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# Tasteless Food Reward

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**Food palatability acts on the dopaminergic reward system to override homeostatic control; however, whether postingestive calorie load in the absence of taste affects this system remains unclear. In this issue of *Neuron*, de Araujo et al. show that mice lacking functional "sweet" taste receptors (*trpm5*$^{-/-}$) develop a preference for sucrose by activating the mesolimbic dopamine-accumbal pathway, solely based on calorie load.**

There is no question that the current obesity epidemic has galvanized the scientific community to feverishly investigate the neurobiological mechanisms controlling food intake. It is incontrovertible that the hypothalamus regulates the homeostatic control of food intake by receiving, coordinating, and responding to peripheral metabolic cues. The importance of the hypothalamus in body weight regulation is underscored by conditionally knocking out AgRP neurons in the arcuate nucleus in adulthood (Gropp et al., 2005; Luquet et al., 2005), as these mice will starve to death if left unattended. By integrating these metabolic signals, the hypothalamus regulates food intake and energy expenditure to a body weight "set point." However, it is also clear that, in addition to the homeostatic regulation of food intake, there is substantial influence from higher brain centers (Berthoud, 2007).

The mesolimbic dopamine reward system is one such higher brain center that is important in neurobiological control of food intake (Palmiter, 2007). This is clearly demonstrated in dopamine-deficient mice, as they are hypoactive and hypophagic and die of starvation within 3 weeks of age (Szczypka et al., 1999). Activation of mesolimbic dopamine neurons in the ventral tegmental area (VTA) leads to dopamine outflow from the nucleus accumbens (NAc). This mesolimbic dopamine-accumbal projection is critical to reward-related behavior and has been well studied in models of drug addiction (Kalivas and Volkow, 2005). Food palatability and hedonic value are critical to the overall regulation of food intake and significantly contribute to obesity by overriding long-term homeostatic control in today's highly palatable, energy-rich food environment. Highly palatable foods increase dopamine concentrations in the NAc (Hernandez and Hoebel, 1988), and the hedonic value of sucrose can be attenuated by dopamine antagonists (Bailey et al., 1986). The mesolimbic dopamine-accumbal pathway is also targeted by peripheral metabolic hormones that control food intake, including ghrelin (Abizaid et al., 2006) and leptin (Hommel et al., 2006), which indicates that there is significant crosstalk between metabolic hormones regulating homeostatic and reward-based food intake.

Recent evidence suggests that neurons in the hypothalamus can sense and respond to the changes in metabolic value of ingested nutrients. However, it remained to be determined whether the mesolimbic dopamine system, critical for reinforcing food palatability and hedonic value, could also sense metabolic value of ingested nutrients independent of taste. The study by de Araujo et al. (2008), published in the current issue of *Neuron*, investigated this question by cleverly and logically designing a series of behavioral, neurochemical, and electrophysiological experiments in mice that lacked a functional transient receptor potential channel M5 (TRPM5, designated "KO") (Zhang et al., 2003). The TRPM5 ion channel is highly expressed in taste receptor cells (Perez et al., 2002) and is essential for sweet taste signaling (Zhang et al., 2003). This study represents a major step forward in reward-related food intake behavior, as it shows that brain dopamine reward circuits can be controlled by calorie load, independent of food palatability, hedonic value, or functional taste transduction.

In the first set of behavioral experiments, the authors set out to show that KO mice were acutely insensitive to the orosensory or "sweet" rewarding properties of sucrose. As expected, water-deprived WT mice were more strongly attracted to sucrose solutions compared to water (as measured by number of licks for the sucrose solution/number of licks for water), whereas KO mice exhibited no preference for sucrose over water. Additional preference tests confirmed that the KO mice were insensitive to the orosensory "sweet" rewarding properties of sucrose. These sweet-insensitive mice

