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Using Animal Models to Determine the Role of Gustatory Neural Input in the Control of Ingestive Behavior and the Maintenance of Body Weight

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Abstract

Introduction—Decades of research have suggested that nutritional intake contributes to the development of human disease, mainly by influencing the development of obesity and obesity-related conditions. A relatively large body of research indicates that functional variation in human taste perception can influence nutritional intake as well as body mass accumulation. However, there are a considerable number of studies that suggest that no link between these variables actually exists. These discrepancies in the literature likely result from the confounding influence of a variety of other, uncontrolled, factors that can influence ingestive behavior.

Strategy—In this review, the use of controlled animal experimentation to alleviate at least some of these issues related to the lack of control of experimental variables is discussed. Specific examples of the use of some of these techniques are examined.

Discussion and conclusions—The review will close with some specific suggestions aimed at strengthening the link between gustatory neural input and its putative influence on ingestive behaviors and the maintenance of body weight.

Keywords

Taste; Food intake; Meal pattern analysis; Animal models; Gustatory neurotomy

Introduction

Between 2011 and 2012, it was estimated that 35 % of adults in the USA were considered obese (i.e., their body mass index (BMI) was 30 or over) (Ogden et al. 2014). Obesity prevalence has remained high since 2003, despite it being the focus of many public health efforts (Ogden et al. 2014). The cost of obesity has been staggering as well. In 2008, it was estimated that healthcare costs associated with obesity totaled $147 billion (Finkelstein et al.

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2009). On average, in this year, medical costs for obese individuals were $1429 more than individuals of normal weight (Finkelstein et al. 2009). The high prevalence and cost of obesity demonstrates a great need for an effective treatment method.

Decades of research have suggested that nutritional intake contributes to the development of human disease mainly by influencing the development of obesity and obesity-related conditions (e.g., cardiovascular disease, hypertension, type 2 diabetes mellitus) (e.g., Appel et al. 1997; Brinkworth et al. 2009; Dauchet et al. 2007; Ding and Mozaffarian 2006; Herder et al. 2009; Hu et al. 2001; Kris-Etherton et al. 2002; Lindström et al. 2006; McCarron and Reusser 2001; Rouse et al. 1983; Swain et al. 2008). Collectively, these studies suggest that a majority of obesity-related diseases could be prevented by the adoption of healthier eating habits.

To lose weight, it is necessary to decrease daily caloric intake to a level at or below daily energy expenditure. Innumerable weight-loss programs that instruct participants to manipulate dietary intake in an assortment of ways have been tested and implemented with varying degrees of efficacy (Du and Feskens 2010; Hirsch et al. 1998). As with a variety of other chronic diseases, the use of prescription medications or other medical interventions may be warranted for some individuals who are obese (Li and Cheung 2009; Oh et al. 2009). However, any weight loss achieved within weight loss programs or with the use of drug interventions has been shown to be very difficult to sustain for the long term, likely due to compensatory changes in physiological processes, which seem to stimulate weight re-gain (Hirsch et al. 1998; Mathus-Vliegen and de Groot 2013).

The primary action of medications currently being used or developed as treatments for obesity are related to one of the following: modulating hypothalamic food intake regulation, blocking nutrient absorption, modulating fat storage, or increasing thermogenesis (Cooke and Bloom 2006; Hofbauer et al. 2007; Oh et al. 2009). One of the many other factors that influences food intake that has not been targeted by pharmaceutical producers is sensory information/sensory processing. A large amount of sensory information (e.g., chemosensory, thermosensory, mechanosensory) from both the oral-nasal cavity and gastrointestinal tract is sent to the CNS, imparting information related to macronutrient composition, caloric density, osmolarity, and potential toxicity of food (Ahima and Antwi 2008; Morrison and Berthoud 2007; Saper et al. 2002; Zheng et al. 2009). However, it is the sense of taste which acts to protect the rest of the alimentary canal by providing information on which nutrients to ingest and which to reject (Mattes 2003; Scott and Verhagen 2000; Tanaka et al. 2007).

Despite a relatively large body of research that indicates functional variation in taste perception can influence nutritional intake, research demonstrating a definitive role for the gustatory system in the maintenance of food intake and body mass has been sparse. Below, we will review some of the evidence from the human literature that suggest that functional variation in taste perception can influence nutritional intake. We then detail some of the interpretive issues endemic in studies from this literature. We point out where the use of specific behavioral protocols and animal models could potentially help to provide a stronger, more definitive link between taste, ingestive behavior, and body mass accumulation. However, we will first provide a brief primer on the organization of the taste system, with a

focus on the peripheral gustatory system. This emphasis is taken because variation in mammalian taste perception has almost exclusively been associated with functional variation in key components of the peripheral gustatory system.

The Peripheral Gustatory System

The gustatory system acts as a sentinel allowing for the recognition of external chemical stimuli entering the alimentary canal. Together with receptors of the olfactory and somatosensory systems, gustatory receptors recognize distinct characteristics of many chemicals that comprise ingested foods. These perceptions either promote the ingestion or rejection of the food (Kinnamon and Cummings 1992; Small 2012; Small and Prescott 2005).

