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From appetite setpoint to appetition: 50 years of ingestive behavior research

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Abstract

I review the main themes of my 50-year research career in ingestive behavior as a graduate student at the University of Chicago and a professor at the City University of New York. A seminar course with my Ph.D. mentor, S. P. Grossman, sparked my interest in the hypothalamic obesity syndrome. I developed a wire knife to dissect the neuropathways and the functional disorder responsible for the syndrome. An elevated appetite setpoint that permitted the overconsumption of palatable foods appeared central to the hypothalamic syndrome. In brain-intact rats, providing an assortment of highly palatable foods (the cafeteria diet) stimulated diet-induced obesity that mimicked elements of hypothalamic obesity. Studies of the determinants of food palatability led to the discovery of a "new" carbohydrate taste (maltodextrin taste) and the confirmation of a fatty taste. In addition to oral taste receptors, gut nutrient sensors stimulated the intake/preference for carbohydrate- and fat-rich foods via an appetition process that stimulates brain reward systems. My research career greatly benefited from many diligent and creative students, collaborators and technicians and research support from my university and the National Institutes of Health.

Keywords

Hypothalamic obesity; dietary obesity; maltodextrin taste; fat taste; nutrient conditioning; gut nutrient sensing

1. Introduction

It was a great honor for me to receive the 2017 Distinguished Career Award of the Society for the Study of Ingestive Behavior (SSIB) at its 25th annual meeting in Montreal. As a founding member, past-President and past-Treasurer, I have had a long association with the Society which makes this award especially meaningful to me. In this essay, which is based on my presentation at the SSIB Award Symposium, I reflect on my 50 years of research in

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the field of ingestive behavior. Another view of my research career has recently been published [152].

2. Hypothalamic hyperphagia and appetite setpoint

In 1966, I enrolled in the Ph.D. program of the University of Chicago where I was supported by a National Institute of Health (NIH) Traineeship in Experimental-Biological Psychology. In a first year seminar course with Sebastian Peter Grossman, I reviewed the behavioral functions of the hypothalamus and was intrigued by the hyperphagia/obesity syndrome produced by ventromedial hypothalamic (VMH) lesions. Therefore, when I joined Pete Grossman's lab in Fall 1967 this was my research topic, and this and questions derived from it would dominate the rest of my research career. (An interesting SSIB connection: John Brobeck was the first to report that overeating (hyperphagia) was responsible for the massive obesity induced by VMH electrolytic lesions [15]. He received the first Distinguished Career Award at the inaugural SSIB meeting held at Princeton University in 1992 and reflected on his early discovery at the meeting 25 years ago [14]; see commentary by [45]).

In the 1960s, feeding behavior was thought to be largely controlled by a lateral hypothalamic (LH) "hunger center" and a VMH "satiety center." Furthermore, VMH lesions were thought to produce hyperphagia by destroying laterally projecting inhibitory connections to the LH. As a test of this hypothesis, I proposed to transect the neural connections between the VMH and LH while leaving both feeding "centers" intact. Because of their relatively inaccessible location, it was necessary to devise a way to reach the small area with minimal disruption of the overlying areas. To accomplish this, I built a retractable wire knife and reported in my first published paper that ventromedial-lateral (VL) knife cuts between the VMH and LH produced overeating and obesity in rats [116]. This was a topical experiment because it was performed in two other laboratories at about the same time with similar results [6,32]. For my Ph.D. dissertation I compared the effects of different hypothalamic knife cuts and VMH electrolytic lesions on feeding and other behaviors (locomotor activity, affective behavior, gnawing) [88,89].

In 1970, I accepted an assistant professorship in the Psychology Department of Brooklyn College of the City University of New York, where I had received my Baccalaureate degree, and continued my research on hypothalamic hyperphagia. Although the initial knife cut findings appeared to support the VMH-LH dual center model, our subsequent findings obtained with selective hypothalamic and brainstem cuts suggested that destruction of a longitudinal pathway connecting the paraventricular hypothalamus and hindbrain regions was responsible for hypothalamic hyperphagia [9,44,91,105,106,107,125] (see [117] for a review). Studies conducted in Richard Gold's laboratory reached a similar conclusion [33]. However, Gold et al. proposed that ascending noradrenergic and serotonergic pathways were responsible for the overeating syndrome whereas our findings implicated a descending oxytocin pathway.

