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Proceedings of the 2015 A.S.P.E.N. Research Workshop - Taste Signaling: Impact on Food Selection, Intake, and Health

Alan C. Spector, PhD[1], **Carel W le Roux, MD, FRPC, PhD**[2], **Steven D. Munger, PhD**[3], **Susan P. Travers, PhD**[4], **Anthony Sclafani, PhD**[5], and **Julie A. Mennella, PhD**[6]

[1] Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, FL, USA. spector@psy.fsu.edu

[2]Diabetes Complications Research Centre, Conway Institute, University College. Dublin, Ireland., carel.leroux@ucd.ie

[3]Department of Pharmacology and Therapeutics; Department of Medicine, Division of Endocrinology, Diabetes and Metabolism; Center for Smell and Taste, University of Florida, Gainesville, FL, USA. steven.munger@ufl.edu

[4]Division of Biosciences, College of Dentistry, Ohio State University. Columbus, OH, USA. travers.3@osu.edu

[5] Department of Psychology, Brooklyn College of the City University of New York, New York, NY, USA

[6]Monell Chemical Senses Center, Philadelphia, PA, USA. mennella@monell.org

Abstract

This paper summarizes research findings from six experts in the field of taste and feeding that were presented at the 2015 ASPEN Research Workshop. The theme was focused on the interaction of taste signals with those of a postingestive origin and how this contributes to regulation of food intake through both physiological and learning processes. Gastric bypass results in exceptional loss of fat mass, increases in circulating levels of key gut peptides, some of which are also expressed along with their cognate receptors in taste buds. Changes in taste preference and food selection in both bariatric surgery patients and rodent models have been reported. Accordingly, the effects of this surgery on taste-related behavior were examined. The conservation of receptor and peptide signaling mechanisms in gustatory and extraoral tissues was discussed in the context of taste responsiveness and the regulation of metabolism. New findings detailing the features of neural circuits between the caudal nucleus of the solitary tract (NST), receiving visceral input from the vagus nerve, and the rostral NST, receiving taste input, were discussed, as was how early life experience with taste stimuli and learned associations between flavor and postoral consequences of nutrients can exert potent and long-lasting effects on feeding

1. INTRODUCTION

The gustatory system is the gatekeeper for the alimentary tract. Although it is undisputed that the taste properties of food interact with need-state, postingestive events, and prior experience to determine what and how much is consumed, the mechanisms by which these

factors interact is only beginning to be understood. This paper summarizes research findings, presented by 6 experts in the field at the 2105 ASPEN Research Workshop that highlight the complexity of such interactions and their implications for nutrition and health throughout the lifespan. Abbreviations used throughout the text are defined in Table 1.

2. OVERVIEW OF THE GUSTATORY SYSTEM (ALAN C. SPECTOR)

Taste buds, which are distributed in distinct fields in the oral cavity, provide the brain with a chemical analysis of the substances placed in the mouth. One taste bud field is positioned at the tip of the tongue, another in the back, a third on the palate, and finally a few taste buds are found in the laryngeal epithelium – the latter are thought to be more involved with protection of the airways (1;2). A taste bud consists of ~50-100 specialized epithelial cells the apical membranes of which protrude into an opening, called the taste pore, through the stratified squamous epithelium of the tongue. Taste stimuli gain access to the molecular receptors expressed in the apical membranes via this taste pore.

In the last 15 years, there have been groundbreaking discoveries of proteins thought to serve as taste receptors. Of these, one class consists of the G protein-coupled receptors (GPCRs), including the T1R1+T1R3 heterodimer binding with L-amino acids, the T1R2+T1R3 heterodimer binding with sweeteners, and the family of about 25-30 T2Rs which bind with various bitter tasting ligands (3). Other proteins thought to potentially be involved are GPR40 and GRP120, which are proposed to mediate fat taste along with CD36, and splice variants of the mGluR1 and mGluR4 hypothesized to contribute to L-glutamate taste. Although it is thought that the receptors for salt and acid taste are ion channels, exactly which ion channels contribute remains to be resolved. For example, while it is clear that the epithelial sodium channel (ENaC) is critical for normal taste detection and recognition of sodium taste in rodents (4-7), it remains unclear whether it plays a role in human salt taste (8;9). When many of the key taste GPCRs, such as the T1Rs and T2Rs, were discovered they were thought to be restricted to the peripheral gustatory system, but since then it has been shown that they are expressed in a variety of non-gustatory tissues including the gut where they are thought to serve as nutrient sensors (see Section #5).

Each taste bud field is innervated by a different nerve branch from one of three cranial nerves, the facial (7^{th}), glossopharyngeal (9^{th}), and vagus (10^{th}). The taste input in these nerves terminates in an area of the medulla known as the rostral nucleus of the solitary tract (rNST) in a rough, but overlapping orotopic fashion (see (10)). Interestingly, the vast majority of the sensory signals transmitted by the 10^{th} nerve actually arise from the viscera, especially the gut. These terminate directly behind the taste area in the caudal NST (cNST). This anatomical relationship between areas responsive to taste and those responsive to visceral stimulation is maintained throughout much of the brain. Consequently, one can see why the early neuroanatomists categorized the axons of the gustatory nerve branches as *special visceral afferents*. After all, the receptors and subsequent neural signals arising from the oral cavity represent just the first stage of the sensory analysis of ingested contents traveling through the alimentary tract.