To date, there are five well-characterized taste qualities, each of which is associated with a biologically relevant class of compounds: sweet taste is associated with the presence of simple carbohydrates such as glucose and sucrose in the oral cavity, salty taste is elicited by electrolytes such as sodium, umami taste is associated with the presence of L-amino acids in the oral cavity, bitter taste is elicited by the presence of potentially toxic compounds such as some alkaloids found in plants, and sour taste is associated with the presence of acids in the oral cavity (Bartoshuk 1988; Gravina et al. 2013; Lindemann 2001; Yarmolinsky et al. 2009). Additionally, there is emerging evidence that lipids (i.e., non-esterified fatty acids) can be detected by fatty acid receptors on taste receptor cells, leading to the recognition of a putative sixth taste known as “fat taste” (Cartoni et al. 2010; Degrace-Passilly and Besnard 2012; DiPatrizio 2014; Laugerette et al. 2005; Matsumura et al. 2007; Simons et al. 2011).

When present in the oral cavity, these biologically relevant chemical stimuli activate receptors located on specialized anatomical cells located in structures known as taste buds. The peripheral gustatory sensory organ, the taste bud, houses a heterogeneous population of taste receptor cells in a rosette-like structure (Chaudhari and Roper 2010; Lindemann 2001). In mammals, the majority of taste buds are located on the dorsal surface of the tongue. Approximately 10–15 % of taste buds appear in the soft palate (Lundy and Norgren 2004; Spector and Glendinning 2009). A small number of non-lingual taste buds can also be found in the larynx, nasopharynx, and epiglottis. Taste buds on the tongue are located in nipple-like projections referred to as papillae. There are three types of taste bud containing papillae on the tongue (Chaudhari and Roper 2010; Lindemann 1996; Lindemann 2001; Tucker and Smith 1969). The fungiform papillae are dispersed throughout the anterior dorsal surface of the tongue, harboring a small number of taste buds at the apex of the papillae. The foliate papillae are composed of several deep trenches located posteriorly, on lateral portions of the tongue. Finally, posterior to the intermolar eminence and in between the foliate trenches lies the circumvallate papilla, containing the densest region of taste buds in the oral cavity (Lindemann 2001; Montmayeur and Le Coutre 2010).

Taste buds are composed of 50–150 taste receptor cells (Chaudhari and Roper 2010; Delay et al. 1986; Lindemann 2001). These taste cells are categorized into four cell types: type I cells are electron dense, containing dark cytoplasms and indented nuclei. These taste cells are thought to play a “glial-like role” by supporting the structural integrity of the taste bud

and the cells that surround it (Delay et al. 1986; Finger 2005; Murray 1973). They also have the potential to regulate the extracellular environment within the taste bud (Gravina et al. 2013; Suzuki 2007). While type I cells have not traditionally been recognized for the transduction of taste stimuli, recent reports suggest that amiloride-sensitive Na^+ channels are located on type I cells, strongly suggesting their involvement in sodium transduction and subsequent salty taste perception (Chandrashekar et al. 2010; Vandenbeuch et al. 2008; Yoshida et al. 2009). Type II taste cells have a translucent cytoplasm and contain a large round nucleus (Delay et al. 1986; Finger 2005; Murray 1973). These cells express G protein–coupled receptors (GPCRs) and other receptors responsible for recognizing taste stimuli that give rise to sweet, bitter, umami, and fat taste percepts (Adler et al. 2000; Bigiani 2001; Galindo et al. 2012; Hoon et al. 1999; Kitagawa et al. 2001; Laugerette et al. 2005; Li et al. 2002; Matsumura et al. 2007; Nelson et al. 2002). These cells do not make classical synaptic connections with gustatory afferents. They do, however, transmit information to gustatory neurons via chemical communication using pore-forming membrane proteins such as calcium homeostasis modulator 1 (Taruno et al. 2013). Type III taste cells have round nuclei-like type II cells but have dark cytoplasm similar to that of type I cells (Delay et al. 1986; Finger 2005; Murray 1973). This cell type makes traditional synaptic connections with gustatory nerve fibers and expresses various synaptic molecules as well as neurotransmitters (Gravina et al. 2013; Roper 2013; Suzuki 2007) and have been implicated in the transduction of protons and in the subsequent mediation of sour taste perception (Huang et al. 2006a; Huang et al. 2008). Finally, type IV cells are located on the basolateral part of taste buds and are composed of progenitor cells. These cells contain sonic hedgehog genes, which allow for the differentiation and maturation into other taste cell types (e.g., Mbiene and Roberts 2003; Miura et al. 2014).

Taste Receptors

There are many families of receptors expressed in taste receptor cells that are responsible for recognizing stimuli that correspond to each taste quality. These receptors are expressed on microvilli at the apical surface of taste receptor cells (Lindemann 2001). Sweet, bitter, and umami tastes are mediated by GPCRs (Hoon et al. 1999; Kitagawa et al. 2001; Li et al. 2002; Nelson et al. 2002). Receptors of the T1R family are responsible for recognizing stimuli that give rise to sweet and umami taste percepts. There are three members of the receptor family: T1R1, T1R2, and T1R3. Specifically, T1R3 dimerizes with T1R2 to form a heterometric receptor that mediates our perception of sweet taste (Nelson et al. 2001). T1R1 combines with T1R3 to form a receptor that is sensitive to free L-amino acids and mediates our perception of umami taste (Li et al. 2002; Nelson et al. 2002). The T2R family of receptors interacts with various ligands that give rise to a bitter taste percept (Behrens and Meyerhof 2006; Chandrashekar et al. 2000).

