (Zukerman & Sclafani, unpublished observations). As reviewed in detail elsewhere (Sclafani & Ackroff, 2012), the identity of the intestinal and/or post-absorptive nutrient sensors and signaling pathways that mediate postoral appetition and flavor conditioning by sugars and fats is not known and is the subject of current research.

The central mediation of postoral appetition is also incompletely understood. However, there is considerable evidence implicating central dopamine (DA) systems in postoral flavor preference conditioning and appetite stimulation (de Araujo *et al.*, 2012; Sclafani *et al.*, 2011). In particular, postoral infusions of glucose or fat are reported to activate DA circuits as measured by microdialysis, c-Fos and fMRI techniques (Ferreira *et al.*, 2012; Ren *et al.*, 2010; Oliveira-Maia *et al.*, 2011). Furthermore, inhibiting DA signaling with D1 receptor antagonists in the nucleus accumbens, amygdala and medial prefrontal cortex blocks flavor conditioning by IG glucose infusions (Touzani *et al.*, 2010a; Touzani *et al.*, 2009; Touzani *et al.*, 2008). Central opioid signaling does not appear to be critical for postoral glucose conditioning but little is known about the role of other neurochemical systems implicated in

food reward (e.g., endocannabinoid, benzodiazepine, orexin, and ghrelin circuits) in postoral appetite (Touzani *et al.*, 2010b).

Appetition vs. Satiation

Historically, food reward has been attributed to the satiating actions of nutrients (Le Magnen, 1987) and this is still a common view e.g., (Mayer, 2011). There is, however, little direct evidence that satiation *per se* conditions food preferences, and satiation may actually reduce the reward value of food (Rolls, 2006; Simpson & Bloom, 2010). In a test of the satiety-reward hypothesis, Van Vort and Smith (1983) trained rats fitted with a gastric cannula to “real-feed” and “sham-feed” different flavored milk diets; in sham-feeding, ingested liquid diets drain out the open gastric cannula and provide no nutrition or postoral satiation. In two-bottle choice tests the animals did not prefer the flavored milk (CS+real) that was real-fed and satiating over the flavored milk (CS+sham) that was sham-fed and not satiating. The authors concluded that satiation alone was not responsible for food reinforcement and flavor conditioning. In a subsequent study we observed that rats trained to real and sham-feed concentrated (32%) flavored maltodextrin solutions actually preferred the CS+sham to the CS+real solution in two-choice tests (Sclafani *et al.*, 1994). Other animals, however, trained with a less concentrated (8%) and, therefore less satiating maltodextrin solution significantly preferred the CS+real to the CS+sham solution. These findings confirmed that postoral nutrients can reinforce flavor preferences (as in the case of real-fed 8% maltodextrin) but that highly satiating foods (e.g. 32% maltodextrin) may actually reduce postoral reinforcement.

Further evidence for a dissociation between satiation and reward was obtained in a study in which hungry rats were trained to drink different flavored saccharin solutions (CS+8, CS+16 and CS+32) that were paired with IG self-infusions of 8%, 16% and 32% maltodextrin, respectively (Lucas *et al.*, 1998b). All three CS+ solutions were preferred to a CS– solution paired with IG water infusion but, in direct choice tests, the CS+16 was preferred to both the CS+8 and CS+32. Flavor conditioning also varies as a function of nutrient composition. In particular, we (Lucas *et al.*, 1998a) observed that chow-fed rats trained 24 h/day preferred a flavor (CS+HF) paired with a high-fat diet (HFD) IG infusion over a flavor (CS+HC) paired with an isocaloric high-carbohydrate diet (HCD) infusion; both flavors were strongly preferred to a water-paired CS– flavor. The HFD was less satiating, i.e., suppressed chow intake less, than the HCD. Reducing the satiating potency of the HCD, by diluting it with water, to that of the HFD resulted in equal preferences for the CS+HCD and CS+HFD even though the CS+HCD was now paired with a hypocaloric diet. These and other results (Warwick & Weingarten, 1996; Booth *et al.*, 1972; Sclafani, 2002) indicate that postoral reward effects of nutrients vary as a function of nutrient concentration and composition but that the most concentrated (and satiating) nutrient source may not be the most reinforcing.