Domains of Taste Function

What most people commonly refer to as *taste* is in reality *flavor*, which represents the perceptual integration of sensations arising from the gustatory, olfactory, and trigeminal systems. Technically speaking, *taste* refers to the perceptual, behavioral, and physiological consequences of stimulation of taste receptor cells in the oral cavity. Taste function is multidimensional (11;12). There is a sensory/discriminative domain that refers to the identification of the stimulus which includes taste quality. There is also a hedonic or affective domain that refers to the motivational properties of the stimuli that either promote or discourage ingestion. Specialists break this up into *appetitive* and *avoidance* behaviors that bring the animal to the taste stimulus or drive it away, and *consummatory* responses that represent the oral actions associated with ingestion or rejection that are triggered by contact of the stimulus with the taste receptors. Finally, the physiological domain refers to physiological reflexes triggered by taste stimuli such as salivation that are thought to promote optimal digestion and assimilation of food and fluids.

3. EXCEPTIONAL CONSEQUENCES OF ROUX-EN-YGASTRIC BYPASS SURGERY: CHANGES IN GLYCEMIC STATUS, GUT HORMONES, AND FOOD PREFERENCES (CAREL W. LE ROUX)

The prevalence of obesity has increased dramatically globally. Obesity will worsen the rates of diabetes, hypertension, heart disease, osteoarthritis, cancer, and other chronic diseases. Medical costs will increase, affecting the health care industry as well as national economies.

Determinants of Food Preferences

Social, cultural, and genetic factors contribute to the development, preservation, and alteration of dietary patterns and food preferences, taste, and food choices (13). Interpersonal similarities such as in a family and group do influence eating behavior and exert direct or indirect social influences (e.g. beliefs, cooking traditions, food rules which a family may teach their children). The rewarding characteristics of food are strongly linked to the sensory input from the gustatory system, which may be a driving force behind food consumption (14). Food likes and dislikes are influenced by physiological factors, similar to those that determine hunger and satiety, but also affected by biological learning. Appetitive and consummatory behavior related to food can be influenced by experience with positive or negative postoral effects of food ingestion (see Section #6).

The majority of the published studies have used scaling methodology to assess the hedonic value of different tasting foods, including those assessing potential changes following Roux-en-Y gastric bypass. Scales have utility in that they are easy to apply and analyze. However they possess limitations including the participant's introspective interpretation of their sensations and are thus subject to variation based on individual differences in prior sensory experience. The subjective interpretation of internal processes may lead to false reporting (15), and may be more of an issue in the context of obesity which still carries significant social stigma. This may lead to a large coefficient of variability, especially in between-group comparisons (16), and may account for discrepancies across studies. The solution to this

problem may be the use of tasks that directly test behavior, which may be more objective when studying human feeding.

Roux-en-Y Gastric Bypass as a Tool to Understand Food Preferences

Studies of human Roux-en-Y gastric bypass (RYGB) patients have thus far predominantly relied on verbal report to determine whether there is a change in food preference after the operation (see (17)). Whether such changes in the motivational properties of select food types occur remains to be resolved, but some authors in search of the mechanisms underlying the proposed paradoxical shift away from high-calorie toward low-calorie foods in the context of weight loss, have begun to examine the effects of RYGB on sensory-discriminative, motivational, and physiological aspects of taste function (see Section #2).

For example, after RYGB, taste detection for sucrose has been shown to marginally improve in humans (18-21). If such changes in taste thresholds for sweeteners extend into the suprathreshold range, then this shift could contribute to a reduction of total caloric intake from sugars. Neuroimaging studies using functional MRI (fMRI) have accelerated our understanding of the contribution of the brain reward systems in eating behavior. The handful of preliminary studies using fMRI have demonstrated a selective reduction in the activation in key brain reward areas in response to high-calorie foods after RYGB (22). An investigation using a progressive ratio task provided evidence that humans do work as hard to obtain a sweet and fatty taste stimulus (chocolate candy) after RYGB (22), which is in contrast to findings in rodents after RYGB where no reduction in breakpoint for high fat and sugar reward was noted (23). Direct testing of consummatory behavior has not yet been done.

Potential Underlying Mechanisms

As gut hormone release is increased after RYGB, it is tempting to implicate such endocrine signals as mediators of the change in taste and food responses. Glucagon-like peptide-1 (GLP-1) receptors are expressed on taste afferent nerve fibers and GLP-1 receptor knockout mice are less responsive to low sucrose concentrations than wild-type mice (24) (see Section #5). Infusions of GLP-1 and PYY in normal weight volunteers have been shown to not only reduce food intake, but to also attenuate neural activation across the brain reward system in response to food pictures (25). Even though postprandial levels of anorexigenic gut hormones (including GLP-1 and PYY) are increased after RYGB in humans, no mechanistic studies have been performed to show that gut hormones are directly and causally responsible for the decreases in food preferences observed. Even if gut hormones alter food choices ‘unconsciously’, there is increasing support in the rat model for the notion that the reduced consumption of sugar and fatty foods after RYGB is the result of a physiologically driven avoidance and learning (see (23;26)).