Salt taste appears to be primarily regulated by the apical ENaC ion channel that allows the direct passage of Na^+ into the cell (Chandrashekar et al. 2010). Sour (acids) detection is not well characterized, but possible mechanisms such as the diffusion of H^+ ions directly into the cell and/or H^+ detection by PKD1-like family receptors are currently being studied (Huang et al. 2006b; Kataoka et al. 2008; Kinnamon and Cummings 1992). Finally, as evidence about a sixth taste continues to emerge, non-esterified fatty acids have now been

shown to interact with various receptors that are expressed in taste cells and are known to be involved in the transduction of these stimuli (Cartoni et al. 2010; Galindo et al. 2012; Gilbertson et al. 1998; Laugerette et al. 2005; Matsumura et al. 2009; Matsumura et al. 2007).

Neurotransmitters and Neuromodulators

The cells in taste buds use both classical and non-classical small molecule transmitters to activate intragemmal nerve fibers, and perhaps to impact upon the functioning of other cells within the bud. Ongoing research in the field aims to shed light on how taste cells communicate with each other and with sensory nerves to discriminate various signals and relay specific information to the brain for conscious recognition of the ingested contents. ATP appears to be the principal neurotransmitter used by taste receptor cells to signal to intragemmal nerves fibers (Finger et al. 2005). However, other transmitters (e.g., acetylcholine, serotonin, norepinephrine, gamma-aminobutyric acid) likely play important roles in modulating taste cell functions through autocrine and paracrine signaling and thus may help to shape the output of the taste bud (see Roper 2013 for a comprehensive review).

Peptide Regulators of Peripheral Taste Function

Evidence suggests significant taste information processing occurs within the taste bud and between afferent cranial nerves targeting the central nervous system (CNS) (Chaudhari and Roper 2010; Dotson et al. 2013; Yarmolinsky et al. 2009). Recent studies have revealed that certain metabolic peptides may mediate aspects of gustatory processing. Indeed, an extensive palette of metabolic peptides has recently been associated with specific subtypes of taste receptor cells. In addition to their well-established roles outside the gustatory system, these orally expressed metabolic peptides/receptors have been shown to modulate taste responsiveness (see Cai et al. 2014; Dotson et al. 2013 for a review).

This recent revelation of metabolic influence upon taste responsiveness offers new strategies and therapeutic alternatives to offset a severe worldwide obesity epidemic. The ability to modulate taste responsiveness without disturbing fine-tuned postprandial hormone and peptide orchestration, responsible for metabolic homeostasis, could potentially bear significant benefits for a growing population.

Taste, Food Intake/Preference, and Metabolic Disease

It has been hypothesized by many that taste strongly affects ingestive behavior and, as such, nutrient intake. A large body of research indicates that individuals who possess heightened taste perception differ in their intake of foodstuffs (see Dotson et al. 2012a and Hayes et al. 2013 for a review). To illustrate, decades of research have shown that enhanced bitter taste perception is associated with the avoidance of certain foods, including specific fruits and vegetables (e.g., Dinehart et al. 2006; Drewnowski et al. 1997, 1998, 1999, 2000; Fischer et al. 1961; Glanville and Kaplan 1965; Jerzsa-Latta et al. 1990; Tepper et al. 2009). For example, the perceived bitterness evoked by tasting various types of vegetables (e.g., brussels sprouts, kale, asparagus) was shown to predict the preference for those vegetables, as well as self-reported measures of vegetable intake (Dinehart et al. 2006). Indeed, bitter

taste perception is thought to have evolved to detect toxins in plants, vegetables, and foods and to modulate the ingestion of them (Ames et al. 1990; Drewnowski and Gomez-Carneros 2000).

The most well-characterized human taste phenotype is the relative responsiveness of individuals to the bitter taste evoked by the compounds phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) (see Wooding 2006 for a review). It has been proposed by many (e.g., Dinehart et al. 2006; Duffy and Bartoshuk 2000; Tepper 2008) that taste sensitivity/responsiveness to PROP/PTC can be used as a marker for individual differences in taste perception that influence food preferences and intake. For example, children identified as insensitive to PROP consumed more vegetables than did "taster" children during a free-choice intake test (Bell and Tepper 2006). These children also expressed greater "liking" for raw broccoli relative to taster children in a hedonic test (Bell and Tepper 2006). Moreover, genetic variation in the gene *TAS2R38*, which encodes for a T2R receptor that is activated by PROP/PTC, is also associated with vegetable intake (e.g., Sacerdote et al. 2007; Sandell et al. 2014). Genetic variation in the gene *TAS2R38* has also been associated with macronutrient selection in preschool children (Hoppu et al. 2015). Additionally, in a sample of female subjects, sensitivity/responsiveness to the bitterness of PROP was shown to be associated with lower acceptance of cruciferous and selected green and raw vegetables (Drewnowski et al. 1998, 1999, 2000). Similarly, female PTC non-tasters reported greater use of cooked turnip and raw watercress than did PTC tasters (Jerzsa-Latta et al. 1990). Colon cancer patients who tasted PROP as more bitter also reported less vegetable intake (Basson et al. 2005). Collectively, these data suggest that individuals that have a strong response to bitter taste, along with a concomitant altered perceived taste sensation evoked by certain foods, such as vegetables, reduced their intake of these foods, thereby leaving them susceptible to perturbations in metabolic homeostasis. Consistent with this postulation, bitter taste sensitivity/responsiveness has been associated with daily energy intake, BMI, adiposity, and risk factors for cardiovascular disease (Choi and Chan 2014; Duffy 2004; Fischer et al. 2014; Goldstein et al. 2005; Kamphuis and Westerterp-Plantenga 2003; Keller et al. 2014; Shafaie et al. 2013; Tepper 1999; Tepper et al. 2008; Tepper and Ullrich 2002).

