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Sensory Systems for Sugar-Induced Cephalic Phase Insulin Release

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Abstract

Purpose of Review This review aims to discuss and summarize the peripheral sensory mechanisms involved in the induction of the early phase of insulin release, known as cephalic phase insulin release (CPIR), triggered by stimuli related to food, particularly sugars.

Recent Findings At least, two distinct systems on the tongue are responsible for detecting oral sugars. The first system involves the G-protein-coupled receptor Tas1r2/Tas1r3, which can detect not only sugars but also artificial sweeteners and sweet proteins. The second system relies on glucose transporters, specifically recognize and transport monosaccharides. The Tas1r2/Tas1r3 receptor utilizes a signal transduction pathway involving gustducin, phospholipase β2, and transient receptor potential channel M5 to depolarize taste cells. On the other hand, glucose transporters facilitate the transport of monosaccharides into cells, where their degradation produces ATP. This ATP inhibits the metabolic sensor K_{ATP} channel, ultimately leading to cell depolarization. Recent studies in mice have demonstrated that glucose transporters and K_{ATP} channels, rather than the Tas1r2/Tas1r3 receptor, are essential for the induction of CPIR.

Summary The detection of sugars in the oral cavity relies on two essential mechanisms: the Tas1r2/Tas1r3 receptor and glucose transporters. Notably, oral glucose transporters are likely to play a significant role in the induction of sugar-induced CPIR. As a result, these two sugar detection systems may have distinct roles in maintaining energy homeostasis within the body.

Keywords Tas1r2/Tas1r3 · Glucose transporter · Sugar · Sweet taste · Food intake

Introduction

Insulin plays a crucial role in reducing plasma glucose levels by facilitating the absorption of glucose into muscle, adipose tissue, and liver cells. Its secretion is triggered by blood glucose, resulting in an increase in plasma insulin following food ingestion. However, even before the rise in plasma glucose levels after a meal, the stimulation of sensory systems in the head and oropharynx region initiates an early release of insulin from pancreatic β-cells [1–3]. This early phase of insulin release, known as cephalic phase insulin release (CPIR), is elicited by food-related stimuli, particularly sugars such as glucose and sucrose [4–7]. Sugars are typical tastants for sweet taste, and therefore, other sweet-tasting substances, for example, artificial sweetener saccharin, have also been reported to induce CPIR [1, 5, 8–10]. However, conflicting reports exist regarding the ability of artificial sweeteners to elicit CPIR, with some studies showing no such effect [11–14].

Taste receptors located on the taste cells are responsible for detecting oral sugars. Two types of receptor systems are known to be involved: the Tas1r2/Tas1r3 sweet receptor and glucose transporters. The Tas1r2/Tas1r3 receptor is the primary sensor for sweet tastants, capable of detecting sugars, artificial sweeteners, and even sweet proteins [15]. Studies have demonstrated that mice lacking functional Tas1r2/Tas1r3 receptors exhibit either abolished or significantly reduced gustatory nerve responses to sweeteners [16, 17]. On the other hand, glucose transporters

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(GLUTs) and sodium-glucose transporters (SGLTs) serve as specific sensors for glucose. In mice, certain gustatory nerve fibers respond to sugars but not artificial sweeteners, and their responses to glucose + NaCl are notably suppressed by phlorizin, an SGLT inhibitor [18••]. Recently, such glucose specific taste response mediated by SGLT was reported to be increased by a multifunctional regulatory peptide adrenomedullin [19•]. This finding provides further support to the notion that glucose transporters serve as sugar sensors in taste receptor cells. These sensory mechanisms likely play significant roles in sugar-induced CPIR.

The sense of taste is a significant component of the sensory system that influences our food intake. However, other sensory cues, such as visual, olfactory, and somatosensory signals, also play crucial roles in determining our food intake. For instance, visual and olfactory cues associated with foods we dislike can inhibit our consumption of those particular foods. Moreover, nociceptive signals in the oral cavity trigger the aperture reflex, which disrupts the ingestion of food bolus. In the central nervous system, these sensory signals are integrated and utilized to elicit appropriate reactions and behaviors. An illustrative example is the experience of many patients who undergo enteral tube feeding, a method that bypasses oral ingestion and swallowing of food. These patients often report experiencing diarrhea [20]. This highlights the fact that not only taste, but also other sensory signals resulting from food intake, can contribute to the initiation of various reactions, including changes in physiology and behavior.