Although a need for more robust and reliable behavioral methodologies in humans and harmonization of the animal models of bariatric surgery exists, whether the shift in food preferences away from energy-dense foods after RYGB has an independent effect on weight loss or whether it is just an epiphenomenon of surgery is unclear. It is possible that the changes in food preferences might take place alongside the reductions in hunger if both

processes share the same underlying mechanisms. These uncertainties do not detract any value from the importance of studying the mechanisms underlying food preferences; if anything, their in-depth understanding could first enable the personalization of bariatric surgery and, more importantly, accelerate the development of novel pharmacological targets. Such pharmacological agents could act via the gut selectively on the brain reward system.

In conclusion, the question remains whether the obese have different reward responses to fat and sweet taste and whether this is the result or cause of their obesity. Obesity is most likely not a homogeneous condition and methodologies used to study the condition may in themselves introduce unwanted variation in the investigation of taste reward. Studying humans after Roux-en-Y gastric bypass with direct measures of behavior may allow us to investigate potentially large effect sizes in shifts of food preference. Our research methods will need to be improved and complemented by the application of multiple techniques in order to allow us to understand and treat this complex condition more effectively.

4. LINKING NEUROBIOLOGICAL PROCESSES TO TASTE FUNCTION IN ANIMAL MODELS (ALAN C. SPECTOR)

Assessment of Taste Function in Rodent Models

The most popular behavioral measure of taste function in rodents, a common animal model in taste research, is the two-bottle preference test in which one bottle contains a taste solution and the other contains either water or a different taste solution; relative intake is quantified over a 24 h period. The two-bottle preference test is a straightforward measure and simple to use. However, although it is uncontested that taste influences intake, there are nongustatory factors that do as well - most notably postoral stimulation. To avoid these limitations, investigators often adopt the use of specialized testing devices, sometimes called gustometers, which allow for the delivery of small volumes of taste stimuli and the measurement of immediate responses; two features that increase confidence that the behavior is orosensory-guided. Some of these devices can also make use of taste stimuli as discriminative cues in which a thirsty rodent can be trained to respond one way (e.g., lick a right-hand spout, press a right-hand lever) when the stimulus sampled is a specific tastant and respond another way (e.g., lick a left-hand spout, press a left-hand lever) when the stimulus is water or a different tastant. Correct responses are reinforced (e.g., water) and incorrect responses are punished (e.g., time-out, shock). In this task, the taste is merely serving as a discriminative signal for responding one way or another, but the responses are not driven by the motivational properties of the stimulus. This has been very effective for assessing the contribution of various brain regions to processing of taste signals in the sensory-discriminative domain of taste function (see (27)).

Assessment of function in the hedonic/affective domain is often achieved by allowing the animal very brief access to a taste solution via a drinking spout (usually 5-10 s) and then measuring the licking responses generated by the stimulus. Generally, the taste stimuli are randomly presented in a session (commonly 30 min in duration). This so-called brief access taste test is an effective way for assessing the motivational potency of the taste stimuli examined (27).

One method that is quite effective in the assessment of the appetitive component of taste-guided behavior is called the progressive ratio task (see (27;28). In this procedure, a response (licking, lever pressing, etc.) is trained with a progressive ratio schedule of reinforcement. An animal is trained to perform a response a certain number of times and then receives a reinforcer (which can loosely be considered a reward) such as a small amount of sucrose solution. After each reinforcer delivery the response requirement increases until the animal ceases to respond in the session. The number of responses on the last completed ratio is considered the breakpoint, which is taken as a measure of the motivational efficacy of the reinforcer under the test conditions.

Assessment of Taste-Related Motivation after RYGB in the Rat Model

As noted by Dr. le Roux, humans reportedly decrease their preference for high fat and sugary foods after Roux-en-Y gastric bypass (RYGB) surgery (29-32;32;33). This has been assessed primarily through means of verbal report such as dietary recall and remains to be confirmed with direct measurement (see (34)). In rat models of RYGB, however, there is clear evidence that taste preference for sugar and fats decreases after the surgery (21;23;26;35-37). Preference for a high-fat maintenance diet (HFD) over standard laboratory chow declines after RYGB in rats. Interestingly, often times, this change is not initially observed but occurs progressively over days (e.g., (23;37)). Also, HFD preference by rats that have received RYGB still remains above indifference despite being lower than what is observed in sham-operated controls (23;35;37). In 24-h two-bottle intake tests, rats that have received RYGB show markedly reduced preferences for sucrose pitted against water across a broad concentration range relative to sham-operated controls (21). The same is true for the soybean fat emulsion Intralipid (35; Fresenius Kabi, UK). However, as is true for the reduction in HFD preference after RYGB, the sucrose and Intralipid preferences never drop substantially below 50%. In other words, it is not as though the rats completely avoid ingesting these taste stimuli. Importantly, preference-avoidance functions in 24-h two-bottle intake tests involving stimuli representing other basic taste stimuli such as NaCl (salty), citric acid (sour), and quinine (bitter), appear to be unaffected by RYGB surgery in rats (21).