Although less well studied, variation in sweet taste responsiveness also impacts vegetable preference and intake. For example, as with the perceived bitterness of certain foods, perceived sweetness was shown to predict the preference for sampled vegetables, as well as vegetable intake in adults (Dinehart et al. 2006; Drewnowski et al. 1999). It has also been demonstrated that a higher preference for sucrose solutions was associated with increased preferences for sweet desserts (Drewnowski et al. 1999). The perceived sweetness of foods has also been shown, by multiple investigators, to be correlated with BMI (Bartoshuk et al. 2006; Drewnowski et al. 1985; Salbe et al. 2004). Responsiveness to other taste qualities has also been associated with energy consumption and BMI (Bertoli et al. 2014; Fischer et al. 2014; Keast et al. 2014; Skrandies and Zschieschang 2015). It has been well documented that taste responsiveness can also influence alcohol ingestion and preference (e.g., Allen et al. 2014; Bachmanov et al. 2003; Blednov et al. 2008; Blizard 2007; Brasser et al. 2010, 2012; Dotson et al. 2012c; Duffy et al. 2004a, b; Hayes et al. 2011, 2013; Hinrichs et al. 2006; Kampov-Polevoy et al. 1998, 2014; Lange et al. 2010; Lanier et al. 2005; Wang et al.

2007) providing another route through which gustatory functioning may impact upon body weight maintenance and adiposity.

The association between food intake, body weight maintenance, and taste functioning is further highlighted by data from human clinical studies on the effects of taste loss that result from various clinical conditions or the treatment of such conditions. For example, otitis media and tonsillectomy, both of which can result in damage to gustatory nerves, are associated with enhanced palatability of energy-dense foods and with weight gain (Bartoshuk et al. 2012; Huang et al. 2012; Landis et al. 2005; Peracchio et al. 2012). Reports have suggested that surgical interventions in the head and neck area can lead to reports of taste defects and weight loss (Caldas et al. 2013; Woschnagg et al. 2002). Several studies have suggested that stroke patients with damage to area associated with gustatory functioning report taste abnormalities and have weight regulation problems (Dutta et al. 2013; Finsterer et al. 2004; Green et al. 2008; Heckmann et al. 2005). A significant fraction of cancer patients have altered taste perception and exhibit both decreased food intake and weight loss (Baharvand et al. 2013; Boltong and Keast 2012; Cohen et al. 2014; Comeau et al. 2001; Epstein and Barasch 2010; Hutton et al. 2007; Mahmoud et al. 2011; Mattsson et al. 1992; Peregrin 2006; Sánchez-Lara et al. 2010). Individuals from other various clinical populations, such as chronic hepatitis C (Klimacka-Nawrot et al. 2010; Musialik et al. 2012), HIV/AIDS (Heald and Schiffman 1997), and myasthenia gravis (Kabasawa et al. 2013) patients, also display taste and appetite abnormalities. Many drugs used to treat chronic medical conditions also impact upon taste perception and lead to dysgeusia (Doty et al. 2008; Imoscopi et al. 2012). Poor appetite, weight loss, and under-nutrition are frequently observed among elderly admitted to hospital (Mowe and Bohmer 2002; Mowe et al. 1994). Research has suggested that taste perception is impaired during normal aging (Bartoshuk 1989; Boesveldt et al. 2011; Cowart 1989; Heft and Robinson 2010; Methven et al. 2012; Mojet et al. 2001; Murphy 1993; Schiffman 1997; Stevens 1996), even more so in hospitalized older adults (Solemdal et al. 2014; Toffanello et al. 2013). Taste loss may be one of several factors contributing to poor appetite, reduced dietary intake, and weight loss in elderly patients (Chen et al. 2001; Fuchida et al. 2013; Schiffman and Graham 2000; Schiffman and Wedral 1996; Ship et al. 1996). Lastly, patients whose primary complaint is taste loss have also shown nutritional abnormalities (Malaty and Malaty 2013; Mattes and Cowart 1994; Mattes-Kulig and Henkin 1985).

Problems with the Strength of the Link Between Gustatory Functioning and Ingestive Behavior/Body Mass Accumulation

Lack of Gustatory Specificity

In reports that have demonstrated an association between the functioning of a particular component of the gustatory system (e.g., taste receptors) and food intake/body mass, the authors have hypothesized that any observed association was mediated by that component's influence on taste perception. While it is intuitive, and perhaps parsimonious, to assume that taste functioning directly and substantially influences nutrient preference and intake, it is also possible that taste function varies along with some other factor that is more directly influencing ingestive behaviors. Indeed, in addition to their expression in the oral-nasal