In addition to investigating the neuroanatomy of the hypothalamic hyperphagia, our studies explored the functional disorder responsible for the increased food intake and obesity. A classic study by Miller et al. [63] reported that rats with VMH lesions, despite their extreme

hyperphagia, displayed signs of decreased rather than increased hunger. In particular, VMH rats worked less for food in an operant lever press task and consumed less of a bitter quinine-adulterated chow than did control rats. Subsequent studies confirmed that VMH rats were “finicky” eaters that underate unpalatable foods and overate the most when fed palatable high-fat or high-sugar diets [19,144]. Other studies indicated that diet finickiness and hyperphagia can be dissociated by electrolytic lesions that damage different portions of the medial hypothalamus [36]. The VL knife cut animals in our studies, which have minimal brain damage, also worked less for food and underate quinine-adulterated chow, but only when they were obese. When their body weight was at control levels they worked as much or more for food than controls and consumed similar amounts of quinine-adulterated chow [90,118,130]. In one notable experiment, VL cut rats overate and gained weight rapidly when fed a preferred high-fat diet for 50 days, but when switched to a quinine-chow diet, underate for 20 days until they reached the body weight level of control animals on the same diet [130].

The elevated body weights displayed by VMH animals and their recovery of their obesity following a fast or a period of forced-overfeeding suggested to some investigators that medial hypothalamic lesions disrupted the “lipostatic” regulation of body weight rather than food intake control per se [38,43]. According to this view, some signal associated with obesity inhibits food intake, and VMH damage reduces the sensitivity to this signal, resulting in overeating until a higher adiposity level is reached. Based on our findings that obese VL-cut rats do not work hard for food or eat unpalatable foods but do so when tested at lean body weights, we proposed that the hypothalamic cuts specifically disrupted an “upper lipostat” or appetite setpoint that normally limits weight gain (adiposity) when the food environment is very favorable, i.e., abundant, easily available palatable foods. The knife cuts do not disrupt a “lower lipostat” or hunger set point that limits weight loss when feeding conditions are unfavorable, i.e., food difficult to obtain or unpalatable. Note that the concept of body weight or adiposity setpoint(s) remains controversial, and weight regulation can occur in the absence of a setpoint mechanism [20,65].

Another treatment that dramatically illustrated the defense of lean but not obese weight levels by VL knife cut rats is intestinal surgery. Following jejunoileal bypass or ileal transposition surgery, obese VL rats were hypophagic for several weeks until they reached the body weight levels of control rats [47,120]. This massive weight loss could not be attributed to an inability of the resected gut to absorb food because the same surgeries produced much smaller weight losses in the non-obese control animals. Rather, following bypass surgery the hypothalamic obese animals appeared less willing (or less able) than controls to tolerate the inhibitory signals generated by ingested food. At least some of these signals appeared to be aversive because obese bypass rats acquired a strong aversion to a novel flavor experienced in the post-surgical period [121].

3. Dietary hyperphagia and obesity

Along with our work on hypothalamic obesity, we conducted studies on diet-induced obesity in rats. Prior studies reported that feeding rats a high-fat diet from an early age produced excessive weight gains over several months [62,74]. However, our initial attempts to induce

adult-onset obesity in rats with high-fat chows were not successful (see also [71]). We therefore used a more extreme diet: we fed rats an assortment of palatable foods purchased at a nearby supermarket (e.g., cookies, cheese, marshmallows, chocolate, peanut butter, sweetened condensed milk) in addition to high-fat chow and plain chow. This proved very successful and the rats fed the “supermarket” diet (subsequently referred to as the cafeteria diet) rapidly gained weight relative to control rats fed only chow. The dietary obese rats, like hypothalamic obese rats, underate quinine adulterated diets, displayed reduced motivation to work for food rewards, and reduced deprivation-induced activity [128,129]. In a highly cited paper [86], Stanley Schacter had noted similarities in the feeding behaviors of hypothalamic obese rats and obese humans, such as diet finickiness and reduced food motivation. (For commentary and analysis of Schacter’s work see [34,81].) Given that human obesity is rarely associated with hypothalamic damage, we proposed that dietary obesity was a more appropriate animal model of the human condition than hypothalamic obesity.