This review aims to provide an overview and analysis of the peripheral sensory mechanisms involved in the sugar-induced CPIR. First, sugar sensing mechanisms on the tongue were summarized. Then contribution of these mechanisms to sugar-induced CPIR is discussed.

Detection of Sweeteners by Tas1r2/Tas1r3

The discovery of the sweet taste receptor, Tas1r2/Tas1r3, occurred in the early 2000s, as reported by several studies [21–27]. Tas1r2/Tas1r3 is a G-protein-coupled receptor with a large extracellular domain known as the Venus flytrap domain (VFTD), which is crucial for detecting various sweet compounds. Activation of the Tas1r2/Tas1r3 receptor by sweet compounds in taste cells initiates an intracellular signaling cascade including gustducin [28], phospholipase Cβ2 [29], inositol-1,4,5-triophosphate receptor type 3 [30], and transient receptor potential channel M5 [29, 31]. This cascade leads to taste cell depolarization and the generation of action potentials [32–34]. The action potentials trigger the opening of the calcium homeostasis modulator 1/3 (Calhm1/3) channel, which releases ATP from taste cells [35, 36]. The released ATP binds to and activates purinergic P2X2/3 receptors on the gustatory nerve fibers [37], allowing the transmission of sweet signals to the central nervous system.

Tas1r2/Tas1r3 receptors have the capability to detect various substances, including sugars, artificial sweeteners, and sweet proteins. Sugars such as sucrose and glucose, as well as artificial sweeteners like sucralose, have been shown to bind to the VFTD of both Tas1r2 and Tas1r3 [38–40]. However, there are differences in sweet sensitivity to aspartame and neotame between humans and rodents. Humans perceive these artificial sweeteners as sweet, while rodents either do not detect them or have a weak preference [41, 42]. This disparity is due to the varying binding affinity of these artificial sweeteners to human or rodent Tas1r2/Tas1r3 receptors [27, 43]. Certain proteins, such as Brazzein, Monelin, and Thaumatin, possess a sweet taste in humans. These sweet proteins can also bind to and activate human Tas1r2/Tas1r3 receptors in heterologous expression assays [44, 45]. Consequently, taste signals mediated by Tas1r2/Tas1r3 receptors are not exclusive to sugars, which are the primary energy sources for our bodies. In mice lacking the *Tas1r2* and/or *Tas1r3* genes, a preference for sweet compounds, including sugars, is lost [16, 17, 46], suggesting a strong correlation between these signals and innate preference for sweet compounds. However, mice lacking the *Tas1r3* gene still exhibit residual responses to sugars, particularly glucose [17], implying the existence of additional receptor(s) involved in sugar detection in the oral cavity.

Oral Sugar Detection by Glucose Transporters

Glucose transporters play a crucial role in facilitating the absorption of dietary carbohydrates in the intestine. Given the similarities between intestinal cells and taste receptor cells, it is plausible that these transporters may also function in detecting sugars in the oral cavity if they are present in taste cells. Interestingly, the sweet receptor Tas1r2/Tas1r3 has been reported to be expressed in intestinal cells [47, 48]. Conversely, several glucose transporters (Glut1, Glut2, Glut4, Glut5, Glut8, and Glut9) and the sodium glucose transporter Sglt1 have been found to be expressed in the taste tissues of rodents [49–51]. In the pancreatic islet cells, the ATP-sensitive potassium channel (K_{ATP} channel) plays a crucial role in depolarization and insulin secretion, as it is inhibited by ATP generated during glucose metabolism [52, 53]. Histological studies have shown the expression of K_{ATP} channel subunits, specifically sulfonylurea receptor 1 (Sur1) and potassium inwardly rectifying channel 6.1 (Kir6.1), in taste cells [33, 51]. Some of these transporters and K_{ATP} channel subunits are likely to be

expressed in Tas1r3-positive taste cells, suggesting their potential involvement in sweet-sensitive taste cells.