cavity, it is now well known that many molecules traditionally associated with the functioning of the gustatory system, particularly those expressed in taste receptor cells, are expressed in tissues all over the body where they appear to aid these tissues in sensing the general chemical milieu of their respective environments (Behrens and Meyerhof 2010, 2011; Dotson et al. 2010). For example, taste receptors, as well as other key components of the gustatory sensory transduction cascade, are expressed in tissues of the gastroin-testinal tract, where they appear to play a role in hormone secretion as well as in the nutrient-dependent regulation of metabolism (Akiba et al. 2009; Batchelor et al. 2011; Bezencon et al. 2006, 2007; Daly et al. 2012, 2013; Dotson et al. 2008, 2010; Dyer et al. 2005, 2007; Hass et al. 2010; Jang et al. 2007; Janssen and Depoortere 2013; Janssen et al. 2011; Jeon et al. 2011; Kaji et al. 2009; Kokrashvili et al. 2009a, b; Mace et al. 2009; Margolskee et al. 2007; Max et al. 2001; Moran et al. 2010, 2014; Rozengurt et al. 2006; Sternini 2007; Swartz et al. 2012; van der Wielen et al. 2014; Widmayer et al. 2011, 2012; Young et al. 2009). Thus, functional variation in any of these molecules could impact upon food intake via their influence on postingestive functioning (postingestive functioning has been shown to have a substantial impact on ingestive behaviors; see Smith 1998 for a comprehensive review). Canonical “taste” transduction components have also be shown to be expressed in the liver (Taniguchi 2004; Toyono et al. 2007), pancreas (Kojima et al. 2014; Kyriazis et al. 2012, 2014; Medina et al. 2014; Nakagawa et al. 2009; Taniguchi 2004), adipose tissue (Masubuchi et al. 2013; Simon et al. 2013), kidney (Kiuchi et al. 2006; Rajkumar et al. 2014), heart (Foster et al. 2013), respiratory system (Deshpande et al. 2010; Lee et al. 2014; Shah et al. 2009; Tizzano et al. 2011), thymus (Max et al. 2001), lymphocytes (Kiuchi et al. 2006; Masubuchi et al. 2013; Simon et al. 2013), leukocytes (Malki et al. 2015), sperm (Kitagawa et al. 2001; Kiuchi et al. 2006; Max et al. 2001; Meyer et al. 2012; Mosinger et al. 2013; Voigt et al. 2012), brain (Max et al. 2001; Ren et al. 2009; Shin et al. 2010b), and other tissues (Wauson et al. 2012, 2013). Thus, it cannot be ruled out that functional variation in these key components of the gustatory system, which are conventionally associated with taste function, are impacting upon ingestive behaviors and/or body weight accumulation via their extraoral expression and function.

Lack of Experimental Control

As detailed above, a large body of research suggests a link between taste functioning and food preference and intake. However, there are a substantial number of studies that suggest no links exist (e.g., Choi 2014; Drewnowski et al. 2007; Frijters and Rasmussen-Conrad 1982; Grinker 1978; Kaminski et al. 2000; Mattes and Labov 1989; Niewind et al. 1988; Yackinous and Guinard 2002). These discrepancies in the literature likely result from the confounding influence of a variety of other, uncontrolled, factors that can influence ingestive behavior. Indeed, eating is a complex behavior with multiple factors that can influence the amount of food ingested in a given meal, including, but not limited to, age, sex, prior experiences, social and cultural norms, as well as body, health, and weight attitudes (Beckett et al. 2014; Smith 1996, 2000a). These factors may interact with taste functioning to alter and/or obscure any putative relationship between it and food intake. Unfortunately, few researchers have attempted to control for the influence of the other factors or to assess the combined influence of these factors in a single study (however cf. Bouthoorn et al. 2014; Burd et al. 2013; Duffy et al. 2010). Thus, despite this relatively large

body of evidence that indicates that gustatory functioning can influence nutritional intake, a growing number of researchers are questioning the nature and/or strength of the role that taste functioning plays in the mediation of food intake and maintenance of body weight (e.g., Beckett et al. 2014; Donaldson et al. 2009; Hayes et al. 2013).

Moreover, the direction of the effect is unclear in these studies. When significant associations are observed between variation in taste perception and food intake and obesity, it is assumed that changes in taste functioning are influencing feeding behavior. However, it is also possible that the condition of being obese itself and/or associated physiological changes associated with obesity (e.g., chronic inflammation) could impact upon taste functioning (e.g., Chevrot et al. 2013; Cohn et al. 2010; Feng et al. 2014).

A More Systematic Evaluation of Taste's Influence on Ingestive Behaviors is Needed

As detailed above, the experiments designed to link the functioning of the gustatory system to changes in food intake conducted using human subjects are problematic because the link created between taste and food intake is weak at best because of the correlational nature of these experiments, lack of experimental control, and lack of gustatory specificity. At least partially as a result, treatments for obesity that target the orosensory functioning are virtually nonexistent (although see Allison et al. 2001). Providing convincing evidence that taste can influence the development of obesity could lead to the development of novel treatments that target the gustatory system (Dotson et al. 2010; Sprous and Palmer 2010).

To alleviate at least some of these problems related to the lack of control of experimental variables, some researchers have used animal models in lieu of human experimentation to investigate the link between taste functioning and ingestive behaviors. Controlled animal experimentation has greatly increased our understanding of the functional organization of the taste by allowing for invasive manipulations of the gustatory system that would not be possible in humans. By assessing the functional consequence of a given manipulation, and not just correlating natural phenotypic variation as has been done in the studies detailed in the previous sections of this review, researchers would be able to more strongly link taste perception to ingestive behavior (e.g., Spector 2000).

To further increase experimental control, and hence the power of the potential link that can be established between taste and food intake, the use of a systematic, precise method of measuring food intake is needed. Duffy et al. reported that many of the published studies designed to investigate the link between taste perception and ingestive behaviors often employ food intake inventories that typically include short frequency questionnaires to assess intake of foodstuffs (e.g., saturated fat, fruits, vegetables, whole grains, alcohol) (Duffy et al. 2009). Participants are asked to recall the amount of food eaten, of listed foods, during a specified time frame—a task requiring access to factual memories of past experiences. Participants may under- or over-report intake, leading to inaccurate conclusions about diet-disease relationships. As such, methods focusing less on factual memory would increase the accuracy of dietary assessment. In addition, social valuation bias, which may

cause the underreporting of certain, unhealthy foods (Hebert et al. 2008), may also lead to the underreporting of actual intake by ≥30 % (e.g., Teal et al. 2007).

