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Commentary
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Taste Bud Leptin: Sweet Dampened at Initiation Site

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Abstract

The intriguing observation that leptin decreases sweet-evoked peripheral gustatory responses has aroused much interest (Kawai K, Sugimoto K, Nakashima K, Miura H, Ninomiya Y. 2000. Leptin as a modulator of sweet taste sensitivities in mice. Proc Natl Acad Sci U S A. 97(20):11044–11049.) due to its implied importance in controlling appetite. The effects of this anorexic hormone, however, appear more conditional than originally believed. In this issue of *Chemical Senses*, a careful study by Glendinning and colleagues, find no effects of leptin on sweet-evoked chorda tympani responses, whereas an equally careful study by Meredith and colleagues, find decreased release of ATP and increased release of 5-HT from taste buds in response to sweet stimuli.

Key words: chorda tympani, leptin, taste bud

Although research findings in taste and olfaction contribute to key questions in basic science, it is results directly relevant to human health that more frequently arouse heightened interest. One of the most exciting observations in recent years was the demonstration that intraperitoneal (IP) injection of the anorexigenic hormone leptin, a key regulator of body weight, reduced both peripheral chorda tympani (CT) and glossopharyngeal (GL) responses elicited by oral stimulation with sweeteners (Kawai et al. 2000). This landmark study also revealed that the leptin receptor (LepRbs) was expressed in a subset of taste bud cells and that bath application of leptin hyperpolarized some cells in the bud. Many questions remained but the effects themselves were robust and seemingly straightforward. These findings suggested that part of leptin's action in regulating food intake and body weight is through direct effects on the initial stages of processing in the taste system. The implied interpretation was that leptin, which is produced by adipocytes, and which is therefore more plentiful in well-nourished versus poorly nourished animals and in the sated versus the deprived state, decreases the magnitude of the afferent "sweet" signal, which leads to suppression of intake of these caloric substances (Figure 1).

In this issue of *Chemical Senses*, Steven Roper's group shows that leptin decreases sweet stimulus-evoked release of ATP from taste bud cells but increases 5-HT release. Since ATP is known to have excitatory effects on primary afferent taste fibers, and 5-HT is thought to inhibit ATP release, these findings are in line with the observations of Ninomiya's group. The observations make a coherent, satisfying story. However, a caveat is in order given the recent findings of Scott Herness' group that 5-HT has facilitatory effects on CT responses (Jaber et al. 2014). Moreover, a few years ago, the laboratory of Robert Contreras (Lu et al. 2012) demonstrated that leptin slightly increased, rather than decreased, CT responses to sweeteners. To further complicate the tale, in this issue of *Chemical Senses*, John Glendinning and colleagues report that leptin has no effect on the magnitude of CT responses to sweet stimuli.

What could be the basis for these disparate observations? And, how does the variability impact interpretation of taste-bud leptin's functional significance? One possibility, originally discussed by Contreras and colleagues, is stimulus temperature. Indeed, experiments showing suppression of peripheral sweet-evoked responses used room temperature stimuli whereas those showing slight or no effect used stimuli near normal body temperature. How stimulus temperature could contribute to these effects is not entirely obvious. Larger responses based on temperature-sensitive elements such as TRPM5 in the taste transduction cascade could conceivably obscure suppression (Talavera et al. 2005) but this seems unlikely given the wide range of

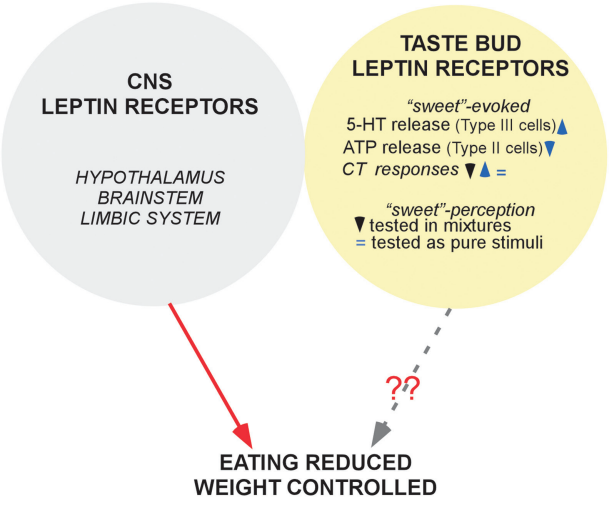

Figure 1. Left: In several brain regions, leptin binding to the long-form of the LepRbs has well-documented anorexigenic effects. Right: The LepRbs is also expressed in taste buds, primarily in Type II cells. Leptin effects on taste bud responses to sweet stimuli are consistent with suppression. Reported peripheral nerve effects, however, are variable, as are behavioral consequences. Symbols indicate more, less or equal effects, blue color new findings.

stimulus concentrations and response magnitudes already scrutinized. To be definitive, the stimulus temperature hypothesis needs direct testing; if proven that increased temperature obscures leptin's effects, its ultimate functional impact would be compromised.

