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# Detection, modulation, and transmission of sweet taste in regulation for energy homeostasis

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**Perception of sweet compounds is important for animals to detect external carbohydrate source of calories and plays a crucial role in feeding behavior of animals. Recent progress in molecular genetic studies provides evidence for a candidate receptor (heterodimers with taste receptor type 1 member 2 and 3: T1R2/T1R3), and major downstream transduction molecules required for sweet taste signaling. Several studies demonstrated that the sweet taste signal can be modulated by a satiety hormone, leptin, through its receptors expressed in a subset of sweet-sensitive taste cells. Increase of internal energy storage in the adipose tissue leads to increase in the plasma leptin level which can reduce activities of sweet-sensitive cells. In human, thus, diurnal variation of plasma leptin level parallels variation of taste recognition thresholds for sweet compounds. This leptin modulation of sweet taste sensitivity may influence individuals' preference, ingestive behavior, and absorption of nutrients, thereby plays important roles in regulation of energy homeostasis.**

**Key words : sweet taste, leptin, modulation, energy homeostasis**

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## Introduction

The sense of taste is important for animals to select nutritious food components and avoid toxic substances. Many mammals are shown to be able to discriminate five taste qualities, such as bitter, sweet, umami, sour and salty by using different taste sensors. For example, bitter taste, detected by the Taste receptor type 2 family (T2Rs) (Chandrashekar et al., 2000), causes aversive actions in animals and humans to protect the organism from ingesting toxic substances, whereas sweet taste, detected by heterodimers of taste receptor type 1, member 2 (T1R2) and member 3 (T1R3) (Nelson et al., 2001), is attractive, indicating caloric energy source. Umami (glutamate) taste, detected by T1R1/T1R3 (Li et al., 2002), is thought to play a role in the detection of protein and amino acids contents in foods. Sensors for salty and sour tastes are proposed to be ion channels which include epithelial sodium channels (ENaCs) (Heck et al., 1984) and taste variant of the transient receptor potential cation channel, subfamily V, member 1 (taste TRPV1) (Lyall et al., 2004) for salty taste, and acid-sensing ion channels (ASICs) (Ugawa et al., 1998) and two TRP channels from the polycystic kidney disease-like family (PKD1L3/PKD2L1) (Ishimaru et al., 2006) for sour taste. Salty taste is devoted to detect minerals and may serve an important function in ion and water homeostasis. Sour taste serves to detect ripeness of fruits and spoiled foods to prevent tissue damage.

The detection of taste compounds by these sensors leads to activation of taste cells through their particular transduction processes, followed by signal transmission to taste nerve fibers and the brain. Recent studies demonstrated that sweet taste signal can be modulated by plasma leptin, a satiety hormone primarily produced in adipose cells. The hormone regulates food intake, energy expenditure, and body weight

mainly via activation of the hypothalamic leptin receptor (Zhang et al., 1994; Flier 2004). We found that sweet-sensitive cells also possess the leptin receptor (Kawai et al., 2000; Ninomiya et al., 2002; Shigemura et al., 2004). Increase of plasma leptin level leads to reduction of taste nerve responses and behavioral preference for sweet compounds.

In this review paper, we focus on sweet taste perception, and summarize the data from recent studies in mice and humans that further addressed signal detection and leptin modulation of sweet taste and its role in the regulation of energy homeostasis.