In our experiments [115,129], rats fed the cafeteria diet for 60 days lost their excess weight when returned to a low-fat chow only diet. Rothwell and Stock [84] confirmed this result in rats fed a cafeteria diet for 17–22 days. However, a subsequent study by Rolls et al. [83] reported persistent obesity in rats fed a cafeteria diet for 90 days before being returned to chow. The various studies differed in a number of respects (rat strain, cafeteria foods used) but the duration of cafeteria feeding and/or degree of resultant obesity may be the most critical variable(s). Mandenoff et al. [60] reported that rats fed a cafeteria diet for 8 weeks had enlarged fat cells (hypertrophy) whereas rats fed the diet for 20 weeks had increased fat cell number (hyperplasia) as well as fat cell hypertrophy. They proposed that fat cell hyperplasia may be responsible for the persistent obesity displayed by rats given extended exposure to a cafeteria diet. The dietary obese rats in the Rolls et al. study not only maintained their obesity when fed chow only, but also recovered their obese state on the chow diet following a four-week fast. Persistently obese rats have not been challenged with a quinine-adulterated diet or by a work requirement and it would be of interest to determine if they defend their obesity in these situations.

Our early cafeteria diet studies stimulated considerable research in other laboratories [73,85]. Yet the cafeteria diet was criticized because its nutritional composition is uncontrolled, given that the animals can chose among a variety of different foods [64]. The complexity of the diet also makes recording nutrient and energy intakes difficult although not impossible [41,78] and simplified versions of the diet with only 3 or 4 food choices are effective [82,103]. An alternative to the multi-food cafeteria diet is to feed rats a composite diet that is high in fat and sugar (as opposed to the high-fat diets used in early studies). Barry Levin used such an “high energy” (HE) diet and observed that only about half of the rats became obese (diet-induced obese, or DIO rats) while the remaining rats were diet resistant (DR rats) [57]. In contrast, we observed that all rats fed the cafeteria diet gained more weight than chow-fed controls [129]; see also [85]. Together, these results suggests that the propensity to obesity is influenced by the composition and/or variety of foods offered to rats. This is further indicated by Levin’s findings that DR rats, although they failed to gain weight on the HE diet, did so when fed a palatable liquid diet (chocolate Ensure) in addition to or instead of the HE diet [55,56]. Note that the liquid diet was less energy dense than the HE

diet as well as chow, showing that that energy dense foods are not required to induce obesity in rats.

4. Bitter Taste and diet finickiness

It was long assumed that hypothalamic obese animals reject quinine-adulterated chow because of its unpalatable bitter taste [63] but this assumption was challenged by results we obtained with another bitter compound, sucrose octaacetate (SOA) [104]. In a short-term choice test, hypothalamic obese and control animals strongly preferred (>80%) a 0.1% quinine-chow to a 1% SOA-chow, indicating that at these concentrations the SOA diet was less preferred than the quinine diet. Yet, when offered the diets as their only food for 3 days, obese rats fed SOA-chow continued to overeat relative to control rats while obese rats fed quinine-chow ate less than controls. [104]. These and other findings indicated that the intake of quinine-chow was determined not by its bitter taste alone. Instead, toxic postoral effects of quinine, not shared by SOA, suppressed food intake and did so in part by conditioning an enhanced aversion to bitter taste [8,48,49,104]. As discussed below, subsequent studies revealed that postoral factors also modulate the preference for palatable high-sugar and high-fat foods.

