# Modulation of Taste Sensitivity by GLP-1 Signaling in Taste Buds

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**Modulation of sensory function can help animals adjust to a changing external and internal environment. Even so, mechanisms for modulating taste sensitivity are poorly understood. Using immunohistochemical, biochemical, and behavioral approaches, we found that the peptide hormone glucagon-like peptide-1 (GLP-1) and its receptor (GLP-1R) are expressed in mammalian taste buds. Furthermore, we found that GLP-1 signaling plays an important role in the modulation of taste sensitivity: GLP-1R knockout mice exhibit a dramatic reduction in sweet taste sensitivity as well as an enhanced sensitivity to umami-tasting stimuli. Together, these findings suggest a novel paracrine mechanism for the hormonal modulation of taste function in mammals.**

*Key words*: **glucagon-like peptide-1; hormone; sweet; umami; glutamate**

The sense of taste strongly affects ingestive behavior and nutrient intake by providing important information about the quality of food.[1] Stimuli that give rise to the basic perceptual taste qualities of sweet, bitter, salty, sour, or umami (the savory taste of L-glutamate) stimulate discrete subsets of taste receptor cells found within taste buds of the tongue and soft palate.[1] Each taste cell type (i.e., sweet-sensitive, bitter-sensitive, etc.) appears to express a distinct receptor or receptor family that mediates the transduction of a select group of taste stimuli.[1] In the case of sweet, bitter, and umami sensitive cells, these taste receptors initiate a G protein-coupled signaling cascade that leads to cellular activation and generation of a neural signal to the brain.[1] Interestingly, components of the G protein-coupled taste transduction cascade, including T1R (sweet and umami) and T2R (bitter) taste receptors and the G protein subunit α-gustducin, are also expressed in cells of the lower gastrointestinal tract, where they are involved in the nutrient-dependent regulation of metabolism (e.g., Refs. 2–11). For example, glucose-dependent secretion of incretin hormones (e.g., GLP-1) from enteroendocrine L cells is mediated by the T1R3 taste receptor subunit and by α-gustducin.[8] The molecular similarities between enteroendocrine L cells of the gut and taste receptor cells of the oral cavity suggested that GLP-1 signaling could play a role in gustatory function. We combined immunohistochemical, biochemical, and behavioral approaches to investigate this possibility.[12]

We found GLP-1 expressed in two subsets of taste cells in the mouse circumvallate papillae (CV)[12]: nearly 60% are immunopositive for the G protein α-gustducin (though only 34% of α-gustducin-positive taste cells express

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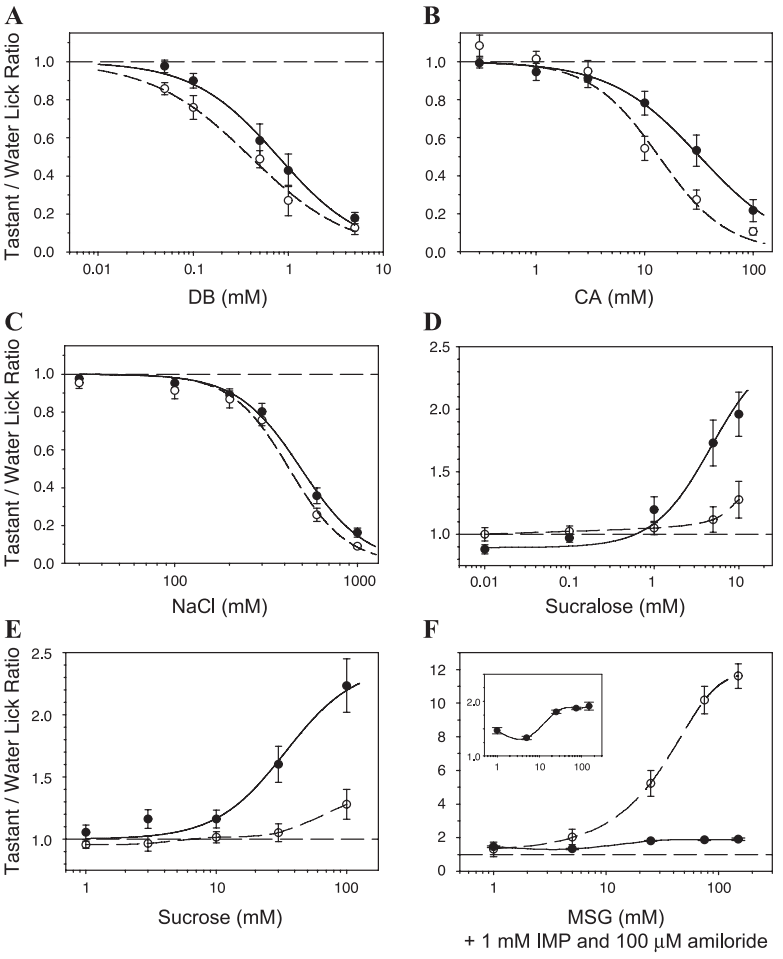