## Detection, transduction and transmission of sweet taste signal to the brain.

It has been proposed that two G-protein-coupled receptors, T1R2 and T1R3, dimerize to form a sweet taste receptor (T1R2/T1R3) that can bind a broad array of sweet compounds including external caloric energy sources (Nelson et al., 2001). Binding of sweet compounds to T1R2/T1R3 leads to activation and dissociation of the subunits of the coupled heterotrimeric G protein, probably gustducin (Ggust) (Wong et al., 1996) but possibly other G proteins too. The dissociated βγ subunits of the Ggust activate phospholipase C (PLCβ2), which hydrolyzes phosphatidylinositol bisphosphate ($PIP_2$) into diacylglycerol (DAG) and inositol trisphosphate ($IP_3$) (Margolskee, 2002). Subsequently, $IP_3$ activates the type III IP3 receptor ($IP_3R3$), leading to the release of $Ca^{2+}$ from intracellular stores (Hisatsune et al., 2007). Rapid increases in $[Ca^{2+}]i$ open basolaterally located transient receptor potential cation channel, subfamily M, member 5 (TRPM5) channels. (Huang et al., 2002). Recent studies demonstrated that taste cells expressing sweet, umami and bitter taste receptors, such as T1Rs and T2Rs (receptor cells), do not possess synapses with taste nerve fibers, whereas taste cells possessing synapses do not express taste receptors but ion channels including acid-responsive PKDs (presynaptic cells) (Tomchik et al, 2007). Both of receptor cells and presynaptic cells are shown to produce action potentials in response to taste stimuli (Medler et al., 2003; Yoshida et al., 2006). In sweet-sensitive cells, therefore, the $Na^+$ influx from TRPM5 channels may lead to membrane depolarization and generation of action potentials. Our recent studies demonstrated that responses profiles of taste cells generating action potentials are not substantially different from those of single taste nerve fibers innervating the cells, indicating information derived from receptor cells generating action potentials may form a major component of taste information that is transmitted to gustatory nerve fibers (Yoshida et al., 2006). Adenosine 5'-triphosphate, ATP, is proposed to be release from the receptor cells through hemichannels and act as a neurotransmitter (Huang et al., 2007; Romanov et al., 2007). Our recent study indicates that action potentials trigger ATP release from the receptor cell in a spike-frequency-dependent manner (Murata et al., unpublished observation). The released ATP activates purinergic P2X receptors in taste fibers which convey sweet taste information to the brain (Finger et al., 2005). TRPM5 channel involved in the transduction of sweet taste acts as a thermosensor ($15 - 35^oC$ ). Activation of this channel by temperature peaking at $35^oC$ near body temperature, leads to increase of the sweet sensitivity of the cell (Talavera et al., 2005).

## Reduction of sweet sensitivity by increase of internal energy storage

Leptin, the product of the obese gene (*ob*), is a hormone primarily produced in adipose cells. It regulates food intake, energy expenditure, and body weight mainly via activation of the hypothalamic leptin receptor (Ob-Rb) (Flier 2004). Mutant mice that have defects in either leptin or the leptin receptor, such as *ob/ob* and *db/db* mice, are hyperphagic, massively obese, and diabetic (Zhang et al., 1994; Halaas et al., 1995). We found that Ob-Rb is also expressed in the taste organ. The hormone directly acts on taste receptor cells via Ob-Rb expressed in these cells and it specifically inhibits peripheral gustatory neural and behavioral responses to sweet substances without affecting responses to sour, salty and bitter substances in lean mice (Kawai et al., 2000; Ninomiya et al., 2002; Shigemura et al., 2004). The strength of suppressive effects by leptin was at most about 30% of control responses, and the effect may saturate when plasma leptin concentration reaches about 15 - 20 ng/ml (Kawai et al., 2000). It was also revealed that outward currents of isolated taste bud cells in response to depolarizing voltage steps were increased during bath application with leptin to the cells. Such selective inhibition of sweet taste responses by leptin was not observed in leptin receptor-deficient *db/db* mice (Kawai et al., 2000; Shigemura et al., 2004). We recently developed a loose patch configuration to record taste responses from single cells of taste buds isolated from the fungiform papilla (Yoshida et al., 2006). In this system, taste stimulation can be applied restrictedly to the apical side of taste cell membrane and action potentials of the cell to the stimulation can be recorded from the basolateral side of the taste cell. By using this recording system, we examined leptin effects on taste responses of taste receptor cells, and found that about 50% (8 out of 16) of sweet-responsive taste cells showed clear reduction of impulse frequency in response to saccharin Na during bath application of 20 ng/ml leptin to the basolateral membrane of the cell and recovery after wash-out of leptin (Yoshida et al., unpublished observation). These results suggest that leptin may be a sweet taste modulator that may take part in the regulation of food intake.