Experimental evidence supporting the role of glucose transporters as sugar sensors was demonstrated through the recording of sugar responses in gustatory nerve fibers [18••]. Gustatory nerve fibers that exhibited the highest response to sucrose were categorized into three groups: phlorizin-sensitive type, phlorizin-insensitive type, and a mixed type. Phlorizin, a competitive inhibitor of Sglt1, was used to determine whether the responses of the phlorizin-sensitive fibers originated from taste cells expressing Sglts. Indeed, certain taste cells displayed apical uptake of a fluorescent glucose analog 2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)Amino)-2-Deoxyglucose (2-NBDG) via glucose transporters [18••]. Potential mechanisms for glucose detection by taste cells can be outlined as follows: (1) Some taste cells may possess both glucose transporters and K_{ATP} channels, (2) Glucose taken up through the apically expressed glucose transporters is metabolized within taste cells, leading to ATP production, (3) Increases in intracellular ATP concentrations result in the closure of K_{ATP} channels, depolarizing the taste cells, and (4) Transmitters, possibly ATP, are released to activate gustatory nerve fibers.

The glucose-transporter dependent system is capable of detecting glucose and monosaccharides, but it can not directly sense di-, oligo-, and polysaccharides such as sucrose and polycose because these molecules can not enter cells through glucose transporters. To enable the detection of di-, oligo-, and polysaccharides by the glucose-transporter dependent system, additional components are necessary to break down these saccharides into monosaccharides. Salivary amylase (Amy1) and pancreatic amylase (Amy2) are enzymes responsible for hydrolyzing starch and producing disaccharides. In the brush border cells of the intestine, various disaccharidases such as maltase-glucoamylase, sucrase-isomaltase, and lactase are expressed. These enzymes further break down the disaccharides into monosaccharides, which are then absorbed into the cells through glucose transporters [54, 55]. Examination of the presence of these amylases and α-glucosidase in taste tissues has revealed that taste cells also express all of these components [56]. Blocking α-glucosidase on the tongue has been shown to decrease gustatory nerve responses specifically to disaccharides (such as sucrose and maltose), but not to monosaccharides (such as glucose and fructose) or noncaloric sweeteners (such as sucralose and SC45647), in both wild-type and Tas1r3-KO mice [56]. This suggests that the α-glucosidase expressed in taste cells plays a crucial role in the detection of disaccharides on the tongue. A summary of possible mechanisms for sugar detection via glucose transporters is summarized in Fig. 1.

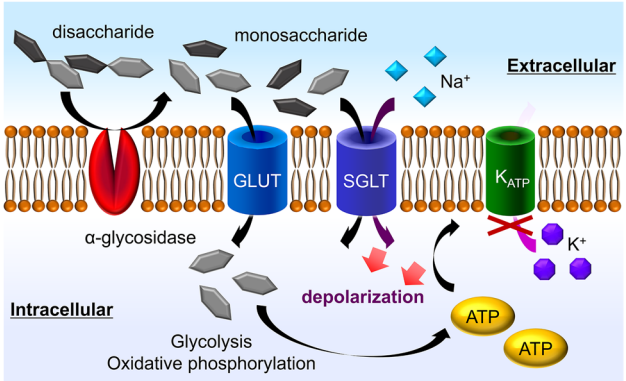

Fig. 1 Possible mechanism for sugar detection via glucose transporters in taste receptor cells. The glucose transporters present in taste receptor cells have the capability to transfer glucose from the apical side. Glucose undergoes metabolic processes such as glycolysis and oxidative phosphorylation, resulting in the production of ATP. Consequently, intracellular ATP levels are increased. This increase in ATP concentration causes the closure of ATP-sensitive K channels (K_{ATP} channels). Subsequently, the taste cell becomes depolarized, leading to the generation of action potentials. Sodium-glucose transporters (Sglts) have the ability to transport both Na^+ and glucose. Therefore, the activation of Sglts alone can potentially depolarize taste cells. Disaccharides such as sucrose are enzymatically digested by α-glucosidase expressed on the taste cells. This digestion process produces glucose, which is then transported into the taste cell through glucose transporters.