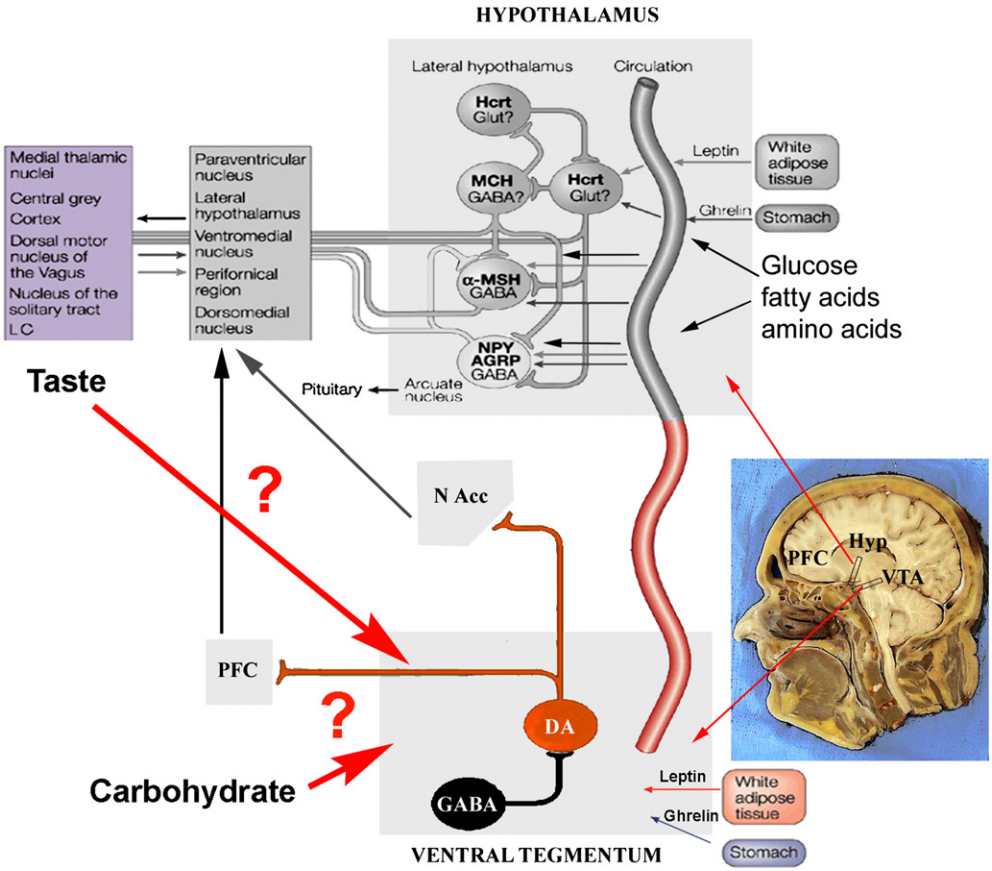


**Figure 1. Schematic Illustration Depicting Some of the Major Findings of de Araujo and Oliveira-Maia et al**

Taste alone (noncaloric sweetener), taste with caloric value (sucrose solution), or caloric value only (in the absence of taste receptors) can all equally activate the midbrain reward circuitry. To date, major emphasis has been placed on the hypothalamus and its various circuits, including orexin (ORX/Hcrt)- and melanin concentrating hormone (MCH)-producing neurons in the lateral hypothalamus as well as neuropeptide Y (NPY)/agouti-related protein (AgRP)- and α-melanocyte-stimulating hormone (α-MSH)-producing neurons in the arcuate nucleus, as a homeostatic center for feeding, responding to various peripheral metabolic hormones and fuels. The mesencephalic dopamine system is also targeted by peripheral hormones that affect and alter behavioral (and potentially endocrine) components of energy homeostasis. The results by de Araujo and Oliveira-Maia et al. highlight, however, that without classical hedonic signaling associated with reward-seeking behavior, the midbrain dopamine system can be entrained by caloric value arising from the periphery. While the precise signaling modality that mediates caloric value on dopamine neuronal activity remains to be deciphered, overall it is reasonable to suggest that distinction between hedonic and homeostatic regulation of feeding is redundant. DA, dopamine; GABA, γ-aminobutyric acid; Glut, glutamate.

then allowed the authors to test the critical question of whether animals can detect the caloric value of ingested substances.

WT and KO mice were exposed to a "conditioning protocol" that allowed KO mice to associate sipper side with postingestive caloric load (i.e., water versus the highly caloric sucrose solution). Strikingly, their results indicated that both WT and KO mice consumed more sucrose. As their prior experiments had clearly shown that the KO mice were unable to detect the sweet taste of the caloric sucrose drink, these results argued that KO mice were making a choice preference purely based on the detection of the postingestive reinforcing properties of the sucrose solution (increased caloric load). As a critical control, the authors then repeated the experiments with sucralose, a noncaloric but highly palatable sucrose-derived sweetener. Interestingly, the WT mice consumed more sucralose than water during the conditioning period, but the KO mice did not. Thus, the WT mice were reinforced by sweet taste, regardless of whether the drink was the highly caloric sucrose or the noncaloric sucralose. Conversely, the KO mice showed a specific preference for caloric content and were not influenced by sweet taste, in the absence of any caloric advantage. Importantly, the authors also excluded the possibility that differences in plasma glucose underlay the observed effect.

