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REVIEW

Sweet taste receptor in the hypothalamus: a potential new player in glucose sensing in the hypothalamus

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Abstract The hypothalamic feeding center plays an important role in energy homeostasis. The feeding center senses the systemic energy status by detecting hormone and nutrient levels for homeostatic regulation, resulting in the control of food intake, heat production, and glucose production and uptake. The concentration of glucose is sensed by two types of glucose-sensing neurons in the feeding center: glucose-excited neurons and glucose-inhibited neurons. Previous studies have mainly focused on glucose metabolism as the mechanism underlying glucose sensing. Recent studies have indicated that receptor-mediated pathways also play a role in glucose sensing. This review describes sweet taste receptors in the hypothalamus and explores the role of sweet taste receptors in energy homeostasis.

Keywords Hypothalamus · Sweet taste receptor · Glucose sensing · T1R2 · T1R3

Introduction

The feeding center in the hypothalamus plays an important role in energy homeostasis. The hypothalamic feeding center controls systemic energy balance by regulating food intake, heat production, and glucose homeostasis [1, 2]. These homeostatic regulations reflect the systemic energy status, which is detected via hormones and nutrients. The arcuate nucleus (ARC) in the hypothalamus plays an important role in sensing the systemic energy status [1, 2]. Due to the structural characteristics of the blood–brain barrier (BBB), peripheral molecules can easily enter the ventromedial ARC [3–6]. The ARC contains several groups of neurons that are related to energy homeostasis, including orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons and anorexigenic proopiomelanocortin (POMC) neurons [1, 2]. Receptors of metabolic hormones, including leptin and ghrelin, are abundantly expressed in the ARC and play critical roles in energy homeostasis [1, 2, 6–8]. Nutrients including glucose, free fatty acids, and amino acids are also sensed in the ARC [9–13]. These hormonal and nutritional inputs regulate neuronal activity and transcription of the hypothalamic feeding center neurons, especially in the ARC, and these changes are transmitted to second-order neurons in the ARC and other brain areas. In these circuits, multiple systemic energy signals are integrated into feedback regulation of feeding and metabolism, resulting in energy homeostasis [1, 2]. Sensing the systemic energy status is a key process because it is the initial step of homeostatic energy regulation. The understanding of the mechanisms underlying hormonal regulation of ARC neurons was greatly advanced by the discovery of several major metabolic hormones, such as ghrelin and leptin [14–16]. However, the underlying mechanism of nutrient sensing is still unknown. Recent studies have indicated a potential contribution of the sweet taste receptor to nutrient sensing in the feeding center. This review focuses on the sweet taste receptor and discusses its contribution to nutrient sensing, especially glucose sensing.

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Glucose sensing in the hypothalamus

Glucose is the primary energy source for animals, especially vertebrates and some invertebrates. Glucose-sensing cells, which change cellular activity in response to glucose concentration, are located in certain parts of the body, including the hypothalamus, pancreatic β-cells, and intestinal L-cells [17]. Glucose-sensing neurons in the hypothalamus were originally found by Oomura and Anand in 1964 [18, 19]. Glucose-sensing neurons in the hypothalamus are divided into two groups. One group consists of glucose-excited neurons (or glucose-responsive neurons), which are activated by high concentrations of glucose and inhibited by low concentrations of glucose. The other group consists of glucose-inhibited neurons (or glucose-sensitive neurons), which are inhibited by high concentrations of glucose and activated by low concentrations of glucose [20]. In the hypothalamus, these glucose-sensing neurons are distributed in the ARC, ventromedial hypothalamus (VMH), lateral hypothalamic area (LH), and paraventricular hypothalamus (PVH) [12]. Both glucose-excited and glucose-inhibited neurons are located in the ARC [21–23], but the neurotransmitters contained in glucose-sensing neurons in the ARC remain controversial. It has been reported that the glucose-excited neurons in the ARC consist of POMC neurons [24–26], while other groups have reported that glucose-excited neurons primarily consist of a population distinct from POMC neurons [23, 27]. Glucose-inhibited neurons mostly consist of a subpopulation of NPY neurons [6, 23, 28]. Interestingly, hypothalamic tanycytes, specialized glial cells located at the edge of the third ventricle, are also sensitive to high concentrations of glucose [29, 30]. However, the mechanism by which glucose sensing in tanycytes is transmitted to hypothalamic neurons is not well understood. Glucose sensing in the hypothalamus contributes to multiple energy homeostatic phenomena including food intake, glucose homeostasis, and energy expenditure [11, 12]. Mechanisms underlying glucose sensing in the hypothalamus have been reported. The ATP-sensitive K^+ channel [25, 31], AMP-activated protein kinase (AMPK) [26], uncoupling protein 2 [25, 32, 33], and glut2 [34] have been reported to be involved in the underlying mechanisms of glucose sensing in glucose-excited neurons. Additionally, Na^+, K^+-ATPase [35, 36], AMPK [37], and glucokinase [38] have been reported to contribute to glucose sensing in glucose-inhibited neurons. Furthermore, ATP-mediated mechanisms underlie the high glucose-induced cellular activation of tanycytes [29, 39]. These mechanisms are directly related to glucose metabolism and ATP production. Glucose sensing in glucose-excited neurons is similar to the response to high concentrations of glucose that is observed in pancreatic β-cells. Although the ATP-mediated pathway, including the ATP-sensitive K^+ channel, plays a major role in the glucose response in β-cells, recent evidence suggests that a sweet taste receptor-mediated pathway also contributes to the glucose responsiveness of β-cells [40–44]. Similar to the response in β-cells, hypothalamic glucose sensing could be mediated by the sweet taste receptor.

