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# Mechanism of fat taste perception: Association with diet and obesity

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ABSTRACT

Energy homeostasis plays a significant role in food consumption and body weight regulation with fat intake being an area of particular interest due to its palatability and high energy density. Increasing evidence from humans and animal studies indicate the existence of a taste modality responsive to fat via its breakdown product fatty acids. These studies implicate multiple candidate receptors and ion channels for fatty acid taste detection, indicating a complex peripheral physiology that is currently not well understood. Additionally, a limited number of studies suggest a reduced ability to detect fatty acids is associated with obesity and a diet high in fat reduces an individual's ability to detect fatty acids. To support this, genetic variants within candidate fatty acid receptors are also associated with obesity reduced ability to detect fatty acids. Understanding oral peripheral fatty acid transduction mechanisms and the association with fat consumption may provide the basis of novel approaches to control development of obesity.



**Contents**



## 1. Introduction

Obesity is a contributor to the major causes of global disease burden, including cardiovascular diseases, cancer and diabetes [1,2]. Both genetic and environmental factors are implicated in obesity: family and twin studies estimate the genetic contribution between 45% to 75% [3] and genome wide association studies (GWAS) implicating loci like FTO and MCR4 [4]. Furthermore, a lack of physical activity and high caloric food consumption such as diets rich in fats and sugars are commonly accepted environmental factors associated with the development of obesity [5].

The sense of taste functions as a nutrient sensing system, and any irregularity may contribute to excess energy intake and obesity. This

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review explores the association between taste and obesity by examining the evidence for gustatory mechanisms of fatty acid chemoreception (fat taste) and how these mechanisms may be implicated in the reported associations between fat taste threshold, weight gain and obesity.

## 2. The taste system and gustatory anatomy

The function of the taste system in humans is to determine if the food is nutritious and safe to consume, as well as to prepare the digestive tract for the processing of the nutrients consumed [6]. The machinery of taste is located in the oral cavity, with the gustatory papillae housing groups of 50–100 taste receptor cells (TRCs) in structures called taste buds. The papillae are divided into three types according to the topographical representation on the tongue: fungiform, foliate and circumvallate papillae [7].

The TRCs are morphologically distinct with four different types of cells—classified as type I, II, III and the Basal (IV) cells with different functional significance [8]. Type I cells are glial-like cells [9] with many electron-dense granules in the apical cytoplasm [10]. Type II are spindle shaped cells, with large nuclei and short microvilli that protrude from the apical region [10]. Type II cells are associated with the taste of sweet, bitter and umami compounds [11]. Phospholipase Cβ2 (PLCβ2), an essential second messenger during the transduction of these tastes, is a commonly used marker for type II cells [12,13]. Type III cells are slender shaped with large vesicles in the nuclear region and a single microvillus that protrudes into the taste pore [10]. They contain synapses with primary sensory terminals, express synapse-related proteins, and are often referred to as presynaptic cells [14]. The basal (type IV) cells appear to be immature or undifferentiated and their function is unknown.

After the excitation of the primary sensory afferent fibres by the TRCs [15], the gustatory signals are transmitted from the taste buds to the central nervous system (CNS) through cranial nerves [16], which forms the sense of taste and informs the acceptance or rejection of the food [17]. While the events triggered by a specific tastant within the taste cell have been established, the signal processing from the taste cell through nerve fibres to form a specific taste percept remains unclear.

## 3. The five taste primaries

Taste is responsible for recognising and distinguishing key dietary components. It is believed to have evolved to help intake of essential and scarce nutrients, while preventing the consumption of toxic and indigestible substances [8,18]. The five taste primaries—sweet, bitter, umami, sour and salty—enable humans to perceive desired nutrients at the appropriate levels as pleasant and many toxins at harmful levels as unpleasant [6].