While the prior results clearly indicated that metabolic value can be sensed, it remained to be determined whether the brain's reward regions, known to be activated in response to sweet taste, were also involved in caloric monitoring. To assess this question, de Araujo et al. went on to examine dopamine levels in the NAc of the WT and KO mice using in vivo microdialysis. In WT mice, both sucralose and sucrose significantly increased NAc dopamine above baseline, confirming that dopamine release in the NAc reinforces the hedonic value "taste" of sugars, even if no calories are present. On the other hand, KO mice exhibited no increase in NAc dopamine upon ingestion of sucralose, although they showed

significant increases in NAc dopamine after sucrose consumption, indicating that caloric load activates the brain dopamine reward system independent of "sweet" taste sensation.

It is interesting to note that naive unconditioned KO mice showed increased NAc dopamine after 30 min exposure to sucrose. However, during the brief access tests, unconditioned KO mice did not exhibit increased sucrose consumption or preference, indicating that NAc dopamine release to sucrose is immediate and a prerequisite to establish and manifest the rewarded behavior. The authors suggest that "the putative role of dopamine transmission in overeating and obesity might not be restricted to oral hedonics; rather, dopamine signaling could influence behavior also by coding for the food's nutritive value." While the results herein undoubtedly show that caloric load affects the brain dopamine reward system independent of taste in KO mice, WT mice neither showed greater licking preference nor increased dopamine release for sucrose, compared to sucralose, suggesting that caloric load does not add more reinforcing power beyond taste alone. Future studies are needed to clarify whether this caloric load component can affect obesity, independent of food palatability.

To further illustrate the importance of the brain dopamine reward system in mediating this response to calorie load, the authors performed electrophysiological measurements of the NAc and orbitofrontal cortex (OFC) to demonstrate effective modulation of the brain reward circuitry in response to dopamine release in the NAc. Their results suggest that the OFC, unlike the NAc, is not engaged during calorie intake. However, these results should be interpreted with caution, as the authors were forced to analyze electrophysiological properties in response to water trials uniformly dispersed between sucralose or sucrose sessions to avoid a confounding variable in the OFC, where neurons are known to respond to stimulus attributes such as viscosity.

Despite the clear implications of these data, one important caveat must be mentioned; all experiments involved food and water deprivation, except for an initial two-bottle preference test. Food restriction itself may be intrinsically rewarding (Fulton et al., 2006), as it dramatic increases circulating ghrelin released from the stomach, and ghrelin is known to activate the mesolimbic dopamine system and increase dopamine release in the NAc (Abizaid et al., 2006). Thus, the observed activation of the dopamine reward system by calorie load in this paper may be potentiated due to the food-restricted state.

Like most important and interesting papers, the results presented here raise many more intriguing future questions. Obvious mechanistic questions need to be addressed, such as how is caloric load sensed by the dopamine reward system? Is nutritional information on caloric load conveyed via vagal afferents through the brainstem to regulate VTA dopamine neuronal function, and does caloric load affect satiety signals from the digestive tract? Additionally, do certain types of sugars affect the reward system differentially (i.e., fructose), and does the same phenomenon occur when calories come from different types of food (for example, do calories from lipids produce a stronger effect)? Finally, can caloric load also affect other cognitive functions, such as learning and memory?

All of these questions are extremely important to understanding the pathogenesis and sociology of human obesity. For example, high-fructose corn syrup is a ubiquitous sweetener in American society, and evidence suggests that fructose is not as effective as sucrose in terminating a meal. It may be that fructose produces stronger activation of the reward system and that removing high-fructose corn syrup as a sweetener will curb some desire for these products. Regardless, the present study alone will further galvanize the scientific community to understand how higher cognitive centers in the brain control food intake and body weight regulation. It also effectively adds to the growing body of information showing that metabolic cues are not solely the domain of the hypothalamus and that much more crosstalk occurs between metabolic cues and higher brain centers than previously believed (Figure 1). Thus, categorizing food intake as hedonic versus homeostatic may not only be redundant, but also misleading.

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