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Review

The taste of sugars

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ABSTRACT

Sugars evoke a distinctive perceptual quality ("sweetness" in humans) and are generally highly preferred. The neural basis for these phenomena is reviewed for rodents, in which detailed electrophysiological measurements have been made. A receptor has been identified that binds sweeteners and activates G-protein-mediated signaling in taste receptor cells, which leads to changes in neural firing rates in the brain, where perceptions of taste quality, intensity, and palatability are generated. Most cells in gustatory nuclei are broadly tuned, so quality perception presumably arises from patterns of activity across neural populations. However, some manipulations affect only the most sugar-oriented cells, making it useful to consider them as a distinct neural subtype. Quality perception may also arise partly due to temporal patterns of activity to sugars, especially within sugar-oriented cells that give large but delayed responses. Non-specific gustatory neurons that are excited by both sugars and unpalatable stimuli project to ventral forebrain areas, where neural responses provide a closer match with behavioral preferences. This transition likely involves opposing excitatory and inhibitory influences by different subgroups of gustatory cells. Sweeteners are generally preferred over water, but the strength of this preference can vary across time or between individuals, and higher preferences for sugars are often associated with larger taste-evoked responses.

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Nearly all mammals can respond to sugars by taste. This is not surprising, given that glucose is an essential source of energy, and survival depends on blood glucose concentrations being maintained within narrow limits. Other sugars, such as sucrose and fructose, are useful to animals because they can be converted to glucose, to which these compounds taste similar. Short-chain polysaccharides and starches can also be converted, but a larger amount of energy is required; although the former can induce taste responses directly, they do so using different mechanisms than those activated by sugars (Sclafani, 1991; Sako et al., 1994).

Ingestion of sugars immediately stimulates neural and behavioral responses that are distinct from those evoked by compounds with salty, sour, bitter, and umami tastes. In humans, sugars generate the distinctive taste quality of sweetness. There is no way for rodents to verbalize such perceptions, but the unique reactions that they demonstrate to sugars confirm that these compounds can be considered to have a unique taste quality for them. For example, rats trained to bar-press for sugars do not generalize the behavior to compounds known to taste salty, sour, or bitter to humans (Morrison, 1969), and rodents that are made ill after ingesting sugars avoid a variety of compounds that humans label "sweet", but not non-sweet compounds (Nowlis et al., 1980; Ninomiya et al., 1984a). Throughout this review, compounds will be considered to taste "sweet" to rodents if they are treated similarly to sucrose in such behavioral tests, with the caveat that such taste quality perceptions must be inferred. The distinctive taste of sugars is useful, in that it provides an immediate signal that a source of readily available calories has been sampled.

After sugars stimulate gustatory transduction mechanisms, the neurons that receive the resulting signals serve several important roles. A specific taste quality perception is generated, which allows sugars to be differentiated from other compounds. Perceptions of taste intensity also occur and allow animals to react appropriately to different concentrations of sugars. In addition, perceptions of palatability and reward help to guide consumption of sugars based on a dynamic process than can accommodate short-term changes in physiological state and long-term changes due to learning or development. For example, the significance of sugar consumption for an animal varies depending on whether or not it has eaten recently, and gustatory cells alter their responses accordingly in a way that helps to maintain glucose homeostasis. This review describes the different gustatory aspects of sugars in rodents, for which there is detailed information about taste-evoked neural activity at all levels of the gustatory system. Sugars are given the most emphasis, since they are the most biologically relevant sweeteners, but other compounds that taste similar to sugars are also considered.

1. Transduction mechanisms and central projections

When sugars are ingested by a rodent, they come in contact with taste buds in the tongue and other parts of the oral cavity, such as the soft palate and nasoincisor ducts. In the tongue, taste buds can be found within protuberances called papillae. Fungiform papillae are found on the anterior two-thirds of the tongue, whereas circumvallate and foliate papillae are located on the posterior one-third. Each of these buds forms a complex, interactive unit with approximately 50–150 taste receptor cells, some of which project into the taste pore at their apical ends to allow binding of compounds, and some of which contact peripheral gustatory nerves to allow transmission of action potentials to the brain (Fish et al., 1944; Miller, 1995; Herness and Gilbertson, 1999).