Similar findings have been obtained in human flavor conditioning studies. As recently reviewed by Yeomans (2012), flavor preference conditioning has been studied in humans by training subjects to ingest flavored drinks or foods that differ in caloric density but are matched in flavor intensity and palatability. Conditioned flavor preference and acceptance are then measured using rating scales and intake tests. Several studies report increased preference (liking) for the flavor associated with the more energy-rich food source, but this is not always the case (Yeomans, 2012). According to Yeomans, conditioned preferences are more likely with a flavor associated with a moderate energy load rather than a high energy load which may have aversive satiating effects.

Another approach to the study of satiation and food reward is to examine the ability of “satiety” hormones to condition flavor preferences. Early investigators hypothesized that

nutrient conditioned flavor preferences are mediated by the release of CCK (Mehiel & Bolles, 1988). In a test of this idea, we trained hungry rats to drink CS+ and CS- solutions paired with intraperitoneal injections of CCK octapeptide (0.125 – 4 ug/kg) and saline, respectively (Pérez & Sclafani, 1991). In subsequent choice tests, rats displayed a significant, but weak preference for a CS+ paired with a low dose of CCK (0.5 ug/kg) that did not suppress intake. However, rats trained with higher CCK doses (2 – 4 ug/kg) that suppressed intake displayed either no preference or avoided the CS+ flavor. In a second study, treating rats with a dose of the CCK receptor antagonist devazepide that increased intake had no effect on flavor conditioning by maltodextrin infusions (Pérez *et al.*, 1998). Taken together, these findings indicate that a non-satiating dose of CCK can condition a mild flavor preference, but that CCK signaling is not required for carbohydrate-conditioned preferences. A possible role of CCK in protein-conditioned preferences has been suggested (Peuhkuri *et al.*, 2011) but remains to be determined. There are as yet no reports of flavor preference conditioning by other gut satiety hormones. Rather, flavor aversions and/or reduced food reward have been reported with PYY and GLP-1 or GLP agonists (Thiele *et al.*, 1997; Chelikani *et al.*, 2006; Kanoski *et al.*, 2012). The satiating actions of gut hormones and stomach distention are mediated in part by vagal afferent projections to the brain (Berthoud, 2008). Vagal afferent signaling, however, is not essential for postoral flavor-nutrient conditioning, which further argues for a distinction of appetite and satiation processes (Lucas & Sclafani, 1996; Sclafani & Lucas, 1996; Sclafani *et al.*, 2003; Uematsu *et al.*, 2010; Zukerman *et al.*, 2011)

While there is little evidence that gut satiety hormones enhance food reward, numerous studies indicate that the orexigenic hormone ghrelin promotes food reward (Olszewski *et al.*, 2008; Dickson *et al.*, 2011). In particular, ghrelin injections increase the intake of sweet solutions, food-conditioned place preferences, and lever pressing for food reward (Skibicka *et al.*, 2012), while ghrelin antagonism or gene deletion attenuates place preference conditioning and food reinforced behavior (Dickson *et al.*, 2011; Olszewski *et al.*, 2008; Perello & Zigman, 2012). Systemic administration of ghrelin by itself was found to condition a place preference in rats (Jerlhag, 2008) and conceivably ghrelin may also condition flavor preferences as well, but this remains to be determined. Ghrelin levels are increased when animals are food-restricted and it is not surprising that the hormone enhances food reward. However, nutrient intake or infusions suppress ghrelin release (Foster-Schubert *et al.*, 2008; Williams *et al.*, 2003) which argues against a direct role of ghrelin in the preference conditioning response to IG glucose and fat infusions (Sclafani & Ackroff, 2012; Ackroff *et al.*, 2010). Nevertheless, the role of ghrelin in nutrient conditioning warrants investigation.

