*Obesity*

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# Can Reprogramming Taste Modulate Excess Food Intake?

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## 1 | Introduction

Taste may play a clinically relevant role in the development of obesity by influencing food preferences, appetite regulation, and energy intake (Figure 1). Alterations in suprathreshold perceived taste intensity and hedonic responses at food-relevant concentrations may lead to larger portion sizes and a preference for energy-dense, sweet foods to achieve sensory satisfaction. Additionally, taste perception interacts with hormonal and neural pathways involved in reward and satiety. Although data from preclinical models suggest that higher body weight is associated with decreased taste papilla density, in humans, the evidence regarding associations between body weight and fungiform papilla density is heterogeneous, without a clear consensus that reduced papilla density is linked to heightened reward-driven eating [1]. Importantly, a direct connection between obesity and taste perception in humans has not been formally proven.

Taste perception is initiated when nonvolatile chemicals in food are placed in the mouth and activate taste receptor cells (TRCs) in taste buds that recognize five primary taste sensory qualities: sweet, umami, bitter, salty, and sour [1]. TRCs are morphologically classified into types I, II, and III, which can be subcategorized based on differences in TRC function, molecular markers, or both. Taste information from TRCs is integrated in the brain with gustatory, olfactory, and chemesthesis-related (trigeminal) signals to create the perception of flavor [1]. Lingual taste buds are highly dynamic and plastic structures because TRCs exhibit extensive transcriptional regulation associated with rapid and continuous turnover. This intrinsic cellular renewal renders taste buds particularly responsive to environmental influences, including dietary composition. Understanding how environmental cues modulate transcriptional states within taste buds offers new insights into the mechanisms linking diet, sensory processing, overeating, and metabolic outcomes. For example, sweet preference is innate and develops before birth, and consuming sweets triggers satisfaction through central reward pathways [1].

Importantly, taste receptors are neither exclusively expressed in oral TRCs nor uniquely tied to conscious taste perception. Many chemosensory receptors are also expressed in extraoral tissues, where accumulating evidence suggests roles in metabolism and internal nutrient sensing [1]. Therefore, epigenetic, transcriptional, and post-transcriptional changes in chemosensory receptors may influence food intake and metabolic outcomes through pathways that are not mediated by altered gustatory perception per se.

## 2 | The Molecular Architecture of Taste Buds

Taste buds exhibit a highly organized molecular architecture composed of multiple, functionally distinct cell types that together enable the detection and transduction of gustatory stimuli. Each cell type is defined by unique transcriptional signatures, signaling pathways, neurotransmitter systems, and paracrine signaling integration. Throughout life, the differentiated TRCs are continuously replaced by progenitor-derived precursors within 7–14 days. The renewal requires coordinated gene regulatory networks for progenitor proliferation, lineage specification, and cell fate. The continuous replacement of taste cells provides opportunities for nutrient signals to influence transcriptional programs that may result in altered food intake and changes in food preferences [2].

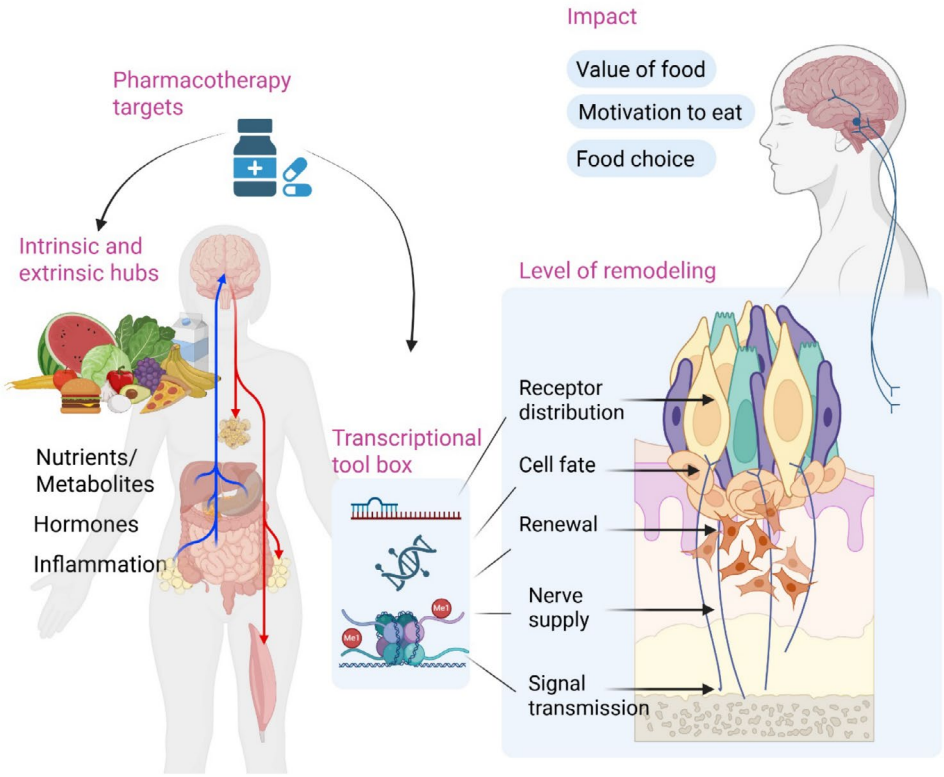


**FIGURE 1** | Contribution of taste-evoked signaling to overeating. Obesity can be related to disruptions in the neural pathways that encourage reward-related eating and suppress homeostatic feedback that drives hunger. People living with obesity may have a different taste perception, and higher body weight is associated with decreased taste papilla density and higher sweetness thresholds. Therefore, taste bud density and function may contribute to the development and perpetuation of obesity. Lingual taste buds can be modulated at multiple levels, including the regulation of taste receptor and signaling molecule expression in adult taste cells, the control of basal cell fate decisions that determine adult taste cell types, and the overall turnover and replacement of taste buds. Additionally, newly generated taste buds must reestablish connections with adjacent nerves, a process essential for effective signal transmission. These events require precise coordination of gene regulatory networks governed by (epi)genetic mechanisms and shaped by both intrinsic and extrinsic stimuli. Pharmacological strategies could target these regulatory factors to ultimately influence taste perception and its downstream effects on food valuation, neural eating circuits, and food preferences. (Figure was created with BioRender.)