5. Sweet taste and the Polycose story

Sweet taste is thought to contribute to the overconsumption of sugar-rich foods such as those included in cafeteria diets. A simple form of diet-induced obesity involves giving rats unlimited access to a sugar solution in addition to chow and water over several weeks [42]. However, it was not clear whether the sweet taste or the nutrient actions of sugar solutions promoted overeating [18,37]. To investigate this issue, we compared the overeating and weight gain response of rats fed chow, water and an isocaloric (32%) sweet sugar solution (sucrose or glucose) or a bland (to humans) maltodextrin solution [92,135]. The maltodextrin used (Polycose) was highly soluble in water and rapidly digested and absorbed as glucose. The results were quite clear: the rats overconsumed the Polycose solution as much or more as the sucrose and glucose solutions and the three saccharides induced similar increases in body weight compared to control rats fed only chow and water [92,135]. While the type of saccharide did not influence weight gain, its physical form had a significant effect. That is, rats offered sugar or Polycose as a dry powder did not gain more than controls, unlike rats fed the saccharide in solution or solid gel form [92,134]. Ramirez [80] also reported that sucrose presented in the form of a solution or hydrated diet promoted greater weight gains than did dry sucrose diets. He further suggested that the high moisture content of cafeteria diet foods contributes to their weight promoting actions.

The Polycose solution findings surprised us; we had expected that sweet sugar solutions would promote greater overconsumption and weight gain than non-sweet maltodextrin solutions. An earlier human study reported that infants consumed significantly more of liquid formula containing sucrose than Polycose, which was attributed to the palatable sweet taste of the sucrose [28]. We considered the possibility that Polycose, while bland tasting to humans, may have a palatable taste to rats. Subsequent experiments proved this to be the case. In short-term sham-feeding tests, rats with a gastric fistula consumed as much

Polycose as sucrose [70,126]. This indicated that Polycose, like sucrose, had a palatable taste because postoral nutritive factors are greatly minimized in sham-feeding tests. In brief-access lick tests, which also limit postoral effects, rats licked as much or more for Polycose as for sucrose or glucose [109] and preferred Polycose to sugars at dilute concentrations in two-bottle tests [124].

We next determined whether Polycose had a sucrose-like taste using a conditioned taste generalization paradigm. Rats that were trained to drink sucrose paired with a LiCl injection subsequently displayed aversions to sucrose as well as fructose and saccharin but not to Polycose. Likewise, rats trained to avoid Polycose displayed aversions to Polycose but not to sucrose, fructose or saccharin [69]. This indicated that Polycose has a palatable, but not a sweet taste to rats. Subsequent studies with knockout (KO) mice missing one or both components of the T1r2+T1r3 sweet taste receptor provided direct evidence that Polycose and sucrose activate different gustatory taste receptors. The KO mice displayed little or no attraction to sucrose solutions but normal or near-normal responses to Polycose in brief-access lick tests [149,150,161]. In contrast, KO mice missing post-receptor taste signaling elements (gustducin, Trpm5, Calhm1, P2X2/P2X3) displayed reduced preferences for Polycose, which confirmed that Polycose palatability is mediated by the gustatory system [98,139,143].

In addition to rats and mice, other mammals (gerbils, hamsters, rabbits, bonnet macaques) appear to have maltodextrin taste receptors [26,52,53,142]. Although we assumed that humans lacked a maltodextrin taste [26], more recent findings indicate otherwise. That is, recent psychophysical experiments indicate that humans can discriminate maltodextrin solutions from water although maltodextrins elicit, at best, a subtle taste sensation [50,51,79]. Other evidence indicated that maltodextrin taste, even when masked by other flavors, can enhance physical performance in humans and may serve as a carbohydrate energy signal [40]. The optimal stimuli to elicit maltodextrin taste in rats and humans (glucose polymers of 4–8 units) are similar, which suggests that the yet to be identified maltodextrin taste receptor are also similar in these species.