Summary

In summary, appetite is stimulated not only by the palatable flavors of sugar- and fat-rich foods but also by the postoral actions of these nutrients. Postoral food reward is often assumed to derive from the food's satiating action, but there is little direct evidence for this view. Instead, flavor conditioning studies indicate that postoral nutrient-conditioned preference and stimulation of intake are mediated by an appetite system that is distinct from the satiation system that suppresses intake. Progress in understanding postoral appetite has been hampered in the past because of the multiple training trials required to establish learned preferences and increased appetite. However, the recent development of conditioning protocols that produce one-trial learning and rapid within session stimulation of intake (Ackroff *et al.*, 2009; Myers, 2007; Zukerman *et al.*, 2011) should facilitate the study of postoral positive controls of feeding.

Acknowledgments

This paper is based on a presentation at the Columbia University Seminar in Appetitive Behavior entitled “The Fortieth Anniversary Celebration: Translational Research in Appetitive Behavior: A 40 Year Retrospective and Look Ahead.” The author has been a member of the Seminar since its inception and gratefully acknowledges the Seminar founder, Dr. Theodore B. Van Itallie, and organizers, Drs. Katherine P. Porikos, Joseph R. Vasselli, and Harry R. Kissileff for maintaining this valuable institution for the last 40 years.

The preparation of this paper was supported by the National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-31135. The helpful comments of Dr. Karen Ackroff are gratefully acknowledged.

Reference List

- Ackroff K, Dym C, Yiin YM, Sclafani A. Rapid acquisition of conditioned flavor preferences in rats. *Physiology and Behavior*. 2009; 97:406–413. [PubMed: 19303888]
- Ackroff K, Sclafani A. Flavor preferences conditioned by intragastric infusions of dilute Polycose solutions. *Physiology and Behavior*. 1994; 55:957–962. [PubMed: 8022918]
- Ackroff K, Yiin YM, Sclafani A. Post-oral infusion sites that support glucose-conditioned flavor preferences in rats. *Physiology and Behavior*. 2010; 99:402–411. [PubMed: 20026145]
- Azzara AV, Sclafani A. Flavor preferences conditioned by intragastric sugar infusions in rats: Maltose is more reinforcing than sucrose. *Physiology and Behavior*. 1998; 64:535–541. [PubMed: 9761229]
- Baker BJ, Booth DA. Preference conditioning by concurrent diets with delayed proportional reinforcement. *Physiology and Behavior*. 1989; 46:585–590. [PubMed: 2602482]