Moreover findings of Glendinning's group, also in the current issue, appear to contradict those of Ninomiya's group regarding behavioral effects of leptin. Based on licking a wide-range of sweetener + quinine (3 mM) mixtures for 10-s, Shigemura et al. (2004) concluded that that behavioral responsiveness to sweet-tasting stimuli was reduced by increases in circulating leptin. However, based on similar 5-s tests of pure sucrose or saccharin, Glendinning and colleagues fail to show an effect of IP leptin. Given that IP injections of leptin have access to central as well as peripheral LepRbs and perception of the intensity of sweetness in a sweet-bitter mixture also involves bitter-suppressive effects, potential explanations for differences in experimental outcomes are many. Regardless, the original simple interpretation that changes in leptin levels decrease peripheral sweet signaling to a degree demonstrable behaviorally is conditional.

In any case, it is clear that behaviorally significant peripheral effects of leptin are subject to additional, probably unidentified influences. Indeed, Niki et al. (2013) recently reported that leptin effects on peripheral taste responses were obscured when baseline circulating levels of leptin exceeded 10 ng/mL. This is not the basis for the lack of effect seen by Glendinning and colleagues, who observed much lower baseline levels of leptin. Their Figure 2 also indicates that ob/ob mice, which do not produce leptin, do not show larger CT control sugar responses. Whereas, Ninomiya's group previously showed that peripheral responses to sweet stimuli were larger in obese db/db mice (Ninomiya et al. 1998; Sako et al. 1996), which lack a functional LepRbs. The situation with obesity is complicated because obese individuals may have higher levels of leptin but yet be leptin-resistant. This is an important reminder of the many sources of regulation with potential to affect peripheral taste responses and the complex regulatory pathways that underlie homeostasis.

Points of agreement among reports on the peripheral effects of leptin in the gustatory system are worth noting. A consistent finding is that the LepRbs is expressed on taste bud cells, as shown by immunohistochemistry (Cai et al. 2014; Kawai et al. 2000), polymerase chain reaction (Cai et al. 2014; Kawai et al. 2000; Shigemura et al. 2003), in situ hybridization (Shigemura et al. 2003) or by the transgenic expression of fluorescent markers in the Glendinning group's current study. Interestingly, Glendinning and colleagues' findings reveal that expression of the long form LebRbs is restricted largely to Type II cells, something that had been suspected previously but not conclusively demonstrated. Thus, the interesting observation by the Roper group that sucrose-evoked 5-HT release by Type III cells is augmented by leptin may not directly involve leptin binding to a receptor on Type III cells. Glendinning and colleagues also show that, in contrast to most LepRbs in the brain, leptin does not induce phosphorylation of the transcription factor, STAT3, suggesting that one of the several alternate signaling pathways (Allison and Myers 2014) is probably engaged by leptin in taste bud cells (Figure 1).

Agreement that demonstrated peripheral gustatory effects of leptin are selective for sweet-tasting stimuli is also significant. No influences on salty, sour, and bitter responses were detected. Umami stimuli have not been routinely tested, although alterations in monosodium glutamate responses were not seen in one study demonstrating sucrose-response increases. However, specific susceptibilities of sweet-elicited CNS responses to manipulations related to body weight regulation were seen previously. Changes in blood glucose and insulin suppressed responses to sugars in the first-order taste relay, the nucleus of the solitary tract (Giza and Scott 1983; Giza and Scott 1987; Giza et al. 1992), as did intraduodenal lipid infusions in the parabrachial nucleus (Hajnal et al. 1999). A high-fat diet that produced obesity selectively increased sweet-elicited responses in the parabrachial nucleus in OLETF rats with spontaneous knockout of CCK-1 receptors (Hajnal et al. 2010).

The new findings in this issue of *Chemical Senses* leave the field with an important challenge. Collectively, the existing data make a compelling case that leptin is a significant regulator in the peripheral taste system. However, its function appears to be under more complex control than initially envisioned by Ninomiya and his colleagues. Leptin's biological function in the taste bud may not simply parallel its central role in suppressing food intake, but include other modulatory or even developmental or cell biological roles. Indeed, a large number of peptides, transmitters and their receptors have been identified in the taste bud (reviewed in Dotson et al. 2013; Herness and Zhao 2009; Roper 2013) but understanding the functional logic of taste bud circuitry, including the role of leptin, remains incomplete.

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