The first step in gustatory transduction of sugars is thought to be binding to a receptor that is apically expressed in taste receptor cells and consists of a dimer of the seven-transmembrane-spanning domain proteins T1R2 and T1R3, which are coded for by the genes *Tas1r2* and *Tas1r3*, respectively. The dimer is then coupled to G-proteins for intracellular signaling. The *Tas1r3* gene corresponds to the *Sac* locus (Bachmanov et al., 2001a; Kitagawa et al., 2001; Max et al., 2001; Montmayeur et al., 2001; Nelson et al., 2001; Sainz et al., 2001), which had been proposed to be important in sweet taste based on inherited differences in preferences for saccharin in mice (Fuller, 1974). There is also evidence that T1R3 alone, possibly acting as a homodimer, can bind sugars at high concentrations (Zhao et al., 2003).

In vitro work has shown that expression of the rat forms of T1R2 and T1R3 results in binding of compounds that appear to taste sweet to rodents (Nelson et al., 2001; Li et al., 2002). These include the sugars sucrose and fructose; artificial sweeteners such as saccharin, dulcin, sucralose, and acesulfame-K; the amino acids glycine and D-tryptophan; and other compounds, such as the sugar alcohol D-sorbitol. Binding of the sugars glucose, maltose, lactose, and galactose was found in one study (Li et al., 2002), but not in another that used similar concentrations (Nelson et al., 2001). The diversity of chemical structures for the compounds listed above raises the possibility that there are multiple binding sites on the T1R2/T1R3 receptor, and work with the human sequences of these proteins supports this view (Xu et al., 2004). Specific binding sites have not yet been identified for the rodent forms, though there is evidence that the N-terminal domains of mouse T1R2 and T1R3 are both involved in binding, but to different degrees for different sugars (Nie et al., 2005). The rat form of the receptor differs from the human form, in that it is unable to bind aspartame, which explains why rats do not show strong preferences for this compound (Sclafani and Abrams, 1986). Mice are normally insensitive to aspartame (Bachmanov et al., 2001b), but transgenic animals that express the human form of T1R2 consume it avidly, which is consistent with it tasting sweet to them (Zhao et al., 2003).

Sequences of the *Tas1r3* gene differ between inbred mouse strains that vary in their preferences for sweeteners in two-bottle tests (Bachmanov et al., 2001b; Kitagawa et al., 2001; Montmayeur et al., 2001; Sainz et al., 2001; Reed et al., 2004). The inbred strains used in these studies differ on many genes, but work with transgenic and congenic mouse strains has directly implicated variation in *Tas1r3* as the primary cause of the behavioral differences (Bachmanov et al., 2001a; Li et al., 2001; Nelson et al., 2001; Inoue et al., 2007). In these studies, the *Tas1r3* allele from a strain with high sweetener preferences was expressed on the background of a strain with low preferences, and the resulting animals had high preferences for sweet compounds. Insight into differences between mouse strains has also been provided by work using a binding assay; T1R3 with an amino acid sequence variant found in the high-preferring strains exhibited more effective binding of sugars than did T1R3 with a sequence variant found in the strains with low preferences (Nie et al., 2005). This suggests that the first stage of gustatory transduction has a major impact on the palatability of sweeteners, though it is likely not the sole determinant (see Section 4.2 for a more thorough consideration of this issue).

Studies with knockout mice have provided additional evidence that T1R2/T1R3 is the primary taste receptor for sweeteners. Targeted deletion of *Tas1r2* and/or *Tas1r3* results in dramatic reductions in preferences for sugars and evoked responses in the chorda tympani (CT) nerve (Damak et al., 2003; Zhao et al., 2003). Nonetheless, *Tas1r3* knockout mice prefer high concentrations of sucrose and glucose (Damak et al., 2003). One explanation is that there are other, less sensitive sugar receptors that remain to be determined. For example, the *dpa* locus is known to influence neural and behavioral sensitivity to sucrose in mice (Shigemura