Thus, the intake behavior of rats that have received RYGB as assessed in long-term feeding and drinking tests is consistent with the reports in humans suggesting that such surgery leads to decreases in the preference for high fat and sugary foods. However, does this represent a fundamental surgery-induced change in the palatability of these stimuli? Although intake and preference in two-bottle tests is certainly influenced by taste, there are other factors that can influence the outcome, most notably those of a postingestive origin. As noted above, to circumvent these interpretive limitations, many researchers adopt test procedures in which small volumes of taste stimuli are presented and immediate responses measured. When rats were tested in one such procedure, the brief access taste test, after RYGB, their concentration-dependent responsiveness to sucrose was the same or was even slight greater than that displayed by sham-operated controls. Moreover, the RYGB rats initiated 2-3 times more trials than did the control rats (38). Others have found decreases in sucrose responsiveness after RYGB in rats, but at least some of this disparity can be accounted for by methodological differences in the application of the test (39-41). More to the point, decreases in sucrose responding in the brief-access test are not universally observed. A

similar lack of effect of RYGB for concentration-dependent licking in brief access test has been reported for Intralipid (35).

In support, animals tested in the PR task do not display lower breakpoints for 1.0 M sucrose, 5% Intralipid (Sigma-Aldrich, St. Louis, MO), or chocolate Ensure (Abbott, Columbus, OH) despite showing signs of reduced preference for these items in 2-bottle intake tests (23). Thus, it would appear that the motivational potency of sugar and fat solutions is not compromised by RYGB. The change in preference is likely caused by other factors such as postingestive events. We hypothesize that animals are learning how to adjust their intake of particular food items to minimize negative visceral consequences of their ingestion. We do not believe, however, that this is accompanied by a conditioned change in the palatability of these foods as would be the case if a conditioned taste aversion was formed. Rather, we believe the palatability of the foods for which decreased preference is observed remains stable, but that the animals learn that they can only tolerate so many calories at one time from those energy sources because of the remodeled gut. Of course, this hypothesis remains to be further tested in rats and, if substantiated, the mechanisms would have to be further elucidated. It will also be important to determine if similar processes are at play in humans after RYGB (see Section #3).

5. TASTE RECEPTOR CELL SIGNALING AND EXTRAORAL NUTRIENT SENSING MECHANISMS (STEVEN D. MUNGER)

The initial stage of taste perception is the detection of taste stimuli within the oral cavity. The molecular mechanisms employed by mammals to detect and transduce taste stimuli vary depending on the taste quality they elicit (42). Sweet, bitter and umami stimuli bind to different G protein-coupled receptors (GPCRs) (43). Each type is expressed in a separate population of taste bud cells, but engages similar intracellular signaling cascades (44-46). These receptors are the primary targets of taste stimuli, allosteric modulators, or taste inhibitors (47). However, the taste receptors are not restricted to the gustatory system, and researchers have begun to implicate these proteins in a variety of physiological roles in extraoral tissues, such as in numerous endocrine organs that impact metabolism (48). Similarly, many bioactive peptides implicated in metabolism and/or satiety have been found in taste cells, where they appear to regulate peripheral responses to taste stimuli (49).

Sweet and Umami Taste Receptors

Stimuli that elicit the perception of sweet or umami taste activate members of the Type 1 taste receptor family (T1Rs) (50). The taste receptor composed of subunits T1R2 and T1R3 recognizes every compound we perceive to be sweet, including many mono- and disaccharides (e.g., glucose, fructose, sucrose), certain amino acids (e.g., D-phenylalanine, glycine), and various natural and synthetic low-calorie sweeteners (e.g., aspartame, sucralose, steviol glycosides, cyclamates, miraculin) (51;52). Similarly, sweet taste inhibitors such as lactisole interact with this receptor to prevent activation by sweeteners (and thus inhibit sweet taste) (53). Importantly, the sweet taste receptor contains a number of different (orthosteric and allosteric) binding sites for these sweet stimuli and inhibitors, offering the possibility of differential actions, differential regulation, and synergies

(47;53;54). Umami taste shows evidence of synergistic actions between two types of stimuli: amino acids (L-glutamate, L-aspartate) and 5'-ribonucleotides (inosine and guanosine monophosphates) (55). Each of these stimulus types activates a receptor composed of the subunits T1R1 and T1R3, although they do so by targeting different sites on the receptor (51;52). Other receptors, including certain metabotropic glutamate receptors (mGluRs), have also been suggested to function as taste receptors for L-glutamate (56). However, a role for these receptors remains controversial.

Although T1Rs and T2Rs were first identified in the gustatory system, where they clearly are critical for taste function, these receptors more recently have been reported in a variety of digestive, respiratory, endocrine and neural tissues (57). For example, T1Rs are expressed in pancreatic β cells (58), where they have been implicated in the regulation of glucose responses and insulin secretion (59;60). These receptors also appear to be important in the gut, where they are found to regulate glucose absorption and GLP-1 secretion (61;62).

Bitter Taste Receptors

Bitter-tasting stimuli interact with a different family of GPCRs, the Type 2 taste receptors (T2Rs) (63-65). There are 25 different T2Rs in the human gustatory system, and they are largely, though not exclusively, coexpressed in bitter-sensitive taste cells (63). T2Rs can be functionally grouped into three categories: specialists (responsive to a few structurally-related compounds), generalists (responsive to many compounds of diverse chemical structures), and intermediates (48;66). Many bitter stimuli will activate more than one type of T2R (48;66). There is growing evidence that the bitterness of some compounds can be inhibited by competitive antagonism of their cognate receptors, and both artificial and naturally-occurring inhibitors of subsets of T2Rs have been identified (67;68).