Sugar Detection and CPIR

Among the five basic tastes (sweet, salty, sour, bitter, and umami), sweet taste has been reported to elicit CPIR in humans [5] and rats [9]. However, one study demonstrated that umami taste also induced CPIR in rats [57]. As mentioned earlier, sweet taste can be evoked by various substances, including sugars, artificial sweeteners, and sweet proteins. Consequently, multiple sweeteners have been tested to determine whether they can induce CPIR. In some reports, the nonnutritive sweetener saccharin was found to induce CPIR in both humans and rats [1, 5, 8–10]. However, other studies have shown that oral stimulation with non-nutritive sweeteners did not trigger CPIR [11–14]. In the case of mice, CPIR was not induced by oral stimulation with various non-nutritive sweeteners, including saccharin, sucralose, acesulfame K, and SC45647. However, sugars such as glucose and sucrose did elicit CPIR in mice [14]. Consistent with these findings, Tas1r3-KO mice still exhibited an increase in plasma insulin 5 min after ingesting a glucose solution, and the changes in plasma insulin were comparable between control B6 mice and Tas1r3-KO mice [14, 58••]. These results collectively suggest that the Tas1r2/Tas1r3 receptor is not necessary for sugar-induced CPIR in mice.

Another potential candidate for sugar detection in the oral cavity, contributing to the induction of CPIR, is the

glucose-transporter-mediated system involving glucose transporters (Gluts, Sglts), and the K_{ATP} channel. The involvement of the K_{ATP} channel in sugar-induced CPIR was investigated using knockout (KO) model mice and pharmacological agents targeting the K_{ATP} channel [14]. This study revealed that the increase in plasma insulin 5 min after ingesting a glucose solution was significantly smaller in Sur1-KO mice compared to control mice. Additionally, the mixing of glyburide, a K_{ATP} channel closer, or diazoxide, a K_{ATP} channel opener, with the glucose solution significantly enhanced or reduced the increase in plasma insulin, respectively. Hence, the K_{ATP} channel may play a critical role in sugar-induced CPIR in mice. Regarding the contribution of glucose transporters to sugar-induced CPIR, pharmacological blockers for Gluts and Sglts were applied to the tongues of mice to test whether a blocker mixture could suppress sugar-induced CPIR [58••]. Indeed, treatment with phlorizin and phloretin in the oral cavity of mice significantly inhibited the rapid increase in plasma insulin levels after orally ingesting a glucose solution, although a small increase in plasma insulin remained. However, the non-metabolizable glucose analog methyl-α-D-glucopyranoside (MDG) did not induce CPIR in mice [14, 58••], suggesting that the activation of glucose transporters itself may not contribute to the induction of CPIR in mice. On the other hand, Glendining et al., (2017) demonstrated that plasma insulin dynamics were not significantly different between Sglt1-KO and wild-type control mice [14]. However, in this study, only small changes in plasma insulin occurred after orally ingesting a glucose solution even in wild-type control mice. Collectively, it is possible that oral glucose transporters function in detecting sugars to induce CPIR in mice.