Expression of the sweet taste receptor in the hypothalamus

The sweet taste receptor is composed of the heterodimer of taste type 1 receptor 2 (T1R2) and taste type 1 receptor 3 (T1R3). T1R2 and T1R3 are distributed in multiple organs including the tongue, brain, pancreas, intestine, and adipose tissue [45, 46]. T1R2 and T1R3 are widely expressed throughout the brain [47]. RNA expression levels of T1R2 and T1R3 in the hypothalamus are significantly higher than those of the cortex and hippocampus [47, 48], suggesting abundant expression in the hypothalamus. Expression levels of T1R2 and T1R3 in the hypothalamus or hypothalamic cell lines are altered in response to energy status (Table 1). The RNA expression level of T1R2, but not T1R3, is increased in the hypothalamus after 24-h food deprivation, while T1R2 and T1R3 RNA expression levels remain unaltered in the cortex [47]. However, treatment with the satiety hormone leptin reduces the RNA expression levels of T1R2 and T1R3 in the hypothalamic cell line mHypoA-2/12 [48]. Similarly, treatment of cells with a high concentration of glucose reduces the RNA expression levels of T1R2 in the mouse hypothalamic cell lines N38 and mHypoA-2/12 [47, 48], and reduces the expression of T1R2 and T1R3 RNA in the hypothalamus of rainbow trout [49, 50]. These data suggest that expression of the sweet taste receptor is increased during fasting and decreased during satiety. It has also been reported that treatment with sweet taste receptor ligands, a high concentration of glucose, and the artificial sweetener sucralose reduces T1R2 expression [47, 48]. Similarly, in obese model mice with increased blood glucose levels, such as leptin-deficient obese mice (ob/ob mice) and high-fat diet-induced obese (DIO) mice, T1R2 and T1R3 expression is decreased in the hypothalamus [47, 48]. These data indicate that excess amounts of ligands reduce the sweet taste receptor expression levels in the hypothalamus and may cause desensitization of the sweet taste receptor-mediated pathway, including glucose sensing. The reduction of sweet taste receptor-mediated signals during obesity could be related to exacerbation of obesity complications such as hyperphagia and impaired glucose homeostasis. It has been

Table 1 Alteration of sweet taste receptor mRNA expression levels in the hypothalamus after the treatment of specific conditions or in mouse models

Condition	T1R2 expression	T1R3 expression
High glucose	↓ [47–50]	– [47, 48], ↓ [49, 50]
Sucralose	↓ [47]	– [47]
Leptin	↓ [48]	↓ [48]
Fasting mouse	↑ [47]	– [47]
ob/ob mouse	↓ [47], – [48]	↓ [48]
Diet-induced obese mouse	– [48]	↓ [48]

↑ increase, ↓ decrease, – not different

reported that the anorexigenic effect of centrally administered glucose is impaired in DIO mice [51], which could be due to a reduction in the sweet taste receptor. Overall, these data indicate that the expression levels of sweet taste receptor subunits T1R2 and T1R3 are closely associated with ligand concentrations and energy status. Interestingly, T1R3 is also a component of the umami receptor when it couples to T1R1, and alterations in T1R3 expression could also affect the umami receptor in the hypothalamus.