T2Rs also have extraoral roles with consequences for metabolism. The thyroid gland expresses a number of T2R isoforms that have been implicated in the modulation of signaling pathways important for thyroid hormone synthesis (69). T2Rs have also been found in various gut cells (48;70;71), but their roles here are less clear. The broad expression of this receptor family (43;57) along with the ability of many pharmaceuticals (which often have a bitter taste) to activate select T2Rs (66) suggest that extraoral bitter taste receptors could be useful therapeutic targets and/or mediators of many off-target drug effects (69).

Taste Bud Neuropeptides.

It has become apparent that taste receptor cells express a large number of neuropeptides that apparently act as autocrine, paracrine or endocrine signals. These peptides include glucagon-like peptide-1 (GLP-1) (24), glucagon (72), ghrelin (73), neuropeptide Y (NPY) (74), peptide YY (PYY) (75), cholecystokinin (CCK) (76) and vasoactive intestinal peptide (VIP) (77). The receptors for these peptides (also members of the GPCR superfamily) are found on taste cells themselves, or on adjacent nerve fibers that carry taste information from taste buds to the brain (49). While the functions of many of these peptides in taste are not fully understood, some have been linked to the modulation of peripheral taste responsiveness (particularly for sweet stimuli) and may also contribute to coding taste quality information in the gustatory periphery (49).

Conclusions

Taste bud GPCRs, including the classic taste receptors and various peptide receptors, are both essential for normal taste and intriguing targets for modulation of taste function by food and beverage components. Understanding the “pharmacology” of these receptors as well as their effects on the detection and perception of tastes is critical to the goal of reducing sugar, fat and salt while maintaining appealing flavor profiles. This same knowledge could also impact metabolic health through the targeted modulation of extraoral taste receptors found in a variety of organ systems.

6. INFLUENCE OF GUT NUTRIENT SENSING ON FOOD AND FLAVOR PREFERENCES (ANTHONY SCLAFANI)

Food appetite is greatly influenced by taste, odor, and texture stimuli that are integrated in the brain as flavor sensations. The sweet taste of sugar is one of the most potent flavor elements that promotes feeding. Sugar taste is detected in mammals by the proteins T1R2 and T1R3 that form the sweet taste receptor responsive to many different sugars and non-nutritive sweeteners (78). The flavor of fat also enhances the palatability of food. Fat flavor includes a taste component that appears to be mediated by fatty acid receptors including CD36, GPR120, and perhaps GPR40 located in taste receptor cells (79). Food is sensed not only by taste receptors in the mouth but also by taste and other nutrient sensors in the gut (80). These gut sensors generate neural and hormonal "satiation" signals that act in the brain to suppress eating. Gut nutrient sensors can also generate "appetition" signals that stimulate appetite and condition flavor preferences (80;81).

Post-oral appetition is demonstrated in laboratory rodents by the ability of intragastric (IG) nutrient infusions to stimulate the intake of and preference for flavored non-caloric drinks (80). In a typical experiment, mice are trained to drink flavored saccharin solutions (the conditioned stimuli, CS) in alternate training sessions with one flavor (CS+) paired with an IG sugar infusion and a different flavor (the CS−) paired with an IG water infusion. Flavor preferences are then assessed in a two-bottle choice test with the CS+ vs. CS−. Many studies demonstrate that animals consume more of the CS+ solution paired with IG sugar than of the CS− solution paired with IG water during one-bottle training and strongly prefer the CS+ in the two-bottle test. Preferences are learned by food-deprived as well as freely-fed animals and persist for many sessions even in the absence of nutrient infusions.

Comparison of nutrient infusions into the stomach, duodenum, jejunum, ileum, and hepatic portal vein indicate that the upper intestinal tract is a primary site where sugars act to condition preferences for flavored saccharin solutions, although the portal vein region is implicated in some forms of sugar conditioning (80). Intestinal sugar is sensed by T1R2/T1R3 "sweet" receptors but several findings indicate that these receptors do not mediate sugar appetition. In particular, T1R3 knockout (KO) mice, which are indifferent to sugars in the mouth, show normal preferences for a CS+ flavor paired with IG sucrose infusions (82). Also, sweet-tasting compounds differ in their ability to condition preferences when infused IG. Whereas sucrose and glucose are very effective, fructose and sucralose are not. These findings implicate glucose-specific intestinal sensors including SGLT1 and SGLT3 in sugar

appetition (83). Consistent with this interpretation is the flavor conditioning response of mice to IG infusions of the nonmetabolizable glucose analog α-methyl-D-glucopyranoside, which is an SGLT1/SGLT3 ligand (83).

