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# Behavioral evidence that select carbohydrate stimuli activate T1R-independent receptor mechanisms

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ABSTRACT

Three decades ago Tony Sclafani proposed the existence of a polysaccharide taste quality that was distinguishable from the taste generated by common sweeteners and that it was mediated by a separate receptor mechanism. Since that time, evidence has accumulated, including psychophysical studies conducted in our laboratory, buttressing this hypothesis. The use of knockout (KO) mice that lack functional T1R2 + T1R3 heterodimers, the principal taste receptor for sugars and other sweeteners, have been especially informative in this regard. Such KO mice display severely diminished electrophysiological and behavioral responsiveness to sugars, artificial sweeteners, and some amino acids, yet display only slightly impaired concentration-dependent responsiveness to a representative polysaccharide, Polycose. Moreover, although results from gene deletion experiments in the literature provide strong support for the primacy of the T1R2 + T1R3 heterodimer in the taste transduction of sugars and other sweeteners, there is also growing evidence suggesting that there may be T1R-independent receptor mechanism(s) activated by select sugars, especially glucose. The output of these latter receptor mechanisms appears to be channeled into brain circuits subserving various taste functions such as cephalic phase responses and ingestive motivation. This paper highlights some of the findings from our laboratory and others that lend support for this view, while emphasizing the importance of considering the multidimensional nature of taste function in the interpretation of outcomes from experiments involving manipulations of the gustatory system.

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The publication of Tony Sclafani's impressive compendium of papers published in a dedicated issue of *Neuroscience and Biobehavioral Reviews* (Nissenbaum & Sclafani, 1987) had a tremendous influence on experimental pursuits of carbohydrate taste. Along that theme, this paper deals with saccharide sensing by the gustatory system - a topic for which Tony Sclafani's and Karen Ackroff's interests intersect with our own. We do this as an homage for the significant contributions that both of them have made to the science of ingestive behavior. The work presented in the following pages is not meant to provide a comprehensive review of the issue, but to merely highlight a few key findings from our laboratory and Tony Sclafani's, as well as some others, that provide significant support for the view that select carbohydrate stimuli, including some sugars, engage more than one taste receptor mechanism.

## 1. A heuristic framework of taste function

At the outset, it would be worthwhile highlighting a heuristic multidimensional framework for understanding taste function [see (Spector, 2000) for more detail]. First, taste serves a sensory-discriminative role that helps animals identify stimuli. Perceptions of quality and basic stimulus strength fall under this functional domain. Second, taste serves to promote or discourage the consumption of foods and fluids. The motivational, reward, and hedonic properties of a taste stimulus are part and parcel of this domain of function that we refer to as ingestive motivation [see (Spector, 2000)]. Students of motivational processes further divide such behavior into an *appetitive* and a *consummatory* component. Appetitive behavior refers to the approach toward, or away from in the case of avoidance, a taste stimulus. Consummatory behavior refers to the oromotor actions supporting the ingestion, or rejection in the case of aversion, of the taste stimulus triggered by the activation of oral receptors. Finally, taste plays a role in physiological processes that prepare the body for the arrival of food and fluids via

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so-called cephalic phase reflexes. A clear example of a cephalic phase reflex is the salivation elicited by the "sour" taste of a lemon. Importantly, in the context of this framework, the input from a given taste receptor could, by virtue of its neuronal connections, be channeled into circuits that subserve one (or more) of these functions, but not another. Given the multidimensional nature of gustatory function, the types of tasks used to assess taste responsiveness must be considered in the interpretation of experimental outcomes.

## 2. The multiple taste receptor model for carbohydrates

Three decades ago, Tony Sclafani hypothesized the existence of a polysaccharide taste that was discriminable from that of sugars and other sweeteners and mediated through a separate receptor mechanism in rodents (Nissenbaum & Sclafani, 1987). This hypothesis was based on a series of clever behavioral experiments demonstrating that rats treat the taste of Polycose (a prototypical maltodextrin with an average molecular weight of 1000) differently from other sweeteners despite the fact that these animals find all of these stimuli palatable. At the time, there was also growing evidence suggesting that sucrose was discernable from the glucose disaccharide, maltose. For example, Spector and Grill (Spector & Grill, 1988), as well as Nissenbaum and Sclafani (Nissenbaum & Sclafani, 1987), demonstrated that although rats will cross-generalize taste aversions conditioned to maltose and sucrose, indicative of some degree of qualitative similarity, they display a greater aversion to the sugar that serves as the conditioned stimulus, which suggests there must be some discriminable feature between the two sugars.