Following the activation of taste cells by sugars, the signals are transmitted to gustatory nerve fibers, the central nervous system, and subsequently, vagus nerve fibers to induce CPIR. The transmission of signals from sweet taste cells to gustatory nerve fibers involves the release of ATP from sweet taste cells via Calhm1/3 and the activation of P2X2/X3 receptors on the gustatory nerve fiber [59•]. However, both Calhm1-KO mice and P2X2/X3 double KO mice still displayed a rapid increase in plasma insulin levels after orally ingesting a glucose solution, similar to their wild-type control mice [14]. This suggests a possibility that Tas1r-independent sugar detection mechanisms might employ a non-purinergic transmission pathway at the synapse between taste cells and gustatory nerve fibers. One potential candidate for this mechanism is peptidergic transmission mediated by glucagon-like peptide-1 (GLP-1). Previous studies have shown that Tas1r3-positive taste cells express GLP-1 [60]. GLP-1 is released from sweet-sensitive taste cells and may function as a neurotransmitter to activate gustatory nerve fibers [61]. This system could operate independently of the channel synapse in sweet-sensitive taste cells and potentially contribute to sensory signaling for the induction of CPIR. Additionally, taste cells are known to release acetylcholine in response to sweet-bitter mixtures [62]. Solitary chemosensory cells (SCCs) in the nasal cavity, which share properties with type II taste bud cells (sweet, bitter, and umami cells), express choline acetyltransferase [63]. Similar types of cells are found in the trachea, auditory tube, urethra, and thymic medulla, all expressing choline acetyltransferase [64–67]. While the expression of choline acetyltransferase in sweet-sensitive taste cells has not been confirmed, it is plausible that acetylcholine may function as a neurotransmitter from sugar-sensitive taste cells, in addition to purinergic transmission. Further studies are required to elucidate the mechanisms underlying the transmission of signals from sugar-sensitive cells to gustatory nerve fibers.

Other Sensory Cue for CPIR

When animals consume food, not only the sense of taste, but also other sensory systems such as touch and thermal sensors in the oral and pharynx region will be activated. These somatosensory signals elicited by food intake play a significant role in gastrointestinal functions and potentially contribute to the induction of CPIR. In mice, direct infusion of glucose into the gut did not trigger the rapid phase of insulin responses in both Tas1r3-KO and wild-type mice [7, 58••]. Hence, glucose signals from the gut and intestine alone might not be sufficient to induce CPIR. However, when intragastric infusion of glucose was combined with water drinking (without chemical cues from the tongue), a slight but significant increase in plasma insulin levels was observed 5 min after glucose administration [58••]. Consistent with this finding, mice treated with inhibitors for glucose transporters on the tongue still exhibited a small but significant increase in plasma insulin levels 5 min after glucose administration [58••]. Ingestion of MDG with gastric infusion of glucose solution also elicited small but significant rapid increase in plasma insulin level. These results suggest that somatosensory signals from the oropharynx region contribute to the induction of CPIR. However, the rapid phase of insulin response is minimal when chemical cues or signals derived from glucose transporters on the tongue are omitted. Overall, somatosensory signals may have a supportive or synergistic effect on the induction of CPIR in conjunction with oral sugar signals. Somatosensory signals from the oropharynx region propagate through the trigeminal nerve, glossopharyngeal nerve, and vagus nerve. Taste signals, on the other hand, propagate through the facial nerve (chorda tympani nerve and greater petrosal nerve), or glossopharyngeal nerve, and vagus nerve. These signals are likely integrated in nuclei of central nervous system, such as the nucleus of the solitary tract and the dorsal motor nucleus

of the vagus nerve. The integration of signals from different modalities would enhance efferent signals to β-cells in the islets, ultimately leading to the induction of CPIR. Further investigation is needed to explore this possibility in future studies.

Conclusion

Although the mechanism for the induction of CPIR is still controversial, taste cells located on the tongue are considered crucial for detecting the chemical signals involved in CPIR. Given that CPIR is prominently elicited by sugars, the sugar detection system on the tongue plays a fundamental role in CPIR. Recent studies have demonstrated that the sugar-specific detection system, comprising glucose transporters and the K_{ATP} channel, functions to detect sugars on the tongue and contributes to the induction of CPIR. However, due to the challenges associated with experimental designs, it is important to acknowledge the possibility that other sensory cues may also contribute to the induction of CPIR. Further investigations are necessary to enhance our understanding of the underlying mechanisms involved in CPIR.

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Declarations

Human and Animal Rights and Informed Consent No.

Competing Interests The author declares no competing interests.

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- • Of importance
- •• Of major importance

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