Fat, like sugar, is sensed in the gut where it generates satiation signals that suppress eating and also appetition signals that stimulate eating (80). IG infusions of Intralipid, a soybean oil emulsion, in mice promote the intake of and preference for a CS+ flavored saccharin solution relative to a CS− solution paired with IG water infusions. Studies of mice lacking specific fatty acid sensors have provided information on the gut sensors that mediate fat appetition. CD36 KO mice, which have attenuated preferences for fatty acid solutions and lipid emulsions, displayed normal preferences for a CS+ flavor paired with IG Intralipid infusions (84). In contrast, double knockout mice missing both GPR40 and GPR120 fatty acid sensors were significantly impaired in their flavor conditioning response to IG Intralipid infusions (85). Although GPR40 and GPR120 sensors have been implicated in fatty acid taste, KO mice missing one or both of these sensors display normal preferences for Intralipid in two-bottle preference tests (85). Thus, as in the case of sugars, different sensors appear to mediate oral and post-oral fat preferences.

Although rodents are very attracted to sugar solutions and fat emulsions, mixtures of the two nutrients are typically the most preferred (86;87). IG infusions of sugar and fat-rich liquid diets are also very effective in stimulating intake and conditioning flavor preferences (87). Recently we reported that IG infusions of low concentrations of sugar (glucose) and fat (Intralipid), that individually produce little or no preference, conditioned a strong CS+ preference when combined (88).

The appetition signals generated by sugar and fat in the gut remain to be identified. To date, flavor preferences conditioned by IG sugar and fat infusions have not been blocked by visceral nerve deafferentation, which implies a gut-brain hormonal pathway, but this remains to be verified (80). At the level of the brain, gut appetition signals enhance the reward evaluation of flavor cues in part by activating brain dopamine reward circuits (89;90). Taken together, the results obtained with rodents indicate that the potency of sugar- and fat-rich foods to stimulate appetite and promote obesity involves the stimulation of both oral and post-oral sensors that activate brain reward systems.

7. NEURAL INTERACTIONS INTEGRATING TASTE AND VISCERAL SIGNALS AND INFLUENCE ON FEEDING BEHAVIOR (SUSAN P. TRAVERS)

Neural signals from taste buds profoundly affect the function of the gastrointestinal (GI) tract and likewise, signals from GI receptors modify the reactions of the animal to tastes. For example, even prior to swallowing, tasting nutritive compounds like sweet sugars exert pro-digestive effects, causing insulin release (e.g, (91)) and increasing gastric emptying (92). In contrast, the taste of normally avoided bitter stimuli exert functionally opposed effects such as decreasing gastric emptying and gastric acid production (92;93). Likewise, sensations from the GI tract modify behavioral responses to taste and flavor. For instance, the sensation of satiety generated by stretch receptors in the gut and by the action of GI peptides like cholecystokinin reduces the intake of normally preferred foods (94) whereas positive

nutritive gut signals can promote ingestion during a meal (95) (see Section #6). Thus, although taste and visceral signals are conveyed to the brain over separate cranial nerves, these signals must interact centrally.

Classic neuroanatomists realized that oral taste signals traveled over the 7th and 9th cranial nerves to enter the rostral NST whereas signals from the gut traveled over the 10th cranial nerve to enter the same nucleus, but at the opposite end. The work in our lab has demonstrated that, despite this initial separation, there are reciprocal connections between the rostral and caudal NST. Thus, there is a neural substrate for interaction between taste and visceral information at the very first CNS processing station (96-98).

To demonstrate the rostral to caudal projection, we placed anterograde neural tracers in the rostral NST. Anterograde tracers are transported from the soma of neurons to their terminal endings, revealing the functional connections of cells at the injection site. These injections were made under neurophysiological guidance and were purposely small, so that we could verify that the injection was accurately placed in an orally-responsive region. These experiments revealed a strong connection from the rostral to the caudal NST. Moreover, some of the injections were performed using AAV cre-dependent viruses in mice that express cre under the control of the promotor for GAD65, an enzyme responsible for the synthesis of the inhibitory neurotransmitter GABA. Thus, a component of this connection is inhibitory. Indeed, this inhibitory projection not only targeted the caudal NST but also the nearby dorsal motor nucleus of the vagus that houses preganglionic parasympathetic neurons and the hypoglossal nucleus that contains tongue motor neurons. This inhibitory connection likely mediates, in part, the suppressive effects of unpalatable foods on consumption and GI function.

Similar experiments demonstrated an influence of the caudal, visceral NST on the rostral, taste zone. Confined injections of anterograde tracers in the caudal NST clearly demonstrated a projection to the rostral part of the nucleus. Injections of a cre-dependent AAV virus in mice that express cre under the control of the promotor for GAD65 or dopamine-beta hydroxylase suggest that (separate) components of this pathway are GABAergic and catecholaminergic. Complimentary experiments employing retrograde tracers and immunohistochemistry or fluorescent reporter mice supported these results and suggest that there are other excitatory components of this pathway as well. Thus, the influences of signals from the gut on reactions to taste can be both excitatory and inhibitory.

An important characteristic of the caudal to rostral pathway was apparent in scrutinizing the details of its topography. The projection was most prominent in the regions of rostral NST that contribute directly to consummatory oral behaviors (chewing and swallowing) and reflexive behaviors such as salivation. The modulatory substrate was more modest in areas of the nucleus that receive direct input from taste afferents and which in turn project to higher levels of the nervous system. However, simultaneous injections of two different anterograde tracers into the taste and visceral regions of the NST revealed an additional, very robust substrate for interaction between taste and visceral signals in the parabrachial nucleus of the pons, a nucleus that projects directly to forebrain structures involved in both perception and homeostasis. In closing, the anatomical circuits described here provide a

potential structural substrate for the integrated contribution of gustatory and visceral circuits on behavioral and physiological processes.