## 3 | Different Layers of Transcriptional Remodeling

### 3.1 | Environmental, Inflammatory, and Metabolic Hubs

Transcriptional remodeling of taste receptors in the tongue may provide a mechanistic link between food exposure, altered taste perception, and food intake. For example, a study aiming to assess associations between diet-mediated changes to fatty acid taste (FAT) receptors and FAT perception in humans found that exposure to high versus low fat diets alters transcription of the free fatty acid receptor 2 gene, which was accompanied by altered taste sensitivity, food preferences, and intake [3]. However, evidence for associations between TRC expression, taste perception, and food intake in humans remains limited and to some extent controversial [1].

In rodent models, the number of taste buds has been associated with diet-induced or systemic inflammation, leading to reduced taste bud renewal and impaired differentiation of progenitor cells under high fat feeding conditions [4]. Proinflammatory cytokines and oxidative stress interfere with key developmental pathways that govern taste cell lineage specification and survival, resulting in altered cellular composition and diminished receptor expression [5].

Another level of regulation arises from hormonal responsive networks harbored by taste buds. Through these mechanisms, certain hormones act as a metabolic cue that tunes taste bud function according to energy status. Hormone receptors such as the leptin receptor are expressed in taste buds. For example, activation of leptin signaling suppresses sweet taste sensitivity by reducing the excitability of sweet-responsive taste cells [6]. Under physiological conditions, this inhibitory effect can limit excessive sugar intake. However, in obesity and leptin-resistant states, leptin signaling in taste buds is impaired, leading to heightened sweet taste responsiveness and increased preference for sugar-rich foods. Likewise, glucagon-like peptide-1 (GLP-1) receptors are expressed on gustatory afferent nerve fibers and neighboring taste cells. Local GLP-1 signaling enhances taste-evoked neurotransmission, increasing sensitivity to nutrient-related stimuli such as sugars and amino acids. This paracrine signaling pathway allows taste buds to amplify signals associated with caloric content before ingestion [7]. Nutrients or metabolites affect receptor expression, proliferation, and cell fate decisions. However, the mechanisms regulating transcriptional shifts in taste bud signatures are not well understood. Both

epigenetic and post-transcriptional control mechanisms may be important regulatory elements.

### 3.2 | Epigenetic and Post-Transcriptional Hubs

Epigenetic mechanisms such as DNA methylation, histone modifications, and microRNAs regulate chromatin accessibility and transcriptional responsiveness to dietary and hormonal cues. While diet-induced methylation changes have been reported for taste receptor genes in blood and other tissues, evidence from taste epithelium remains scarce. One notable example comes from grass carp, where a shift from carnivory to herbivory is associated with increased DNA methylation upstream of the umami receptor T1R1 and reduced receptor expression [8]. Beyond DNA methylation, chromatin modifiers regulate taste bud maintenance while inflammatory cues induce cell-type-specific chromatin accessibility changes at bitter taste receptor loci in mice [9, 10]. Collectively, these findings indicate that epigenetic regulation modulates progenitor differentiation, receptor expression, and taste bud plasticity, linking nutrient sensing to long-term changes in taste perception and food intake behavior.

## 4 | Therapeutic Potential

Different taste perception in people living with obesity compared to people with normal weight suggests that modulating taste perception represents a potential target in the treatment or prevention of obesity. Glucose, amino acids, and fatty acids can act as ligands for taste receptors, providing feedback that reshapes receptor gene transcription and metabolic signaling, potentially restoring taste sensitivity in obesity. Other dietary components such as secondary plant products, for instance, or microRNAs offer an additional layer of control by modifying histone marks, chromatin accessibility, and mRNA stability. Finally, nutrient-responsive hormones including GLP-1—the backbone of several obesity pharmacotherapies—link systemic metabolic state to taste receptor transcription. Indeed, endogenous secretion of GLP-1 is regulated by the sweet-taste receptor TAS1R1, and GLP-1 receptor agonist treatment may dampen the preference for sweet and umami tastes by modulating oral GLP-1 receptor signaling [1, 7]. To what extent obesity pharmacotherapies exert effects on the taste perception-brain axis needs to be better studied. Ultimately, targeting taste-related obesity mechanisms represents a promising research field.

## 5 | Conclusion

The regulation of taste perception and transmission of taste signals to gustatory neuronal networks provides insights into human eating behavior and food preferences and may link food consumption to obesity and metabolic diseases. A better understanding of how the food we consume activates hedonic and homeostatic pathways in neurocircuits regulating appetite and satiety may help to update guidelines for nutrition therapy, define personalized diets for the treatment of obesity, and even facilitate the development of pharmacotherapies targeting the taste (patho-)physiology in people with obesity. In addition, future research should focus on defining the contribution of incretin-based obesity pharmacotherapies to changing taste perception and food preferences at the level of molecular taste bud modulation.

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**Conflicts of Interest**

M.B. received honoraria as a consultant and speaker from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, MSD, Novo Nordisk, Novartis, and Sanofi. K.R.-Z. declares no conflicts of interest.

**Data Availability Statement**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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