Our discovery of a maltodextrin taste in rodents meant that comparisons of the feeding response to maltodextrins and sugars could not address the role of taste palatability in promoting carbohydrate-induced overeating and obesity. To resolve this issue we used a different approach to separate carbohydrate taste and postoral actions.

6. Flavor-nutrient conditioning: the electronic esophagus preparation

In addition to investigating Polycose taste in rodents, we also determined whether postoral effects contributed to its attractiveness. For this purpose, we developed an “electronic esophagus” (EE) preparation which allowed rats to self-administer a Polycose solution directly into the gut, i.e., their licking response to a sipper tube activated a pump that delivered the Polycose via an implanted intragastric (IG) catheter [25,127]. We used a flavor conditioning protocol to evaluate the appetitive (reward) effect of the Polycose infusion. Rats were given 23 h/day access to different flavored solutions on alternate one-bottle training days; chow was available ad libitum. The two flavors had fruit-like odors and a

common sour taste (unsweetened grape or cherry Kool-Aid) that were equally unattractive relative to plain water. The intake of one flavor (the CS+) was paired with volume-matched IG infusions of Polycose (16 or 32%) while the other flavor (the CS−) was paired with water infusions. During training, the rats consumed more total fluid (oral + infused) on CS+ days than on CS− days. Furthermore, when given a two-bottle choice test they displayed a strong preference for the CS+ flavor (≥ 90%) over the CS− flavor. These results demonstrated that the postoral actions of Polycose, in the absence of a palatable taste, can stimulate intake and produce a strong conditioned flavor preference. We confirmed these findings in subsequent studies with rats and mice infused with different glucose-containing saccharides (glucose, sucrose, maltose, maltodextrin) [10,22,75,108,113,114]. In contrast, isocaloric fructose infusions were much less effective in conditioning flavor preferences, which indicated that postoral nutrient reinforcement was not related to calories, per se (see below) [97,108,111].

Using the EE preparation we returned to the question of the role of taste in carbohydrate-induced overeating and obesity [123]. Rats fitted with IG catheters were given ad libitum access to chow and different drinking fluids paired with gastric infusions. One group was given a highly attractive solution (P+S, 2% Polycose + 0.2% saccharin, [110]) paired with IG infusions of 30% Polycose. A second group was given a mildly unattractive solution (0.03% SOA) paired with IG infusions of 32% Polycose. A third (control) group was given plain water paired with IG water infusions. The P+S group consumed substantially more flavored solution and thus self-infused more Polycose than did the SOA group over the 4-week experiment. Furthermore, P+S rats consumed 34% more calories (Polycose + chow) and gained more weight than did the control group. In contrast, the SOA rats consumed only 13% more calories and failed to gain reliably more weight than did the control group. In subsequent two-bottle choice tests, the control rats preferred plain water to the SOA solution (by 71%), documenting the unattractive taste of the bitter SOA, while the SOA rats preferred the SOA solution to water (by 71%), documenting the ability of IG Polycose to condition a flavor preference. The P+S group displayed a 98% preference for P+S over water, which presumably represents the inherent preference for maltodextrin and sweet tastes as well as a conditioned preference produced by the IG Polycose infusions. These results demonstrate that taste palatability contributes to the overeating and weight-promoting actions of carbohydrate solutions, although postoral actions alone are sufficient to condition a flavor preference and promote mild overeating. Other experiments confirmed that taste palatability influences the amount of carbohydrate and/or energy consumed by mice [30,113,114].

7. Operant licking as a measure flavor and nutrient motivation

In our early studies of hypothalamic and dietary obesity we used an operant lever press task to measure food motivation. More recently we adopted an operant lick task [61] to study the appetite for sweets and flavor-nutrient conditioning. Rats were trained to lick a sipper tube for small drops (0.065 ml) of sucrose delivered to the sipper tube on a Fixed Ratio (FR) schedule (20 licks/reward). In 1- or 24-h tests, licks and intakes increased as concentration increased from 1 to 8%, but then declined at higher concentrations (16–64%) due to the satiating actions of the ingested sugar. However, when the rats were required to lick on a Progressive Ratio (PR) schedule, in which the lick requirement increased with successive reinforcements (20, 21, 22, etc), their licks and break point (highest ratio reached) increased

monotonically with concentration. This occurred because the PR schedule reduced overall sugar intakes so satiety was no longer a limiting factor.