## Diurnal variation of taste recognition thresholds for sweet compounds parallels variation of plasma leptin in human.

It has been shown in both rats and humans that there is a diurnal pattern in circulating leptin levels (Saladin et al., 1995; Ahima et al., 1996). In humans, leptin levels start rising before noon and peak between 23:00 h and 01:00 h, after which the levels decline until morning (Shinha et al., 1996).This diurnal pattern can be phase-shifted when meals are shifted. For example, when meals were shifted by 6.5 h without changing the light or sleep cycles in humans, the plasma leptin levels were similarly shifted by 5-7 h (Schoeller et al., 1997). The nocturnal rise of leptin does not occur if the subjects are fasted (Boden et al., 1996). If leptin acts as a modulator for sweet taste sensitivity, and it shows diurnal variation, then it follows that the threshold for sweet taste may show correlated diurnal variation.

To examine this possibility, we measured recognition thresholds of non-obese subjects (BMI < 25) for various taste stimuli and plasma leptin levels at several times during the day under normal meal conditions with 3 meals, and restricted meal conditions with 1 or 2 meals per day (Nakamura et al., 2008). In the normal feeding condition, leptin concentrations started rising before noon and peaked in the night. This rise in leptin occurred later in the 2 and 1 meal conditions resulting in a phase shift of diurnal variation. With regard to taste recognition thresholds, similar to plasma leptin levels, significant time-dependent increases in thresholds for sucrose, glucose and saccharin were observed in the normal meal condition (Nakamura et al., 2008). That is, subjects needed higher concentrations of these sweeteners to detect the stimulus quality when they were tested in the evening compared to the morning. There was also a phase shift in 1 or 2 meal conditions eliminating the time dependent changes in sweetener recognition threshold. Diurnal variations in sweetener thresholds were significantly different among 3 meal conditions. This diurnal variation is sweet-taste selective: it was not observed in thresholds for other taste stimuli (NaCl, citric acid, quinine and mono-sodium glutamate) (Nakamura et al., 2008). Recently, we measured recognition thresholds of obese subjects (BMI > 25) for sweet compounds and plasma leptin levels at several times during the day under normal meal conditions with 3 meals, and found that the diurnal variations for sweet recognition thresholds disappeared in the obese subjects (Sanematsu et al., unpublished observation). Mean plasma leptin level of the obese subjects at morning was already about 20 ng/ml, which may be around the saturation level of leptin effect in mice (about 15 - 20 ng/ml) (Kawai et al., 2000).Therefore, lack of diurnal variation for sweet recognition thresholds in obese subjects may be due to their higher basal plasma leptin levels.

This paper summarized the data from recent mouse and human studies that addressed signal detection and leptin modulation for sweet taste (Kawai et al., 2000; Ninomiya et al., 2002; Shigemura et al., 2004; Nakamura et al., 2008). The data from human study indicate that the taste recognition threshold of non-obese humans for sweet compounds have a diurnal variation that parallels that for leptin levels, being lowest in the morning and highest at night. When leptin levels were phase shifted following imposition of 1 or 2 meals per day, the diurnal variation of thresholds for sweet sugars shifted in parallel (Nakamura et al., 2008). This synchronization of diurnal variation in leptin levels and sweet taste recognition thresholds suggest a mechanistic connection between these two variables. This linkage between the leptin levels and responsiveness to sweet compounds may be comparable with those found in mouse taste cells in the oral cavity (Kawai et al., 2000) and the gut (Margolskee et al., 2007). Thus, leptin may act as a modulator of sweet taste responses in mammals having a role in maintaining energy homeostasis.

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