In addition to being able to more accurately determine actual food intake, the use of systematic, precise intake measuring techniques also allow researchers to ask questions related to exactly how the ingestion occurs (i.e., the assessment of ingestive behavior), in addition to how much an individual ingests over some period of time (i.e., food intake; Smith 2000c). Most mammals, including humans, eat in discrete bouts or meals (Collier 1980; Davis 1989; Strubbe and Woods 2004). The processes governing the onset and offset of a meal in essence determine the total intake of the animal and represent the major behavioral mechanism by which energy balance and ultimately body mass are controlled (Cummings and Overduin 2007; Davis and Campbell 1973; Meguid et al. 1998; Smith 1996; Strubbe and Woods 2004). Accordingly, a comprehensive understanding of the mechanisms underlying the regulation of food intake, as well as its dysfunction, as occurs in the case of obesity, requires an analysis of how various endocrine and neural signals interact to control ingestive behavior. Meal pattern analysis provides just that: a detailed analysis of the size, frequency, and temporal distribution of meals in free feeding animals. Moreover, facets of these patterns (e.g., meal size versus meal number) are neurally dissociable (Meguid et al. 1996, 1997, 1998; Smith 2000b). Decades of research have demonstrated that an assortment of factors can influence these parameters including changes in diet, deprivation, diurnal and ovarian rhythms, pregnancy and lactation, operant contingencies, experience, brain lesions, social stimuli, neurotransmitters, neuromodulators, and drugs (e.g., Boggiano et al. 2007; Burton-Freeman et al. 1997; Cooper et al. 2006; Davoodi et al. 2009; de Castro 2004; de Castro and de Castro 1989; Farley et al. 2003; Larue-Achagiotis and Le Magnen 1980; Leibowitz et al. 1993; Levitsky 1970; Lutz et al. 1995; Melhorn et al. 2010; Moran 2008; Morgan et al. 2002; Richard et al. 2011; Santollo and Eckel 2008; Smith 2000b; Tabarin et al. 2007; Tempel et al. 1989; Varma et al. 1999; Zorrilla et al. 2005). For example, it is well known that when postingestive influences are eliminated or minimized (e.g., via sham feeding), the size of ingested meals increases (e.g., Davis and Campbell 1973; Nissenbaum and Sclafani 1987, 1988; Sclafani and Nissenbaum 1987). What had never been directly investigated using meal pattern analysis was whether taste input does significantly influence long-term food intake and bodyweight maintenance and, if so, how it would be manifested in regard to ingestive behavior (e.g., meal size versus meal number).

The Effects of Gustatory Neurotomy on Body Mass and Food Intake

Our laboratory has used meal pattern analysis to evaluate the influence of gustatory neural input on food intake and body weight accumulation. In these experiments, we were able to more closely link taste functioning to intake by making focal manipulations in rodents. Peripheral gustatory deafferentation was produced in these animals by bilateral transection of the chorda tympani, glossopharyngeal, and greater superficial petrosal nerves. These are the primary nerves that transmit information from taste buds in the oral cavity to the CNS. These nerve transections effectively remove the input from ~90 % of the taste receptor cells, which, in turn, degenerate after nerve transection (e.g., Miller 1977; Spector 2003).

There were two principal outcomes from these experiments. First, rats that had bilateral transection of the chorda tympani, glossopharyngeal, and greater superficial petrosal nerves (i.e., TRIPLEx rats) initially lost significantly more body mass after surgery and stabilized at a significantly lower mean weight relative to control rats (Fig. 1 and Dotson et al. 2012b). That is to say that in the absence of gustatory neural input from the tongue and palate, body mass was more stable compared with the more progressive course of weight gain observed in controls. Second, the loss resulted in a drop in caloric intake that was affected primarily through decreases in meal number and not in the size of the meals that the rats took (Fig. 2 and Dotson et al. 2012b). Interestingly, the post-surgical loss and stabilization in body mass in the TRIPLEx rats is similar to that observed in rats that received Roux-en-Y gastric bypass (Bueter et al. 2011; Hajnal et al. 2010; Le Roux et al. 2011; Shin et al. 2010a). The efficacy of treatment of obesity via gastric bypass is vastly superior relative to what is seen with pharmacological interventions or dietary restriction regimens.

These results are generally consistent with the literature regarding the effects of gustatory neurotomy on body mass and food intake (unfortunately, none of these studies used meal pattern analysis to assess how any observed changes in intake were being manifested). For example, in a report by Grill and Schwartz, rats that had bilateral chorda tympani and glossopharyngeal nerve transections maintained a significant weight loss, relative to controls, 20 days postsurgery (Grill and Schwartz 1992). Another group of researchers reported that when the chorda tympani, glossopharyngeal, and the pharyngeal branch of the vagus nerves were bilaterally transected, rats lost significant levels of body mass, and, depending on the nature and composition of the diet to which the animals have access, these rats do not recover their baseline levels of body mass until anywhere between 1 and 5 weeks (Jacquin 1983; Miller and Teates 1986). Similar results were also seen when these nerves were cut in addition to the anterior palatine nerve, which innervates the taste buds of the incisive papilla in the rat (Vigorito et al. 1987).