8. DEVELOPMENT OF FOOD AND FLAVOR PREFERENCES: BASIC BIOLOGY AND IMPLICATIONS FOR HEALTH (JULIE A. MENNELLA)

Many illnesses of modern society are, in part, the consequence of poor food choices. Although foods high in salt and refined sugars contribute to poor health, people of all ages consume them in excessive amounts, in part because these foods have powerful hedonic appeal, especially for children. There is growing evidence that children live in different "flavor" worlds than adults (99;100).

Children have sensory systems that detect and prefer the once rare calorie- and mineral-rich foods that taste sweet or salty (101), while rejecting the potentially toxic ones that taste bitter (102;103). Such age-related changes in taste perception and preference, documented by experimental research during the past century (102), indicate that the rewarding properties of sweeteners and salt and the aversive properties of bitter-tasting compounds are more pronounced during childhood. Consequently, the taste biology of children does not predispose them to favor the recommended low-sugar, low-sodium, vegetable-rich diets and makes them especially vulnerable to our current food environment of foods high in salt and refined sugars. It also explains why 'taste is a primary reason for noncompliance with medication regimens (104). While encapsulating the medicine in pill or tablet form to avoid unpleasant tastes is effective for adults, this is problematic for children, many of whom cannot or will not swallow pills and thus often forced to ingest their medication in a liquid formulation.

If this is the bad news, the good news is that sensory experiences, beginning early in life, can shape preferences (see (99)). Mothers eating diets rich in healthy foods can get children off to a good start since flavors are transmitted from the maternal diet to amniotic fluid and mother's milk, and experience with such flavors leads to great acceptance of those foods. Once weaned, infants can learn through repeated exposure and dietary variety. Such early life experiences with healthy tastes and flavors may go a long way toward promoting healthy eating and growth, which could have a significant impact in addressing the many chronic illnesses associated with poor food choice.

Because the early sensory experiences of the high risk neonate can be drastically different from those of a typical infant, lacking continuity with prenatal sensory experiences, understanding the development and functioning of the chemical senses during early childhood may assist in forming evidence-based strategies to improve the diet for those who experience a discontinuity or disruption in early flavor experiences (105). And finally, children cannot benefit from medicines they will not take and their sensitivity to bitter taste makes this especially challenging (104). More knowledge about the science of distaste and how to ameliorate it and development of psychophysical methods that measure the child's taste experience will help realize a new era in drug development for children—an era that is still in its infancy.

9. FINAL REMARKS

As noted above, by virtue of its position at the opening of the alimentary tract, the gustatory system is well suited for providing the brain with information that can promote or discourage the ingestion of particular types of foods (see Section #2). It is clear that how much and what a person eats has an influence on the etiology, or at least management, of a variety of health disorders including obesity, diabetes, hypertension, cardiovascular disease, and cancer. Thus it is important to understand how the taste system operates and interacts with other signals involved in regulation of energy intake and general nutrition. The findings provided by the six experts participating in this workshop highlighted key examples of this type of interaction. Carel le Roux (see Section #3) and Alan Spector (see Section #4) discussed how taste and visceral signals potentially interact to influence intake and food choice after RYGB - the surgical remodeling of the gastrointestinal tract used to treat morbid obesity and Type 2 diabetes mellitus. Steven Munger (see Section #5) provided an overview of the various G protein-coupled taste receptors that are also expressed in other tissues, notably the gut, and have been implicated in nutrient sensing. In addition, he noted how several key gut peptides associated with feeding and satiation are also expressed in taste buds cells as are their cognate receptors. Anthony Sclafani (see Section #6) provided compelling examples of how neutral flavor signals that are experimentally paired with IG infusions of certain sugars or fat will ultimately be preferred via learning and that the IG infusions can even *promote* intake *during* a meal – a phenomenon he terms "*appetition*". Interestingly, appetition and conditioned flavor preferences depend on the specific nutrient to which the gut is exposed; these phenomena are not governed by the caloric content of the IG infusions in any simple way. Susan Travers (see Section #7) discussed the anatomical organization of neural inputs from the 7th, 9th, and 10th cranial nerves transmitting taste and/or visceral signals to their first destination in the brain – the NST. These signals interact at this early stage of neural processing and can thus potentially have great influence on the behavioral and physiological responses to food. Finally, Julie Mennella (see Section #8) highlighted the need to understand that children live in a taste world fundamentally different than adults. The child's biological drive to avoid bitter and prefer salty and sweet foods may have served children well in a feast-or-famine setting—but today their biology makes them especially vulnerable to food environments abundant in highly processed and palatable foods, rich in added sugars, non-nutritive sweeteners, and salt. It also highlights the need for the development of better-tasting pediatric formulations, many of which are commonly bitter and unpalatable and will not be ingested by children who are unable to swallow encapsulated medication

Our understanding of the mechanisms underlying the integration of taste and visceral signals in the control of feeding and physiology remains in its infancy. However, the research presented at this workshop clearly demonstrates that such sensory interactions do take place and do exert a salient influence on ingestive behavior, which, in turn, has implications for human health and nutrition.

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Table 1

List of abbreviations.

