Taste and the regulation of food intake: it's not just about flavor¹

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Body weight is physiologically regulated by a homeostatic system that tends to maintain remarkably stable levels of adiposity over long time periods, especially resisting volitional weight loss (1). To achieve this, the energy homeostasis system modulates energy expenditure and food intake. The latter consists cumulatively of the number and size of individual meals. Meal frequency is governed in vertebrates primarily by external environmental factors, such as the times of day when food is safely available in the wild or the habitual schedule of meal times in civil society. Hence, the main biological determinant of food intake in most higher-order animals is meal size, which is controlled by satiation: the feeling of fullness that influences when we decide to stop eating a meal (2).

A simplified model of satiation is that it results primarily from 2 categories of signals transmitted from the gastrointestinal tract to the brain (3). The first relates to gastric distension, detected by mechanoreceptors sensitive to tension, stretch, and volume—signals relayed to the hindbrain via vagal and spinal nerves. The second arises from intestinal nutrient sensing and metabolism, which trigger release from enteroendocrine cells of an array of gut peptides—cholecystokinin (CCK),² glucagon-like peptide 1 (GLP-1), peptide YY (PYY), etc.—that signal satiation to the brain via vagal and humoral pathways. Traditionally, satiation is thought to result from the sum of gastric mechanoreception and intestinal chemoreception, both activated by ingested food. New research by van Avesaat et al. (4) in this issue of the Journal provides data that support an extension of this model wherein intestinal satiation results not only from signals related to the caloric content of ingested nutrients but also from noncaloric properties of tastant molecules in food.

Humans detect 5 basic tastes: sweet, bitter, umami (a savory, meaty taste), sour, and salty (5). On the surface of lingual taste-bud cells, the first 3 of these are sensed by discrete G-protein-coupled receptors, whereas the latter 2 activate ion channels. Relatively recent studies showed that intestinal enteroendocrine cells also express taste receptors on their luminal membranes, as well as postreceptor signal-transduction pathways previously thought unique to taste buds. Whereas activation of these receptors on the tongue engages neural pathways that communicate taste to the brain, activation in intestinal cells, at least in vitro, prompts secretion of satiation peptides such as CCK, GLP-1, and PYY.

In their new work, van Avesaat et al. examined the effects of intraduodenally infused tastants on subjective reports of hunger and satiety (assessed by using visual analog scales), as well as on

food intake in a subsequent ad libitum meal (4). On 5 separate blinded occasions, lean, weight-stable subjects received bitter, sweet, or umami tastants; all 3 combined; or water. The infusions contained trivial calories or none at all. The combination of all 3 tastants decreased subjective hunger and the desire to eat while increasing satiety. Interestingly, umami alone yielded virtually identical results, whereas neither sweet nor bitter exerted any effects, suggesting that the combination-infusion results arose entirely from the umami component. The 3-tastant combination also decreased ad libitum food intake by 13%, whereas no single tastant affected intake. No nausea, stomach pain, or bloating was reported with any infusion.

Surprisingly, none of these in vivo infusions affected CCK, GLP-1, or PYY plasma concentrations—even though some elicited satiety and decreased food intake—whereas secretion of all of these satiation peptides is stimulated by noncaloric tastants from enteroendocrine cells in vitro and ex vivo, including with the exact tastants used in this study. Similar in vitro compared with in vivo discrepancies have been reported with artificial sweeteners (5). Conceivably, satiation peptide secretion was stimulated by tastants in this experiment but not sufficiently to affect peptide concentrations in the systemic circulation. This could nevertheless elicit satiation through vagal neurocrine mechanisms, which are likely more important than humoral pathways for the appetite-suppressing effects of these peptides. Alternatively, or in addition, intestinal tastant-related satiation might be mediated through unidentified neural, paracrine, and/or humoral pathways engaged by tastants themselves.

A relevant question is whether tastant-mediated satiation during individual meals interacts with the determinants of long-term body-weight regulation and/or is influenced by recent weight change or environmental factors promoting weight gain. Long-acting adiposity hormones that regulate body weight, such as leptin and insulin, ultimately influence eating behavior at individual meals. Accordingly, leptin and insulin acting in the brain enhance central sensitivity to short-acting gastrointestinal satiation signals, such as

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¹Supported by NIH RO1 grants DK084324, DK089528, and DK103842 (to DEC).

²Abbreviations used: CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY.

First published online September 9, 2015; doi: 10.3945/ajcn.115.120667.

CCK (1). Analogous synergism between short- and long-acting catabolic signals occurs in the gut. For example, the activation of leptin or insulin receptors on enteroendocrine cells augments GLP-1 secretion, and leptin works synergistically with CCK to activate vagal afferents that signal gastrointestinal satiation to the brain (3). Further studies are needed to determine whether tastant-related satiation is modulated similarly by leptin and/or insulin. Leptin acting on the tongue decreases sweet taste responsiveness (6), but it is not known whether such crosstalk occurs for intestinal taste receptivity. Likewise, future investigation should determine whether tastant-mediated satiation is impaired by high-fat feeding or in obese individuals, as are many components of energy homeostasis.

It would also be interesting to clarify whether tastants directly influence glucose homeostasis in addition to satiation. Nutrient-stimulated incretin hormones such as GLP-1 enhance postprandial insulin secretion. Although GLP-1 secretion was originally thought to result from intracellular nutrient metabolism within intestinal L-cells, noncaloric activation of cell-surface tastant receptors on these cells in vitro also stimulates GLP-1 secretion, and one previous study showed that the addition of umami tastant to a meal enhanced postprandial GLP-1 secretion, lowering glucose excursions (7). In a 2008 study, an intestine-brain-liver neurocircuit was found to increase liver insulin sensitivity and reduce hepatic glucose output in response to intestinal nutrients (8). Whether noncaloric tastants can activate this circuit to improve glucose homeostasis remains to be determined.

The findings by van Avesaat et al. that umami was the only tastant to decrease hunger and increase satiety may shed new light on mechanisms of commonly used diets. Most popular diets emphasize carbohydrate restriction, fat restriction, or protein enrichment; and none advocate limiting protein intake for weight loss. Some older research suggests that proteins might be more satiating per calorie than other macronutrients, and proteins suppress the appetite-stimulating gastrointestinal hormone ghrelin better than do equicaloric fats or carbohydrates (9). By enhancing satiation, perhaps umami tastants in proteins reduce appetite disproportionately to the caloric content of protein-rich foods.

Could minimally caloric dietary supplements containing umami tastants help promote weight loss? This seems counterintuitive if such agents were mixed into food, because the prototypic umami tastant—the amino acid salt monosodium glutamate (which was

used by van Avesaat et al.)—enhances flavor and might therefore increase intake. However, the tastant could be delivered in tablet form, bypassing the tongue to engage only intestinal umami receptors. Analogously, the intragastric administration of a noncaloric bitter agonist was shown to decrease hunger scores (10).

Regardless of whether the findings of van Avesaat et al. identify a viable target for novel weight-loss strategies, they nicely expand our understanding of the nuanced manner in which the gastrointestinal tract, the largest endocrine organ in the body, exquisitely regulates food intake and energy homeostasis.

The author is a principal investigator for the COSMID trial, which is funded by Johnson & Johnson, as well as for the ARMMS-T2D trial, which is funded by Ethicon Endo-Surgery and Johnson & Johnson.

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