Function and role of the sweet taste receptor in the ARC

To explore the function of the sweet taste receptor in the ARC, we monitored the cytosolic calcium concentration ($[Ca^{2+}]_i$) in isolated ARC neurons and observed the direct effect of the artificial sweetener sucralose on the response of ARC neurons [22]. Sucralose is a non-nutritive sweet molecule; therefore, the effect of sucralose is assumed to be purely mediated by the sweet taste receptor. Sucralose (10^{-5} to 10^{-2} M) increased $[Ca^{2+}]_i$ in 12–16% of ARC neurons in a dose-dependent manner (Fig. 1a) [22]. An inhibitor of the sweet taste receptor, gurmarin, suppressed the sucralose-induced $[Ca^{2+}]_i$ increase, confirming that the sucralose-induced $[Ca^{2+}]_i$ increase is mediated by the sweet taste receptor (Fig. 1b). The sucralose-induced $[Ca^{2+}]_i$ increase depends on an extracellular Ca^{2+} influx, especially through L-type Ca^{2+} channels. The intracellular signaling pathways downstream of G-proteins may mediate the opening of these Ca^{2+} channels. Our study also revealed that the high glucose response in glucose-excited neurons is partially mediated by the sweet taste receptor (Fig. 1c). Approximately 70% of glucose-excited neurons were suppressed by an inhibitor of the sweet taste receptor [22]. Similar to the anorexigenic characteristic of glucose-excited neurons, the majority of sucralose-responsive neurons are leptin-responsive but not ghrelin-responsive neurons [22]. Furthermore, sucralose-responsive neurons primarily consist of non-POMC neurons [22]. This result is consistent with T1R2 and T1R3 expression in POMC neurons. T1R2 and T1R3 were expressed in approximately 30 and 20% of POMC neurons, respectively [22]. Additionally, POMC neurons comprised only approximately 20% of T1R2 and T1R3 neurons in the ARC [22]. Interestingly, the distribution and role of the sweet taste receptor in tanycytes have also been reported. T1R2 and T1R3 are also expressed in hypothalamic tanycytes [52]. Tanycytes have been shown to increase $[Ca^{2+}]_i$ in response to the administration of high concentration of glucose and artificial sweeteners [29, 52]. Reportedly, the percentage of tanycytes that respond to high concentration of glucose is significantly decreased in T1R2 null mice [52], suggesting that the

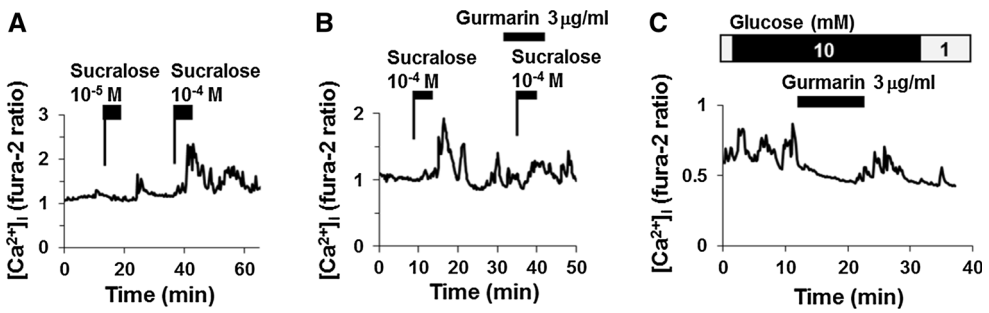

Fig. 1 Sweet taste receptor-mediated signals activate arcuate nucleus (ARC) neurons. **a** An artificial sweetener, sucralose, increased the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) in a single isolated ARC neuron in a dose-dependent manner. **b** The sucralose-induced $[Ca^{2+}]_i$ increase was suppressed by a sweet taste receptor inhibitor, gurmarin. **c** The high concentration glucose-induced $[Ca^{2+}]_i$ increase was suppressed by gurmarin. These data were taken from [22]

sweet taste receptor-mediated pathway plays a role in glucose sensing of hypothalamic tanycytes.