- Baker BJ, Booth DA, Duggan JP, Gibson EL. Protein appetite demonstrated: Learned specificity of protein-cue preference to protein need in adult rats. *Nutrition Research*. 1987; 7:481–487.
- Bédard M, Weingarten HP. Postabsorptive glucose decreases the excitatory effects of taste on ingestion. *American Journal of Physiology*. 1989; 256:R1142–R1147. [PubMed: 2719156]
- Berthoud HR. Vagal and hormonal gut-brain communication: from satiation to satisfaction. *Neurogastroenterology and Motility*. 2008; 20:64–72. [PubMed: 18402643]
- Berthoud HR. Metabolic and hedonic drives in the neural control of appetite: who is the boss? *Current Opinion in Neurobiology*. 2011; 21:888–896. [PubMed: 21981809]
- Booth DA, Lovett D, McSherry GM. Postingestive modulation of the sweetness preference gradient in the rat. *Journal of Comparative and Physiological Psychology*. 1972; 78:485–512. [PubMed: 5016289]
- Campbell CS, Davis JD. Peripheral control of food intake: Interaction between test diet and postingestive chemoreception. *Physiology and Behavior*. 1974; 12:377–384. [PubMed: 4820134]
- Chelikani PK, Haver AC, Reidelberger RD. Dose-dependent effects of peptide YY(3–36) on conditioned taste aversion in rats. *Peptides*. 2006; 27:3193–3201. [PubMed: 16962209]
- de Araujo IE, Ferreira JG, Tellez LA, Ren X, Yeckel CW. The gut-brain dopamine axis: A regulatory system for caloric intake. *Physiology and Behavior*. 2012; 206:394–399. [PubMed: 22406348]
- Deutsch JA, Wang ML. The stomach as a site for rapid nutrient reinforcement sensors. *Science*. 1977; 195:89–90. [PubMed: 831263]
- Dickson SL, Egicioglu E, Landgren S, Skibicka KP, Engel JA, Jerlhag E. The role of the central ghrelin system in reward from food and chemical drugs. *Molecular and Cellular Endocrinology*. 2011; 340:80–87. [PubMed: 21354264]
- Drucker DB, Sclafani A. The role of gastric and postgastric sites in glucose-conditioned flavor preferences in rats. *Physiology and Behavior*. 1997; 61:351–358. [PubMed: 9035269]
- Egicioglu E, Skibicka K, Hansson C, Alvarez-Crespo M, Friberg P, Jerlhag E, Engel JA, Dickson S. Hedonic and incentive signals for body weight control. *Reviews in Endocrine & Metabolic Disorders*. 2011; 12:141–151. [PubMed: 21340584]
- Elizalde G, Sclafani A. Flavor preferences conditioned by intragastric Polycose infusions: A detailed analysis using an electronic esophagus preparation. *Physiology and Behavior*. 1990; 47:63–77. [PubMed: 2109327]
- Erlanson-Albertsson C. How palatable food disrupts appetite regulation. *Basic & Clinical Pharmacology & Toxicology*. 2005; 97:61–73. [PubMed: 15998351]