These results are also generally consistent with the literature regarding the effects of gustatory nerve damage in human subjects. As detailed above, otitis media and tonsillectomy, both of which can result in damage to gustatory nerves, are associated with enhanced palatability of energy-dense foods and with weight gain. Reports have suggested that surgical interventions in the head and neck area can also lead to reports of taste defects. For example, middle ear surgery can cause damage to the CT nerve and lead to taste loss (e.g., Gopalan et al. 2005; Guinand et al. 2010; Huang et al. 2012; Lauerma and Paalassalo 1995; McManus et al. 2011, 2012; Michael and Raut 2007; Saito et al. 2001) and changes in food intake patterns (Lauerma and Paalassalo 1995).

Problems with the Interpretation of Studies Investigating the Impact of “Gustatory” Neurotomies on Ingestive Behavior and Body Mass

The interpretation of findings from studies investigating the impact of cranial nerve transection on ingestive behavior and body mass must be viewed with some degree of caution because, in addition to carrying afferent sensory information from taste buds to the CNS, many of these nerves have other functions. For example, in the experiments where the pharyngeal branch of the vagus was transected, there is no evidence that this nerve

innervates taste buds, but it does provide substantial motor innervation to the pharynx (Contreras et al. 1980; Jinkins 2000), which could have a significant impact upon feeding behavior and body mass (see Dotson et al. 2012b for more details). In addition to innervating taste buds, both the chorda tympani and glossopharyngeal nerves also contain parasympathetic fibers that innervate the salivary glands (Bradley et al. 1985; Contreras et al. 1980; Kim et al. 2004; Smith and Breathnach 1990). Thus, transection of these nerves could affect the salivary content of the oral cavity and, in turn, influence ingestive behaviors. The greater superficial petrosal and glossopharyngeal nerves also possess somatosensory afferents, the loss of which could influence feeding behaviors. Indeed, it has been shown that trigeminal deafferentation of the anterior tongue leads to significant decreases in food intake and body weight (Jacquin and Zeigler 1983). Thus, however unlikely it may be, as a result of these confounding issues, it cannot be entirely dismissed that changes in the salivary content of the oral cavity or a decrease in oral somatosensory signals in rats with gustatory neurotomies could contribute to the change in ingestive behaviors observed in these animals (see Dotson et al. 2012b for a thorough discussion of these issues).

Conclusions and Future Directions

Our “TRIPLEx” data provide strong support for the importance of gustatory neural input in the regulation of body mass (Dotson et al. 2012b). However, given the caveats detailed above, the development of more selective interventions/manipulations that exclusively target gustatory pathways is still needed to establish a rock-solid link between gustatory function and food intake and body mass regulation.

Other methods of manipulating gustatory function, such as the use of genetic knockout mouse models, could be useful in establishing a stronger link. The use of knockout mouse models to examine the functioning of the gustatory system, as well as a variety of other biological functions (Picciotto 1999), has been rapidly expanding. These models have been used to study the role of particular gene products or to inactivate various tissues or biological structures to determine the relative necessity and/or sufficiency of that structure in mediating a given physiological process or behavior. However, there are problems endemic in the use of “global” knockout animals for this purpose: (1) the chronic disruption of the production of a given gene product over the lifespan of the animal and (2) the systemic disruption of that gene product’s influence in all tissues in which it is normally expressed. As detailed in the preceding sections, many molecules traditionally associated with the functioning of the gustatory system, especially those present in taste receptor cells, are also expressed in various other tissues throughout the body. As a result, global knockouts may possess extraneous phenotypes that can influence any dependent variable of interest.

It has been reported upon cursory inspection that animals from many different genetic KO models designed to affect the functioning of the peripheral taste system have no apparent body mass and/or food intake deficits when compared to control animals (e.g., KOs of T1R family genes, PLCβ2, TRPM5, $P2X_2$/$P2X_3$, CALHM1; Cockayne et al. 2005; Jiang et al. 1997; Vingtdeux et al. 2011; Zhang et al. 2003; Zhao et al. 2003). However, upon closer inspection, when researchers have looked for changes in the variables over longer periods of time, differences in body mass and/or food intake have been revealed. For example, it was

reported that CALHM1 KOs were “visually indistinguishable” from their WT littermates (Vingtdeux et al. 2011). However, a more detailed and longer term examinations found deficits in body mass, as well as in macronutrient intake, relative to control mice (Hellekant et al. 2015; Tordoff et al. 2014). Similar results have been observed with other KO models of gustatory transduction in the periphery (TRPM5 and T1R3 KOs; e.g., Damak et al. 2013; Minaya 2014). Collectively, these data strongly suggest that genetic KO designed to affect the functioning of the peripheral gustatory system are effective models to study the influence of taste on ingestive behaviors and body mass accumulation.

To deal with the problems associated with the use of global KO models, the use of tissue-specific, conditional knockout and transgenic mouse models should be used to better and more specifically link ingestive behavior and gustatory functioning. To date, almost no experiments using such models have been used to explore gustatory functioning in intact mice (however, see Chandrashekar et al. 2010). This is likely because of the difficulty in identifying proteins expressed primarily or exclusively in gustatory tissues. The promoters from genes such as these are needed to create constructs/vectors designed to express a given experimental gene in a tissue-specific fashion (Zheng and Baum 2008).