Consistent with this implication, using a gustometer in which small volumes of taste stimuli are delivered and immediate responses are measured, Spector et al. (Spector, Markison, St.John, & Garcea, 1997) trained "thirsty" rats to suppress their licking when they sampled sucrose to avoid a brief foot-shock, but to maintain licking when they sampled maltose. Concentration was varied to render intensity an irrelevant cue. The sugar (sucrose or maltose) that signaled shock was counterbalanced across rats. All animals learned to perform this discrimination with great competence. Performance was unaffected by sham surgery, or bilateral transection of the chorda tympani nerve (innervating taste buds in the front of the tongue), or bilateral transection of the glossopharyngeal nerve (innervating taste buds in the back of the tongue). However, when the chorda tympani nerve was transected in combination with the greater superficial petrosal nerve (innervating the taste buds of the palate), the rats were severely impaired. Thus, rats can discriminate orally sampled sucrose from maltose, and this ability is dependent, in part, on signals arising from the combined gustatory branches of the seventh cranial nerve. The fact that transection of gustatory nerves led to this impairment offers strong support that the behavior was under discriminative control on the basis of taste signals.

Dotson and Spector (Dotson & Spector, 2007) used a similar gustometer to test whether C57BL/6J (B6) mice could discriminate sucrose from glucose, maltose, and fructose. The "thirsty" mice were initially trained in a two-response operant taste discrimination procedure to lick a left (or in other mice a right) response spout after sampling sucrose from a center spout and to lick a right (or in other mice a left) response spout after sampling NaCl. Correct responses were reinforced by the delivery of water and incorrect responses were punished with a time-out. Concentration was varied to render intensity an irrelevant cue. After competent performance was achieved, the mice were tested for their ability to discriminate sucrose from other compounds. With respect to the sugars tested, mice could not discriminate sucrose from glucose. Although mice appeared to discriminate fructose from sucrose slightly (but significantly) above chance level, a close inspection of the data suggested that these animals were potentially using intensity cues. Interestingly, the mice did perform the sucrose vs. maltose discrimination above chance and although performance was modest at best, it could not easily be explained by intensity cues. A human psychophysical study employing a forced-choice sugar discrimination procedure reached a similar conclusion (Breslin, Beauchamp, & Pugh, 1996). In that study, a fixed concentration of one standard sugar was pitted against various concentrations of a comparison sugar to control for intensity differences. There was always a concentration of the comparison sugar that could not be discriminated from the standard sugar. The only exception was maltose, which, while indiscriminable from low concentrations of a fructose standard, was discernable from higher concentrations of a fructose standard. Overall, the results from both human and rodent studies suggest that most sugars, aside from maltose, generate a unitary qualitative taste sensation (i.e., "sweetness").

A mechanistic basis underlying the qualitative similarity of sugars was finally discovered at the start of the new millennium with the identification of the T1R family of taste receptors (Bachmanov et al., 2001; Hoon et al., 1999; Kitagawa, Kusakabe, Miura, Ninomiya, & Hino, 2001; Max et al., 2001; Montmayeur, Liberles, Matsunami, & Buck, 2001; Nelson et al., 2001; Sainz, Korley, Battey, & Sullivan, 2001). It is composed of three members: T1R1, T1R2, and T1R3. The T1R1 combines with T1R3 to form a heterodimer that binds with L-amino acids, and the T1R2 combines with the T1R3 to form a heterodimer that binds with sweeteners. Very strong support for the T1R2 + T1R3 as the principal receptor for natural and artificial sweeteners has been derived from knockout (KO) experiments in which one or both of the subunits have been genetically silenced in mice leading to severe reductions or abolition of behavioral and electrophysiological responses to these stimuli [e.g., (Bachmanov et al., 2001; Hoon et al., 1999; Kitagawa et al., 2001; Max et al., 2001; Montmayeur et al., 2001; Nelson et al., 2001; Sainz et al., 2001)].

The severe effects that genetic ablation of either T1R2 or T1R3 has on the capacity of mice to respond to sugars has provided compelling evidence of the importance of the T1R2 + T1R3 for "sweet" taste. Indeed, polymorphisms in the *Tas1r3* gene in various congenic and inbred strains of mice are associated with differences in responsiveness to sweeteners, corroborating the gene deletion findings (Bachmanov et al., 2016; Eylam & Spector, 2004; Inoue et al., 2004, 2007). For example, Eylam and Spector (Eylam & Spector, 2004) used the gustometer mentioned above along with the two-response operant taste detection procedure to psychophysically measure taste detection thresholds for sucrose, glucose, and the sweet-tasting amino acid glycine, in several strains of inbred mice, some of which are subsensitive to sweeteners due to variation in the *Tas1r3* gene. Interestingly, across all of these mice, sucrose and glucose thresholds correlated quite highly with one another, but did not correlate as well with thresholds for glycine, which is a ligand that also activates the T1R1 + T1R3 heterodimer (Nelson et al., 2002). Importantly, responsiveness to glycine is not thought to be affected by the T1R3 polymorphism (Bachmanov et al., 2016; Inoue et al., 2004, 2007). Thus, with respect to sensory-discriminative taste function as assessed by a signal detection task, sugars (at least sucrose and glucose) appear to activate a common taste receptor(s) consistent with the properties of the T1R2 + T1R3 heterodimer. That said, it is important to note that these findings do not necessarily preclude the existence of T1R-independent taste receptors that are activated by one or more of these sugars, the output of which may be channeled into circuits subserving other taste functions such as ingestive motivation of

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