**Figure 1.** Altered taste responses of GLP-1R$^{-/-}$ mice in brief access taste tests. Taste responses, expressed as taste/water lick ratios and as a function of stimulus concentration, of GLP-1R$^{-/-}$ (dashed lines, open circles) and wild-type (solid lines, filled circles) to (**A**) denatonium benzoate (DB), (**B**) citric acid (CA), (**C**) NaCl, (**D**) sucralose, and (**E**) sucrose, and to (**F**) monosodium glutamate (MSG) in the presence of 100 μM amiloride and 1 mM IMP (inset: magnification of wild-type data). Points are expressed as mean ± SEM. Curves were fit using a 3 or 4 parameter logistic function of the form: $f(x) = [(a - d)/(1 + 10^{(x-c)b})] + d$, where $x = \log_{10}$ concentration, $c = \log_{10}$ concentration at the inflection point, and $b =$ slope. For sucrose (+/+), sucralose (+/+) and MSG (−/−), $a =$ the asymptotic tastant/water lick ratio and $d =$ minimum asymptote of the tastant/water lick ratio. For NaCl, DB, and CA, $a = 1.0$ and $d = 0$. The −/− curves in the sucrose and sucralose graphs and the wild-type curve in the MSG graph could not be fitted to a function. (Panels A–E were modified from Ref. 12, with permission from Wiley-Blackwell.)

GLP-1), while the remainder are serotonergic. Together, GLP-1-positive taste cells comprise ~10% of taste cells in the mouse CV. Using triple-label immunohistochemistry, we showed that all GLP-1-positive/α-gustducin-positive cells express T1R3, a subunit of both the sweet and umami taste receptors. The observed coexpression of GLP-1 and T1R3 suggested a role of GLP-1 signaling in sweet and/or umami taste function.

Further immunohistochemical and biochemical analyses indicated that GLP-1 is

produced in taste cells and suggests it acts locally in taste buds.[12] GLP-1-positive taste cells express prohormone convertase 1/3, the enzyme necessary for the formation of GLP-1 by cleavage from proglucagon, and secrete a bioactive form of GLP-1. The GLP-1 receptor (GLP-1R) is expressed on intragemmal nerve fibers found in close proximity to GLP-1-containing taste cells. Taste buds do not appear to express dipeptidyl peptidase 4, the enzyme that acts in other tissues to degrade GLP-1.

The production of GLP-1 in taste cells and the presence of the GLP-1R on adjacent taste nerve fibers strongly suggest that GLP-1 signaling can affect taste function. To test this hypothesis, we examined behavioral responses of GLP-$1R^{-/-}$ mice to prototypical taste stimuli using a brief-access procedure that minimizes postingestive effects.[13] We reported[12] that there were no significant differences between the responses of GLP-$1R^{-/-}$ and wild-type mice for bitter (denatonium benzoate), salty (NaCl), or sour (citric acid)-tasting stimuli, although GLP-$1R^{-/-}$ mice were somewhat more sensitive to citric acid at the highest concentrations (Fig. 1A–C). In contrast, GLP-$1R^{-/-}$ mice displayed significantly reduced sensitivity to two sweeteners, sucralose and sucrose (Fig. 1D and E). These data indicate that GLP-1 signaling normally acts to enhance or maintain sweet taste sensitivity.

However, it remained unclear whether the actions of GLP-1 signaling are restricted to sweet taste, or if this hormone may also impact sensitivity to other preferred taste stimuli. To begin to address this issue, we recently examined the effects of GLP-1 signaling on taste sensitivity to an umami stimulus. Surprisingly, GLP-$1R^{-/-}$ mice were much more sensitive to the umami stimulus monosodium glutamate (MSG; presented with the umami taste enhancer inosine-5′-monophosphate (IMP) and the salt taste blocker amiloride) than were wild-type controls (Fig. 1F). Thus, GLP-1 signaling impacts sweet and umami taste responses in distinct ways.

Our studies support a model where chemosensing mechanisms are conserved throughout the alimentary canal, and suggest a relationship between the modulation of peripheral sensory function and the metabolic response to food intake. We found that the gut hormone GLP-1 and its receptor are present in taste buds and that GLP-1 signaling plays an important role in the modulation of sweet and umami taste. GLP-1 is also involved in a wide range of other physiological functions, including the regulation of glucose homeostasis and food intake, the control of body weight, neuroprotection and neuronal regeneration in the central nervous system, learning and memory, cardiac function, and bone resorption.[14] It will be important to clearly differentiate the local actions of GLP-1 signaling in taste buds from this hormone's other effects in order to fully understand how hormonal modulation of taste impacts dietary intake.

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### Conflicts of Interest

The authors declare no conflicts of interest.

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