- Ferreira JG, Tellez LA, Ren X, Yeckel CW, de Araujo IE. Regulation of fat intake in the absence of flavor signaling. *Journal of Physiology*. 2012
- Foster-Schubert KE, Overduin J, Prudom CE, Liu J, Callahan HS, Gaylinn BD, Thorner MO, Cummings DE. Acyl and total ghrelin are suppressed strongly by ingested proteins, weakly by lipids, and biphasically by carbohydrates. *Journal of Clinical Endocrinology & Metabolism*. 2008; 93:1971–1979. [PubMed: 18198223]
- French SJ, Cecil JE. Oral, gastric and intestinal influences on human feeding. *Physiology and Behavior*. 2001; 74:729–734. [PubMed: 11790436]
- Gietzen DW, McArthur LH, Theisen JC, Rogers QR. Learned preference for the limiting amino acid in rats fed a threonine-deficient diet. *Physiology and Behavior*. 1992; 51:909–914. [PubMed: 1615051]
- Gowans, SE. Doctoral Dissertation. McMaster University; 1992. Role of portal and plasma glucose elevations in taste-to-postingestive consequence learning.
- Hajnal, A.; Norgren, R. Dopamine release by sucrose. In: Basbaum, AI.; Kaneko, A.; Shepherd, GM.; Westheimer, G.; Albright, TD.; Masland, RH.; Dallos, P.; Oertel, D.; Firestein, S.; Beauchamp, GK.; Bushnell, MC.; Kaas, JH.; Gardner, E., editors. *The Senses: A Comprehensive Reference*. New York: Academic Press; 2008. p. 459–468.
- Holman GL. Intra gastric reinforcement effect. *Journal of Comparative and Physiological Psychology*. 1968; 69:432–441. [PubMed: 5349026]
- Houpt KA. Gastrointestinal factors in hunger and satiety. *Neuroscience and Biobehavioral Reviews*. 1982; 6:145–164. [PubMed: 6285233]
- Jerlhag E. Systemic administration of ghrelin induces conditioned place preference and stimulates accumbal dopamine. *Addiction Biology*. 2008; 13:358–363. [PubMed: 18782383]
- Kanoski SE, Rupprecht LE, Fortin SM, De Jonghe BC, Hayes MR. The role of nausea in food intake and body weight suppression by peripheral GLP-1 receptor agonists, exendin-4 and liraglutide. *Neuropharmacology*. 2012; 62:1916–1927. [PubMed: 22227019]
- Le Magnen, J. Palatability: Concept, terminology, and mechanisms. In: Boakes, RA.; Popplewell, DA.; Burton, MJ., editors. *Eating Habits*. Chichester, England: John Wiley & Sons; 1987. p. 131–154.
- Liang NC, Hajnal A, Norgren R. Sham feeding corn oil increases accumbens dopamine in the rat. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 2006; 291:R1236–R1239.
- Lucas F, Ackroff K, Sclafani A. High-fat diet preference and overeating mediated by postingestive factors in rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 1998a; 275:R1511–R1522.
- Lucas F, Azzara AV, Sclafani A. Flavor preferences conditioned by intragastric Polycose in rats: More concentrated Polycose is not always more reinforcing. *Physiology and Behavior*. 1998b; 63:7–14. [PubMed: 9402608]
- Lucas F, Sclafani A. Flavor preferences conditioned by intragastric fat infusions in rats. *Physiology and Behavior*. 1989; 46:403–412. [PubMed: 2623061]
- Lucas F, Sclafani A. Capsaicin attenuates feeding suppression but not reinforcement by intestinal nutrients. *American Journal of Physiology*. 1996; 270:R1059–R1064. [PubMed: 8928906]
- Mayer EA. Gut feelings: the emerging biology of gut–brain communication. *Nature Reviews Neuroscience*. 2011; 12:453–466.
- Mehiel R, Bolles RC. Hedonic shift learning based on calories. *Bulletin of the Psychonomic Society*. 1988; 26:459–462.
- Myers KP. Robust preference for a flavor paired with intragastric glucose acquired in a single trial. *Appetite*. 2007; 48:123–127. [PubMed: 16979259]
- Oliveira-Maia AJ, Roberts CD, Walker QD, Luo B, Kuhn C, Simon SA, Nicolelis MA. Intravascular food reward. *PLoS ONE*. 2011; 6:e24992. [PubMed: 21980372]
- Olszewski PK, Schioth HB, Levine AS. Ghrelin in the CNS: from hunger to a rewarding and memorable meal? *Brain Research Reviews*. 2008; 58:160–170. [PubMed: 18308399]
- Perello M, Zigman JM. The role of ghrelin in reward-based eating. *Biological Psychiatry*. 2012 in press.