To explore the in vivo role of the sweet taste receptor in the brain, we injected 2.5–250 nmol of sucralose intracerebroventricularly into 24-h fasting C57B6 mice at the beginning of the dark phase and measured the cumulative food intake (Fig. 2a). The cumulative food intake 1–3 h after the injection decreased in a dose-dependent manner. While we cannot exclude the possibility that the sweet taste receptor expressed in brain areas other than the ARC caused an anorexigenic effect as a result of differences in phenotypes, such as differences in behavior phenotypes, the expression level of a neuronal activation marker, c-Fos, was significantly increased in the ARC after the administration of sucralose (Fig. 2b–e) [22], suggesting that at least the ARC neurons were activated. These data imply that activation of the sweet taste receptor in the ARC reduces food intake.

Sweet taste receptor knockout mice

The phenotypic characteristics of the T1R2 knockout mouse and the T1R3 knockout mouse have been reported. While the body weights of T1R2 knockout mice are normal when fed a regular diet and a high-fat diet, fat mass is decreased when these mice are fed a high-fat diet [53, 54]. When fed a high-fat diet, both food intake and energy expenditure are increased in T1R2 knockout mice [53]. Insulin sensitivity is improved during intake of a low-fat/high-carbohydrate diet

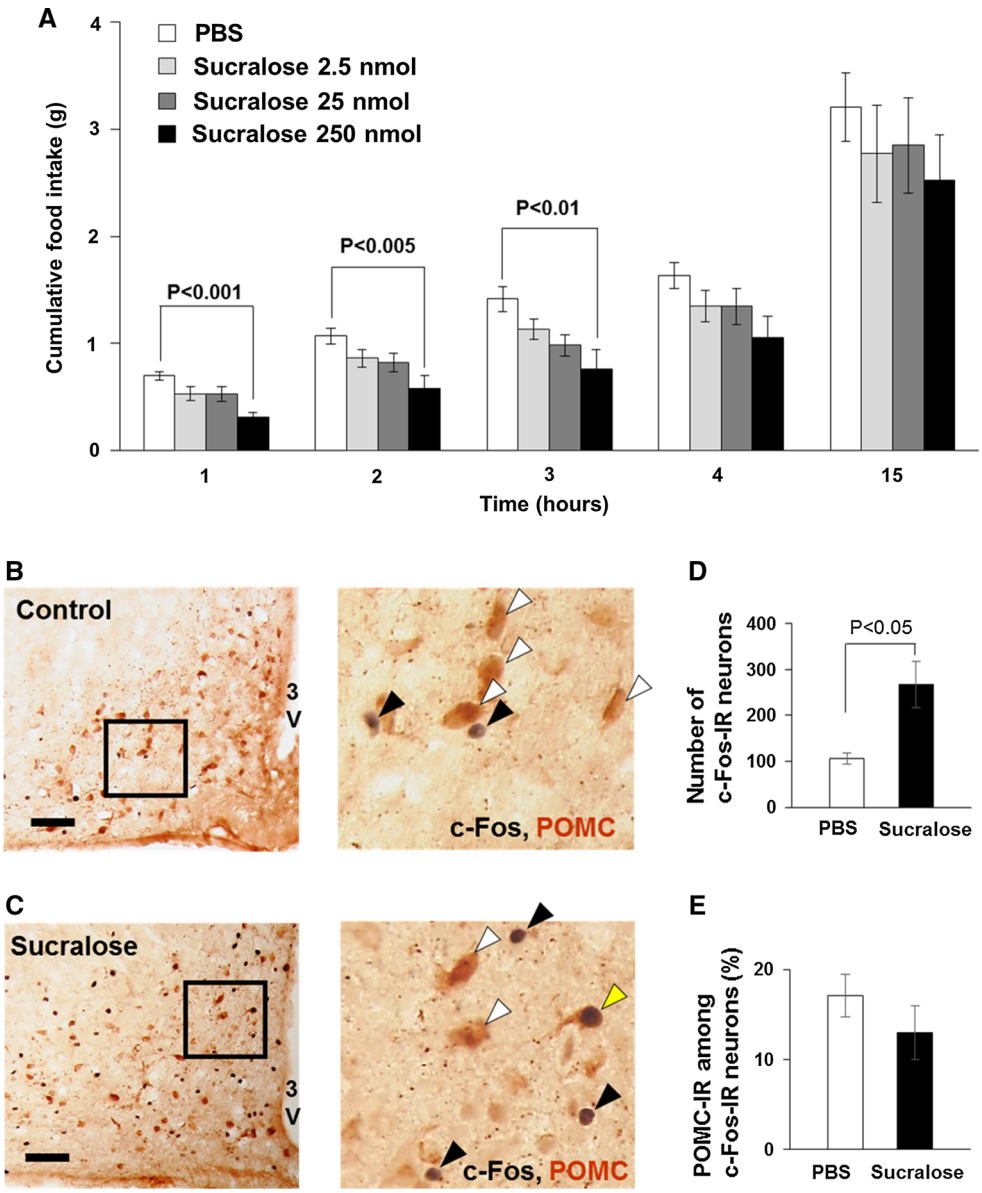

Fig. 2 Cumulative food intake and c-Fos expression after the intracerebroventricular administration of sucralose. **a** Sucralose (2.5–250 nmol) diluted in 0.5 µl of PBS was injected into the lateral ventricle of 24-h fasting C57B6 mice aged 12 weeks at the beginning of the dark phase, and then cumulative food intake was measured ($n = 7$ mouse per group, one-way ANOVA with Tukey's HSD post hoc analyses). Also shown are c-Fos and POMC immunohistochemistry in the ARC after the administration of PBS (**b**) or 0.085 mg of sucralose (**c**). **d** The number of c-Fos immunoreactive (IR) neurons in the ARC. **e** Percentage of POMC-IR neurons among c-Fos-IR neurons. *Scale bar* 100 µm. **b**–**e** were taken from [22]

[53]. The body weight of T1R3 knockout mice is also normal when fed a regular diet or a high-fat diet [54, 55]. However, the fat percentage of T1R3 knockout mice is decreased when fed a high fat diet [54]. Glucose tolerance but not insulin sensitivity is mildly impaired in T1R3 knockout mice fed a high fat diet [54]. Because the hypothalamic feeding center plays an important role in the regulation of energy balance by controlling feeding, energy expenditure, and glucose homeostasis, some of the phenotypes observed in T1R2 and T1R3 knockout mice could be attributable to the sweet taste receptor expressed in the hypothalamic feeding center. Further studies using hypothalamus-specific sweet taste receptor knockout mice are necessary to elucidate the physiological role of the sweet taste receptor in the feeding center.