In a subsequent study we used the PR lick task to evaluate the motivational value of sucrose in inbred mouse strains (C57BL/6J, 129P3/J) that differed in their sweet taste sensitivity due to genetic variations in the T1R3 receptor [94]. We also compared the PR lick response of C57BL/6J mice to different nutritive and non-nutritive sweeteners [138]. In 24-h tests mice licked considerably more and had a higher break point when working for 8% glucose solution than for 0.1% sucralose+saccharin (S+S) solution but more for S+S than for 8% fructose. Brief-access (1-min) choice tests indicated that S+S had a more preferred taste than glucose or fructose, and the stronger PR response to glucose was attributed to the potent postoral conditioning actions of this sugar; fructose, in contrast, has no postoral preference conditioning effect in C57BL/6J mice. Consistent with this interpretation are results obtained in an operant lick study of postoral nutrient conditioning [96]. Rats were trained with two isosweet flavored saccharin solutions. The CS+ and CS− solutions were paired with IG infusions of glucose and water, respectively. A subsequent two-bottle test revealed, as expected, that the CS+ was strongly preferred to the CS−. The rats were then trained in an operant lick task similar to that for oral sweeteners, but now every 20 licks delivered 0.065 ml of the CS+ or CS− to the sipper tube and an equal volume of glucose or water to the stomach. In subsequent PR tests the CS solutions and IG infusions were delivered after progressively increasing lick requirements. The rats licked significantly more and reached a higher break point when reinforced with the CS+ solution/IG glucose than when reinforced with the CS− solution/IG water. Thus, the IG glucose infusions, in addition to conditioning a flavor preference, also increased the incentive value of the CS+ flavor relative to the CS− flavor.

In an innovative modification of the operant lick task, Ferreira et al. [27] trained mice to lick a “dry” sipper tube for IG nutrient infusions (0.06 ml of Intralipid or glucose). The food-restricted animals were initially induced to lick the dry tube by baiting it with chow that could be smelled but not tasted. In subsequent sessions the tube contained no chow and the animals were reinforced only with IG nutrient infusions. This allowed for the measurement of postoral nutrient reinforcement in the absence of oral flavor cues. Ferreira et al. reported that operant dry lick rates were modulated by the energy density of the nutrient infusions. On a FR schedule, animals licked more for dilute nutrient infusions than for concentrated nutrient infusions such that they maintained a constant energy intake. However, on a P R schedule IG infusions of concentrated fat produced higher PR lick rates than infusions of dilute fat [145]. In my laboratory, we confirmed that IG infusions of sugar and fat reinforce operant dry licking in mice as a function of nutrient concentration [99,132]. Our experiments further revealed, however, that the type of nutrient infused greatly influenced operant dry licking. C57BL/6J mice dry-licked at high rates for IG glucose infusions but basically extinguished their licking response when reinforced with isocaloric fructose infusions [132]. This is consistent with the differential flavor conditioning effects of IG glucose and fructose and demonstrate that sugar energy content per se is not the primary determinant of postoral reinforcement.

Given the effectiveness of operant lick tasks to measure taste/nutrient motivation in rodents, we developed an analogous task for human subjects. Humans obviously do not typically consume beverages by licking a tube but they often do so by sipping a straw (e.g., soda, milkshake). Consequently we designed a computer-controlled "sipometer" the allowed subjects to sip a nutritive or nonnutritive beverage through a straw on a continuous reinforcement schedule (essentially free access) or on a PR schedule that required longer and longer sip times to obtain a reinforcement (e.g., 7 ml of beverage). Initial experiments conducted by Harry Kissileff and colleagues investigated the effects of deprivation state (1- or 21-h), taste (sweet or nonsweet), or sleep time (unrestricted or restricted) on sipping motivation [39]. Kissileff [46] has recently reviewed the design of the sipometer and theoretical issues related to human food motivation.