Sweet and umami tastants are detected by the homodimeric or heterodimeric complexes composed of G protein coupled receptors (GPCRs)—T1R1, T1R2 and T1R3 [19]. Bitter taste is mediated by a family of GPCRs called T2Rs [20]. The T1Rs and T2Rs are located in the distinct population of type II taste receptor cells [21], with signal transduction involving a series of reactions (Fig. 1) triggered by the combination of the tastant with a specific receptor. Even though different sweeteners activate the same T1R heterodimers, natural and artificial sweeteners are reported to trigger different signalling pathways. The pathway for sugars is believed to start from the βγ subunits (Gβγ) of the α-gustducin, which involves the activation of PLCβ2 and the production of IP3 [7]. On the contrary, artificial sweeteners activates the α subunit of the α-gustducin and initiates the reaction involving the cAMP [7]. Both pathways ultimately lead to the elevation of cytoplasmic calcium levels. The elevated calcium concentration and IP3 amounts lead to the opening of the transient receptor potential M5 (TRPM5) ion channel [22], and depolarization of the TRC (Fig. 1A). As a result, the neurotransmitter ATP is released into the extracellular space surrounding the activated receptor cell through the Panx1 hemichannel [23,24]. ATP then stimulates multiple targets: one is the gustatory afferent nerve fibres directly. The other is the adjacent presynaptic cells [25], which releases the transmitters including norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT) through synaptic exocytosis [26]. Sour and salt tastes are generally believed to be detected through ion channels (Fig. 1B). Sour taste is considered to be triggered by the intracellular proton concentration change [27] following the fully protonated acids permeating the cell membrane and releasing protons [28]. Several channels have been associated with sour taste, including PKD2L1 and PKD1L3 [29,30]. For salt taste, the principal stimulus ($Na^+$) can permeate through the cation channels on the apical taste buds, leading to the depolarization of the receptor cells (Fig. 1C). The putative candidate is the epithelial-type sodium channel (ENaC) [31,32].

Signal transduction for the five primary tastes involves the release of the neurotransmitters 5-HT, NE and ATP, after TRC stimulation. Thus, the question comes to how the different taste qualities are transported and encoded by the brain. Whether a single nerve fibre conveys a specific taste quality or multiple tastes to the brain has been assessed in previous studies, with the emergence of two main stream theories [33]. Current evidence suggests some of the afferent fibres conservatively tuned to a single taste quality, but others broadly respond to multiple qualities [34,35].

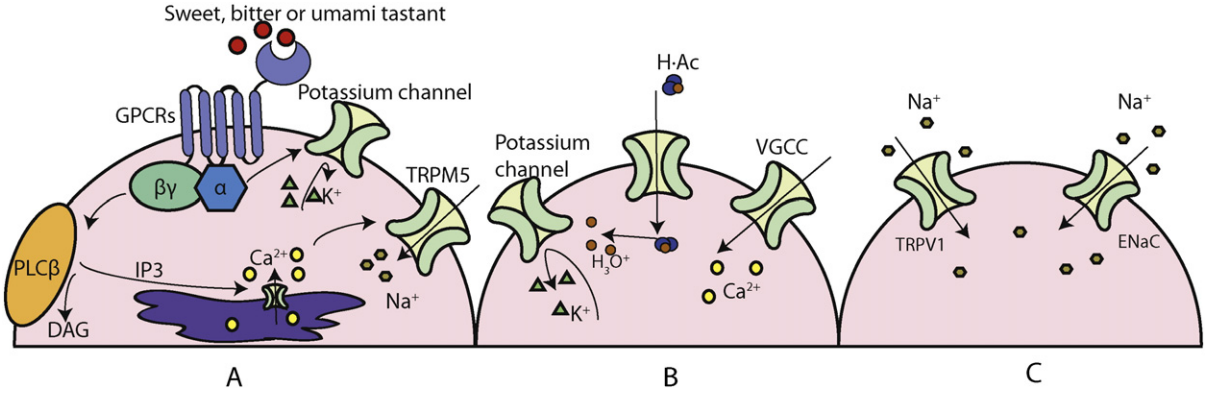


**Fig. 1.** Proposed mechanisms by which five taste qualities are transmitted in taste cells adapted from [8]. (A) Sweet, bitter or umami stimuli bind to the GPCRs on Type II cells activating two parallel pathways. One is from the Gβγ subset, which increases the secretion of $Ca^{2+}$ through a phosphoinositide pathway and depolarises the generator potential of the cell. The other pathway begins from α subset of the α-gustducin (Gα), which leads to the transient change in cAMP and depolarises the cell by the blockage potassium channels. Both pathways lead to the release of ATP though Panx 1 hemichannel pores into the extracellular space. (B) Sour taste transduction occurs in Type III cells. Acids can travel through membrane of presynaptic cells and releases $H^+$ (binds with $H_2O$ to $H_3O^+$) upon disassociation to acidify the cytosol and block the potassium channel as a result. Then the cytoplasmic $Ca^{2+}$ concentration is increased through the $Ca^{2+}$ influx from Voltage-gated calcium channels (VGCC) to release 5-HT and NE through synaptic vesicles. (C) $Na^+$ can permeate through the ENaC or TRPV1 ion channels directly to cause the cell depolarisation.