Abbreviation	Term	Brief Definition
AAV	Adeno-Associated Virus	A small virus that is used as a vector to transduce a specific gene and promoter into a cell.
BP	Breakpoint	An index of motivation measured by the number of responses generated by the subject on the last completed ratio of a Progressive Ratio Task before the subject stops responding.
CCK	Cholecystokinin	A peptide hormone released by enteroendocrine I cells in the small intestine. It is also expressed in taste buds.
CD36	Cluster of Differentiation Type 36 (Fatty Acid Translocase)	A membrane protein that has been implicated in fatty acid sensing in the taste system.
CS	Conditioned Stimulus	A stimulus that comes to predict the presence or absence of a different stimulus, referred to as the unconditioned stimulus, as a result of Pavlovion conditioning.
CS−	Conditioned Stimulus Minus	A conditioned stimulus that predicts the absence of the unconditioned stimulus.
CS+	Conditioned Stimulus Plus	A conditioned stimulus that predicts the presence of the unconditioned stimulus.
ENaC	Epithelial Sodium Channel	An ion channel that is selective for sodium and lithium cations and (among other functions) serves as a receptor for salt taste in rodents.
fMRI	Functional Magnetic Resonance Imaging	A noninvasive procedure used to image areas of activity in brain through the measurement of regional differences in oxygenated blood flow.
GABA	Gamma-Amino Butyric Acid	An inhibitory neurotransmitter
GAD65	Glutamic Acid Decarboxylase Type 65	An enzyme that catalyzes the conversion of glutamate to GABA.
GLP-1	Glucagon Like Peptide Type 1	A peptide hormone released by enteroendocrine L- cells in the small intestine. It is also expressed in taste buds.
GPCRs	G Protein-Coupled Receptors	A large family of proteins that serve as receptors for specific ligands that stimulate a variety intracellular signaling pathways.
GPR120	G Protein-Coupled Receptor Type 120	A G protein-coupled receptor that binds with medium and long-chain fatty acids. It has been implicated in fat taste.
GRP40	G Protein-Coupled Receptor Type 40	A G protein-coupled receptor that binds with medium and long-chain fatty acids. It has been implicated in fat taste.
HFD	High Fat Diet	A diet that is high in fat content relative to other macronutrients.
IG	Intragastric	A term used in the context of delivering fluid stimuli directly to the stomach bypassing the oral cavity.
KO	Knock Out	A term that is used to refer to the deletion or functional silencing of a gene.
mGluR1	Metabotropic Glutamate Receptor Type 1	A member of the metabotropic glutamate receptor family. It binds with the excitatory neurotransmitter glutamate and has been implicated as a receptor mediating umami taste.
mGluR4	Metabotropic Glutamate Receptor Type 4	A member of the metabotropic glutamate receptor family. It binds with the excitatory neurotransmitter and has been implicated as a receptor mediating umami taste.
NST	Nucleus of the Solitary Tract	A region of the medulla that consists of neurons which are the target of incoming axons from the 7th and 9th cranial nerves carrying taste information and from the 10th cranial nerve (Vagus) carrying visceral input and some taste signals. These nerves terminate in a roughly topographic fashion with taste input rostral and visceral input caudal.
PR	Progressive Ratio	A task in which a subject is trained to produce a behavior (e.g., a rat pressing a lever) to receive a small amount of a reinforcer (e.g., sucrose solution). The number of responses required progressively increases after each reinforcer delivery. It is used to measure the motivational potency of

Abbreviation	Term	Brief Definition
		reinforcers while minimizing satiation.
PYY	Peptide Tyrosine Tyrosine	A peptide hormone released by enteroendocrine L cells in the small intestine. It is also expressed in taste buds.
RYGB	Roux-en-Y Gastric Bypass	A bariatric surgical procedure that involves a major remodeling of the stomach and small intestine that is used to treat morbid obesity and Type 2 diabetes mellitus.
SGLT1	Sodium-Glucose Linked Transporter Type 1	A protein that transports sodium and glucose through small intestine mucosal cells and proximal tubule kidney cells and functions as a glucose sensor.
SGLT3	Sodium-Glucose Linked Transporter Type 3	A protein that is thought to function as a glucose sensor in the intestine and portal vein.
T1R1	Type 1 Taste Receptor Family Member 1	A protein subunit that is part of the T1R1+T1R3 heterodimeric taste receptor that binds with L-amino acid
T1R2	Type 1 Taste Receptor Family Member 2	A protein subunit that is part of the T1R2+T1R3 heterodimeric taste receptor that binds with sweeteners
T1R3	Type 1 Taste Receptor Family Member 3	A protein subunit that is part of the T1R1+T1R3 heterodimeric taste receptor that binds with L-amino acid as well as the T1R2+T1R3 heterodimeric taste receptor that binds with sweeteners
T1Rs	Type 1 Taste Receptor Family	A family consisting of 3 members which combine to form heterodimers that serves as G protein-coupled taste receptors for sugars and/or amino acids.
T2Rs	Type 2 Taste Receptor Family	A family consisting of approximately 30 members which serve as G protein-coupled taste receptors for bitter tasting ligands.
VIP	Vasoactive Intestinal Peptide	A peptide hormone expressed in a variety of tissues including taste buds cells and the gut.