8. Postoral appetition and gut nutrient sensing

The EE preparation and operant licking proved to be an invaluable tools to investigate the postoral actions of carbohydrates and other nutrients (fats and proteins) on appetite and flavor preferences. Our original studies involved 23 h/day infusions. To determine how rapidly nutrients act to modify appetite we used short-term sessions (1 h) with continuous recording of the licking response to the flavored solutions. In these experiments, mice were given several daily sessions with a CS− flavor paired with IG water infusion followed by daily sessions with a CS+ flavor paired with IG glucose infusions. The findings revealed that glucose infusions can stimulate ingestion within 10–15 min of the first CS+ training session [158,159,160], see also [68]. Ingestion rates were elevated at the start of the second CS+ training session, indicating that the animal had acquired a learned attraction to the CS+ flavor. This was also revealed by the CS+ preference displayed by animals given a two-bottle CS+ vs. CS− choice following the first CS+ training session [1,66]. We referred to the postoral process that produced rapid stimulation of ingestion and flavor conditioning as "appetition" to distinguish it from the satiation process by which nutrients in the gut suppress appetite and intake [95].

The gastric infusates in these studies, together with the orally consumed fluids, passed from the stomach to the duodenum and then onto the rest of the gastrointestinal tract and post-absorptive sites, so that the locus of glucose appetition action was uncertain. To investigate where glucose acts to condition flavor preferences we trained animals to associate a CS+ flavor with glucose infusions into different visceral sites [5,23,160]. Significant CS+ preferences were produced by glucose infusions into the stomach, duodenum, and jejunum but not into the ileum, hepatic-portal vein or peritoneal cavity. Furthermore, gastric infusions were not effective if the glucose was prevented from emptying into the duodenum by a pyloric clamp [23]. Taken together, these findings implicated the upper intestinal tract as a primary site for glucose-induced appetition. Using different training protocols, other studies reported that hepatic-portal glucose produced conditioned food or position preferences [72,147].

The discovery in 2005 that T1r2 and T1r3 sweet receptor components are expressed in intestinal cells [24] suggested that intestinal sweet receptors might mediate postoral sugar appetition [11]. However, our finding that fructose and glucose, both ligands of the

T1r2+T1r3 receptor, differ significantly in their postoral appetition effects did not support this view [97,108,111,159]. We also found that IG infusions of sucralose, a high-intensity non-nutritive sweetener, failed to condition flavor preferences [112]. Direct evidence that intestinal sweet receptors do not mediate postoral sugar appetition was provided by our findings that IG sucrose infusions stimulate CS+ intake and preference to similar degrees in T1r3 KO and wild-type mice [112]. Instead, flavor conditioning results obtained with different sugars, sugar analogs and pharmacologic blockers indicated that intestinal glucose transporters/sensors (SGLT-1, SGLT-3, and GLUT2) mediate the postoral appetition effects of glucose [119,159].

In addition to our studies of carbohydrate taste and appetition, we conducted parallel studies of dietary fat preference. The preference for high-fat foods was long attributed to their texture and odor properties, but Laugerette et al. [54] published evidence that the CD36 glycoprotein served as a fatty acid receptor on lingual taste cells and mediates the preference for fat-rich foods. We confirmed that KO mice lacking CD36 displayed reduced preferences for fatty acid as well as triglyceride solutions [101]. We also observed significant fat preference deficits in KO mice lacking downstream taste signaling elements (Trpm5 and P2X2/P2X3) [98,101,139]. The G-protein receptors GPR40 and GPR120 were subsequently proposed to serve as additional fat taste receptors [17], although this was not confirmed in later studies [7,136]. Our studies with the EE preparation revealed that fat preference is enhanced by the postoral actions of the nutrient in rats [2,58,156]. In mice, IG infusions of fat stimulated increased ingestion within 20 min of the first infusion, which suggested an intestinal site of action [3,158]. We investigated the role of postoral fatty acid sensors CD36, GPR40 and GPR120 in fat appetition using KO mice. GPR40+GPR120 double KO mice displayed substantial deficits in IG fat conditioning, whereas GPR120 KO and GPR40 KO mice displayed mild to moderate impairments and CD36 KO mice were unimpaired [101,136]. Thus CD36 is important in the mouth and GPR40 and GPR120 in the gut for fat appetite in mice.