- Pérez C, Lucas F, Sclafani A. Devazepide, a CCK_A antagonist, attenuates the satiating but not the preference conditioning effects of intestinal carbohydrate infusions in rats. *Pharmacology Biochemistry and Behavior*. 1998; 59:451–457.
- Pérez C, Sclafani A. Cholecystokinin conditions flavor preferences in rats. *American Journal of Physiology*. 1991; 260:R179–R185. [PubMed: 1992819]
- Peuhkuri K, Sihvola N, Korpela R. Dietary proteins and food-related reward signals. *Food & Nutrition Research*. 2011; 55:5955.10.3402/fnr.v55i0.5955
- Puerto A, Deutsch JA, Molina F, Roll PL. Rapid discrimination of rewarding nutrient by the upper gastrointestinal tract. *Science*. 1976; 192:485–487. [PubMed: 1257784]
- Ramirez I. Stimulation of fluid intake by carbohydrates: interaction between taste and calories. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 1994; 266:R682–R687.
- Ren X, Ferreira JG, Zhou L, Shammah-Lagnado SJ, Yeckel CW, de Araujo IE. Nutrient selection in the absence of taste receptor signaling. *Journal of Neuroscience*. 2010; 30:8012–8023. [PubMed: 20534849]
- Rolls ET. Brain mechanisms underlying flavour and appetite. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2006; 361:1123–1136.
- Ryan KK, Woods SC, Seeley RJ. Central nervous system mechanisms linking the consumption of palatable high-fat diets to the defense of greater adiposity. *Cell Metabolism*. 2012; 15:137–149. [PubMed: 22244528]
- Sclafani, A. Dietary obesity. In: Stunkard, AJ.; Wadden, TA., editors. *Obesity: Theory and Therapy*. New York: Raven Press; 1993. p. 125-136.
- Sclafani A. Flavor preferences conditioned by sucrose depend upon training and testing methods: two-bottle tests revisited. *Physiology and Behavior*. 2002; 76:633–644. [PubMed: 12127003]
- Sclafani A, Ackroff K. The role of gut nutrient sensing in stimulating appetite and conditioning food preferences. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. 2012 in press.
- 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 and Behavior*. 2003; 78:285–294. [PubMed: 12576127]
- Sclafani A, Cardieri C, Tucker K, Blusk D, Ackroff K. Intragastric glucose but not fructose conditions robust flavor preferences in rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 1993; 265:R320–R325.
- Sclafani A, Fanizza LJ, Azzara AV. Conditioned flavor avoidance, preference and indifference produced by intragastric infusions of galactose, glucose and fructose in rats. *Physiology and Behavior*. 1999; 67:227–234. [PubMed: 10477054]
- Sclafani A, Glendinning JI. Sugar and fat conditioned flavor preferences in C57BL/6J and 129 mice: Oral and postoral interactions. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 2005; 289:R712–R720.
- Sclafani A, Lucas F. Abdominal vagotomy does not block carbohydrate-conditioned flavor preferences in rats. *Physiology and Behavior*. 1996; 60:447–453. [PubMed: 8840905]
- Sclafani A, Lucas F, Ackroff K. The importance of taste and palatability in carbohydrate-induced overeating in rats. *American Journal of Physiology*. 1996; 270:R1197–R1202. [PubMed: 8764282]
- Sclafani A, Nissenbaum JW. Robust conditioned flavor preference produced by intragastric starch infusions in rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 1988; 255:R672–R675.
- Sclafani A, Nissenbaum JW, Ackroff K. Learned preferences for real-fed and sham-fed Polycose in rats: Interaction of taste, postingestive reinforcement, and satiety. *Physiology and Behavior*. 1994; 56:331–337. [PubMed: 7938246]
- Sclafani A, Touzani K, Bodnar RJ. Dopamine and learned food preferences. *Physiology and Behavior*. 2011; 104:64–68. [PubMed: 21549727]
- Sherman JE, Hicks CF, Rice AG, Rusiniak KW, Garcia J. Preferences and aversions for stimuli paired with ethanol in hungry rats. *Animal Learning and Behavior*. 1983; 11:101–106.