Potential therapeutic application and side effects of artificial sweeteners

Approximately 5% of orally administered sucralose is absorbed from the intestinal tract into the blood [56]. However, it is not known whether sucralose can penetrate the BBB. Even if sucralose does not penetrate the BBB, it could enter the ARC due to its structural characteristics. In the short term, sucralose in the ARC should induce the anorexigenic effect as seen in our intracerebroventricular administration study. However, it has been noted that sucralose treatment reduces the expression level of the sweet taste receptor in the hypothalamus [47]. Therefore, chronic exposure to sucralose could interfere with the sweet taste receptor-mediated pathway, such as that in the high-glucose response. While this finding is still controversial, the over-consumption of artificial sweeteners has been reported to increase the risk of metabolic diseases such as obesity and diabetes [57–59]. This finding has been attributed to the alterations of microbiota in the digestive system [59]; however, the reduction of sweet taste receptor expression in the feeding center may contribute to these problems. Further studies to clarify the effect of orally administered sucralose on feeding center neurons are thus required. In addition, the sweet taste receptor expressed in the gut could respond to orally-taken artificial sweeteners. The sweet taste receptor and α-gustducin are expressed in enteroendocrine L-cells [60, 61] and play critical roles in the secretion of glucagon-like peptide-1 (GLP-1) [61], a hormone involved in glucose homeostasis and feeding regulation [62]. While orally administered artificial sweetener does not affect GLP-1 secretion in the short term [63], its long-term effects remain unclear. For their successful application to therapies and assessment of side effects, systemic and tissue-specific long-term effects of orally taken artificial sweeteners need to be investigated.

Conclusion

The role of the hypothalamic sweet taste receptor has begun to be revealed. The relationship between the sweet taste receptor and glucose is now better understood. Endogenous sweet molecules are not limited to only glucose; other known and likely unknown endogenous sweet molecules exist, including glycerol and amino acids. Sweet taste could be a meaningful signal in energy homeostasis. Studies to examine the specific role of the hypothalamic sweet taste receptor, such as studies in conditional knockout mice, have not yet been conducted. Thus, further studies are required to uncover the role of the hypothalamic sweet taste receptor, a new player in nutrient sensing.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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