8. Summary and Future Directions

A major emphasis of my research during the last 50 years has been on the sensory features of foods that promote appetite. My interest in this topic was stimulated by the profound effects of dietary manipulations on the food intake and weight gain of hypothalamic obese rats as well as cafeteria-fed rats. When I began my research the appetite stimulating effects of sugar and fat were well known, but sweet taste receptors had yet to be identified; fat taste receptors had yet to be imagined; and the existence of gut nutrient sensors that promote appetition was unknown. The subsequent identification of sweet and fat taste receptors, downstream taste signaling elements and gut nutrient sensors and the development of knockout mice missing these various sensing components have revolutionized the ingestive behavior field.

Our knowledge of oral and postoral taste/nutrient sensors remains incomplete. The T1r2+T1r3 receptor is recognized to serve as the generic sweet taste sensor in mammals, but there is evidence for other oral sugar sensors. In the mouse, the K_{ATP} channel rather than the T1r2+T1r3 receptor appears to mediate the cephalic phase insulin response to sugars

[29,31]. There may be additional taste receptors that allow animals to discriminate between glucose and fructose [87,141] and between fructose and non-nutritive sweeteners [100]. There is strong evidence for the existence of a maltodextrin taste receptor but it has yet to be identified [93,141,161]. Some findings suggest that mice have separate receptors for maltodextrins and starch [139,162]. The existence of T1r2 and T1r3 receptors in the gut and other organs was a major discovery but their exact physiological functions are not fully understood. Available evidence indicates that gut T1r2+T1r3 receptors do not mediate postoral sugar appetition, instead implicating glucose-specific sensors [112,119,159]. Although less potent than glucose, IG fructose infusions condition flavor preferences in rats and some inbred mouse strains (FVB/NJ, CAST/EiJ), but the sensor(s) responsible for this effect remain unknown [4,133,137]. The role of hepatic-portal and brain sugar sensors in appetite and preference condition also requires much more research.

Multiple oral and postoral fat sensors have been identified. Current evidence indicates that CD36, but not GPR40 or GPR120, functions as a fatty acid taste receptor [7,17,54,136]. The fat preference deficits observed in CD36 KO mice are weaker than those observed in mice missing downstream taste signaling elements, suggesting that other fatty acid and perhaps triglyceride taste receptors exist [98,100,101,139]. Intestinal GPR40 and GPR120 fatty acid sensors have a major role in postoral fat appetition but residual fat conditioned preferences displayed by GPR40+GPR120 double KO mice suggest the involvement of other fat sensors [132,136].

An important unresolved question is how gut appetition signals reach the brain. Vagal fibers may carry some signals [146,151] but not others [59,102,122,131,140]. The evidence for gut appetition hormones remains weak, but additional work is needed [76,77,131]. We and other investigators have identified several brain regions and neurochemical systems that mediate postoral nutrient conditioned preferences and this remains an active area of research [13,21,148,157]. Another major issue that requires further research is the role of postoral nutrient appetition in humans. Flavor preference conditioning occurs in children and adults [12,35,153,155], but to date it appears less pronounced and reliable than that observed in rodents [16,67,154]. I hope that my research provides “appetition” signals for other scientists to pursue these future directions.

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Highlights

- SSIB Distinguish Career Award essay, reviewing:
- Studies of hypothalamic hyperphagia pathways and behavioral analysis
- Studies of diet-induced obesity and carbohydrate tastes
- Studies of postoral nutrient conditioning and appetition