- Simpson KA, Bloom SR. Appetite and hedonism: Gut hormones and the brain. *Endocrinology and Metabolism Clinics of North America*. 2010; 39:729–743. [PubMed: 21095541]
- Skibicka KP, Shirazi RH, Hansson C, Dickson SL. Ghrelin interacts with neuropeptide Y Y1 and opioid receptors to increase food reward. *Endocrinology*. 2012; 153:1194–1205. [PubMed: 22210742]
- Smith, GP. Pregastric and gastric satiety. In: Smith, GP., editor. *Satiation: From Gut to Brain*. New York: Oxford; 1998a. p. 10-39.
- Smith, GP. *Satiation: From Gut to Brain*. New York: Oxford University Press; 1998b.
- Smith, GP. The satiating effect of cholecystokinin and bombesin-like peptides. In: Smith, GP., editor. *Satiation: From Gut to Brain*. New York: Oxford University Press; 1998c. p. 97-125.
- Speakman J, Hambly C, Mitchell S, Krol E. The contribution of animal models to the study of obesity. *Laboratory Animals*. 2008; 42:413–432. [PubMed: 18782824]
- Thiele TE, Vandijk G, Campfield LA, Smith FJ, Burn P, Woods SC, Bernstein IL, Seeley RJ. Central infusion of GLP-1, but not leptin, produces conditioned taste aversions in rats. *American Journal of Physiology*. 1997; 272:R726–R730. [PubMed: 9124501]
- Tordoff MG. Intragastric calcium infusions support flavor preference learning by calcium-deprived rats. *Physiology and Behavior*. 2002; 76:521–529. [PubMed: 12126988]
- Tordoff MG, Friedman MI. Hepatic-portal glucose infusions decrease food intake and increase food preference. *American Journal of Physiology*. 1986; 251:R192–R196. [PubMed: 3728707]
- Touzani K, Bodnar RJ, Sclafani A. Activation of dopamine D1 receptors in the nucleus accumbens is critical for the acquisition, but not the expression, of flavor preference conditioned by intragastric glucose in rats. *European Journal of Neuroscience*. 2008; 27:1525–1533. [PubMed: 18336564]
- Touzani K, Bodnar RJ, Sclafani A. Dopamine D1-like receptor antagonism in amygdala impairs the acquisition of glucose-conditioned flavor preference in rats. *European Journal of Neuroscience*. 2009; 30:289–298. [PubMed: 19614979]
- Touzani K, Bodnar RJ, Sclafani A. Acquisition of glucose-conditioned flavor preference requires the activation of dopamine D1-like receptors within the medial prefrontal cortex in rats. *Neurobiology of Learning and Memory*. 2010a; 94:214–219. [PubMed: 20566378]
- Touzani K, Bodnar RJ, Sclafani A. Neuropharmacology of learned flavor preferences. *Pharmacology Biochemistry and Behavior*. 2010b; 97:53–62.
- Uematsu A, Tsurugizawa T, Uneyama H, Torii K. Brain-gut communication via vagus nerve modulates conditioned flavor preference. *European Journal of Neuroscience*. 2010; 31:1136–1143. [PubMed: 20377626]
- Van Vort W, Smith GP. The relationship between the positive reinforcing and satiating effects of a meal in the rat. *Physiology and Behavior*. 1983; 30:279–284. [PubMed: 6844440]
- Villalba JJ, Provenza FD. Preference for wheat straw by lambs conditioned with intraruminal infusions of starch. *British Journal of Nutrition*. 1997; 77:287–297. [PubMed: 9135373]
- Warwick ZS, Weingarten HP. Flavor-postingestive consequence associations incorporate the behaviorally opposing effects of positive reinforcement and anticipated satiety: Implications for interpreting two-bottle tests. *Physiology and Behavior*. 1996; 60:711–715. [PubMed: 8873241]
- Williams DL, Cummings DE, Grill HJ, Kaplan JM. Meal-related ghrelin suppression requires postgastric feedback. *Endocrinology*. 2003; 144:2765–2767. [PubMed: 12810528]
- Woods SC. The control of food intake: Behavioral versus molecular perspectives. *Cell Metabolism*. 2009; 9:489–498. [PubMed: 19490904]
- Yeomans MR. Flavour-nutrient learning in humans: An elusive phenomenon? *Physiology and Behavior*. 2012; 106:345–355. [PubMed: 22465846]
- Yiin YM, Ackroff K, Sclafani A. Flavor preferences conditioned by intragastric nutrient infusions in food restricted and free-feeding rats. *Physiology and Behavior*. 2005; 84:217–231. [PubMed: 15708774]
- Zukerman S, Ackroff K, Sclafani A. Rapid post-oral stimulation of intake and flavor conditioning by glucose and fat in the mouse. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 2011; 301:R1635–R1647.

Ingested nutrients stimulate the release of satiation signals that suppress feeding
Palatable sugar- and fat-rich foods can override satiation and promote overeating
Sugar and fat also generate postoral “appetition” signals that stimulate feeding
New rapid flavor conditioning procedures may facilitate the study of appetite