Additionally, gustatory functioning can be studied by delivering foreign DNA, RNA, and/or siRNA in cells. There are several methods available for transferring foreign genes into cells (e.g., lipofection, particle-mediated gene transfer (gene gun), electroporation, viral gene transfer, nanoparticle-mediated gene delivery; Jin et al. 2009; Stone et al. 2002). The promise of these gene delivery techniques is hampered by the difficulty of in vivo delivery into targeted cells (e.g., taste receptor cells). However, many of these difficulties have been overcome by researchers (e.g., Gray and Zolotukhin 2011; La Sala et al. 2013; Unciti-Broceta et al. 2011; Zhang et al. 2012; Zheng et al. 2012). Similar to the use of tissue-specific knockout models, in spite of the impact that the use of these gene delivery methods has had in biomedicine, there has been relatively limited use of this approach in the chemical senses, especially in the analysis of taste perception. Finally, the use of pharmacological approaches to disrupt gustatory functioning can allow for acute, local disruption in the oral cavity and not in central tissues (Elson et al. 2010; Eylam and Spector 2002).

Thus, the use of such techniques to create animal models that have specific deficiencies in gustatory functioning, in combination with the use of meal pattern analysis, will allow for the investigation of the functions of particular genes in a spatially and temporally regulated fashion, overcoming the issues endemic with genetic association studies as well as those related to the use of gustatory neurotomies and greatly increase the strength of any conclusions derived from experiments designed to investigate the link between taste and ingestive behaviors.

Finally, it should be mentioned that the use of animal models in basic and preclinical biomedical research has focused disproportionately on male animals (Clayton and Collins 2014). However, women now account for roughly half of all participants in NIH-supported clinical research, which is subject to NIH's Policy on the Inclusion of Women in Clinical Research. An over-reliance on male animals may obscure understanding of key sex

influences on health processes and outcomes (Clayton and Collins 2014). Indeed, the National Institutes of Health (NIH) has recently laid out policies dictating that the basic science research that the organization funds must consider both females and males (NIH Notice Number NOT-OD-15-102). Thus, researchers that take advantage of the benefits inherent in the use of animal models in their attempts to further explore the putative link between gustatory functioning and ingestive behaviors should include female animals in their experimental plans.

In conclusion, we are proposing a new line of research that addresses the gaps in our knowledge regarding the strength of association between taste perception and eating behaviors and how perturbations in taste functioning can impact upon energy homeostasis. Indeed, results from sophisticated and carefully crafted animal research studies could greatly advance our scientific understanding—an understanding that could potentially lead to novel therapeutic strategies aimed at reducing food intake and controlling obesity and other lifestyle-related diseases that increasingly plague our society.

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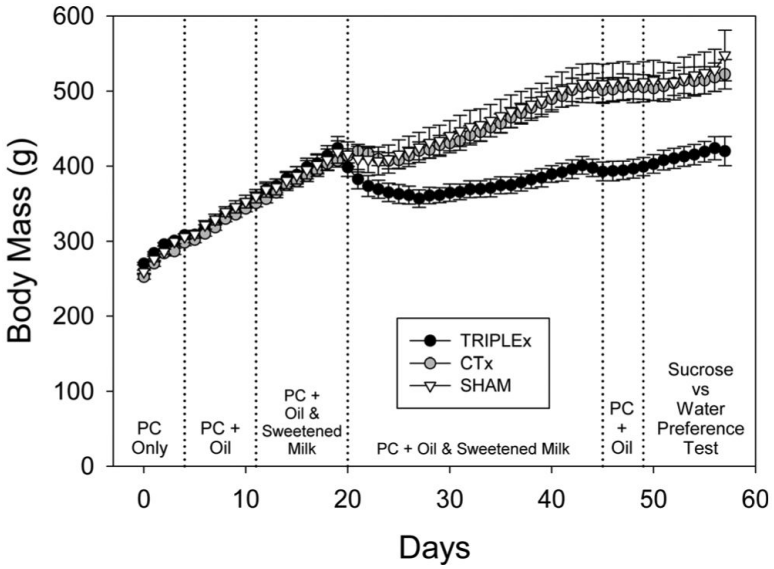

Fig. 1.

Body mass values assessed for sham, CTx, and TRIPLEx groups measured over the entire pre- and postsurgical period (means±SE). *CTx*=rats that had combined bilateral transection the chorda tympani nerve and exposure of the greater superficial petrosal nerve; TRIPLEx=rats that had combined bilateral transection of the chorda tympani nerve, greater superficial petrosal nerve, and glossopharyngeal nerve. Reproduced, with permission, from Dotson et al. (2012b)

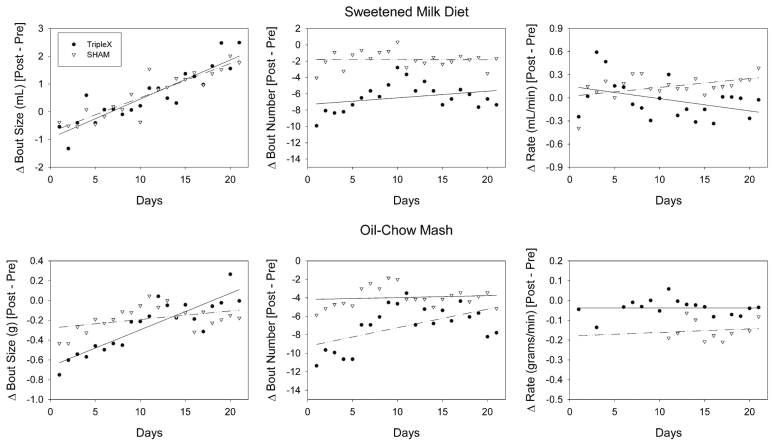

Fig. 2.

Daily meal bout size (*left*), meal bout number (*middle*), and meal bout rate (*right*) when ingesting a sweetened-milk diet (*top*) and an oil-chow mash (*bottom*) by sham and TRIPLEx groups measured for 3 weeks postsurgery. Reproduced, with permission, from Dotson et al. (2012b)