# The sweet taste receptor, glucose transporters, and the ATP-sensitive $K^+$ ($K_{ATP}$) channel: Sugar sensing for the regulation of energy homeostasis

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Abstract

Sugar detection in the oral cavity does not solely depend on the TAS1R2+TAS1R3 sweet receptor. Similar to gut, pancreas, and hypothalamic neurons, in the tongue glucose transporters and ATP-sensitive $K^+$ ($K_{ATP}$) channels are also involved in sugar detection. Among them, the $K_{ATP}$ channel is the target for the antiobesity hormone leptin, which inhibits sugar-sensitive cells such as sweet taste cells, pancreatic β-cells, and hypothalamic orexigenic neurons. Sugar signals from the taste organ elicit cephalic-phase insulin release, and those from the gut contribute to sweet preference for caloric sugars. All of these systems are indispensable for maintaining energy homeostasis. Thus, an exquisite system for sugar detection/signaling to regulate energy homeostasis exists in our body.

Abbreviations:

CALHM1: calcium homeostasis modulator 1, CPIR: cephalic-phase insulin release, GLP-2: glucagon-like peptide-2, GLUTs, glucose transporters, NPY/AgRP: neuropeptide Y/agouti-related peptide, NST: nucleus of solitary tract, PI3K: phosphatidylinositol-3 kinase, POMC: pro-opiomelanocortin, SGLT: sodium-glucose cotransporter, STC-1, secretin tumor cell line, SUR1: sulfonylurea receptor 1, TAS1R2, TAS1R3: taste receptor family 1 member 2, 3, TRPM5: transient receptor potential cation channel subfamily M member 5, WT: wild type

Key words:

gustatory nerve fibers, leptin, cephalic-phase insulin release, sweet taste, food intake

## Introduction

Sugars are detected in oral and extraoral organs, providing critical information to maintain energy homeostasis in our body. For sugar detection, glucose transporters, $K_{ATP}$ channels, and the sweet receptor TAS1R2+TAS1R3 (taste receptor family 1 members 2 + 3) play key roles in many organs, including the tongue, gut, pancreas, and brain. This information is transmitted to various organs via the nervous system and/or humoral factors and helps maintain energy homeostasis (Fig.1). This article discusses these multiple sugar detection systems and their roles in energy homeostasis regulation.

## Sugar sensing in taste systems of the tongue

The heterodimeric complex TAS1R2+TAS1R3 is the major receptor for sweet taste. However, in whole gustatory nerve recordings, *Tas1r3*$^{-/-}$ mice showed a robust response to 500 mM glucose, with no statistical difference from wild type (WT) [1]. Such residual response to glucose in *Tas1r3*$^{-/-}$ mice indicates the existence of TAS1R-independent glucose sensor(s), which are expressed by taste cells that are innervated by gustatory afferent nerve fibers.

We investigated potential gustatory neuron types that code sugar information and how sodium-glucose cotransporters and TAS1Rs are involved [2**]. In whole-nerve recordings, gustatory nerve responses to sucrose and glucose, but not to SC45647 or polycose (sweet tasting compounds that are not involved in sodium-glucose transport), were significantly enhanced by adding NaCl (10 mM), suggesting the possible involvement of sodium-glucose cotransporters. These enhancements were abolished by lingual application of phlorizin, an inhibitor of sodium-glucose transporters. In single-

fiber recordings of WT mice, fibers showing maximal response to sucrose could be classified according to responses to SC45647 and glucose with or without NaCl and/or phlorizin: phlorizin insensitive (28.6%), phlorizin-sensitive glucose (28.6%), and mixed (glucose and SC45647 responding) (42.9%). Among them, phlorizin-insensitive fibers disappeared in *Tas1r3*$^{-/-}$ mice, indicating that this type responds to glucose and other sweet compounds via TAS1R3 and not involving sodium-glucose transporter. In *Tas1r3*$^{-/-}$ mice, the response of mixed-type fibers to glucose + NaCl was phlorizin sensitive, and their response to SC45647 was greatly diminished, suggesting that mixed-type fibers possess both sodium-glucose cotransporters (SGLTs) and TAS1R3.

In addition to SGLTs, glucose transporters (GLUTs) also contribute to glucose detection in taste cells since significant inhibition of apical glucose uptake of taste cells by phloretin, an inhibitor of GLUTs, was demonstrated using a fluorescent glucose analog [2**]. Although glucose transport by SGLT1 reached maximal at 30-50 mM glucose [3], transport by GLUTs does not saturate since GLUTs are passive transporters. Therefore, at higher glucose concentrations, GLUTs may play a greater role in glucose detection.

A previous immunohistochemical study demonstrated that SGLT1 and GLUTs are preferentially expressed in TAS1R3-positive taste cells [4]. A total of 80–85% of taste cells that express sulfonylurea receptor 1 (SUR1), a $K_{ATP}$ subunit downstream of glucose transporters in other tissues such as pancreatic islets, coexpress TAS1R3 in the circumvallate and foliate papillae. Our study suggests that SGLTs are expressed by 72% of sweet taste cells [2**]. This suggests that, of those cells, 60% coexpress TAS1R2+TAS1R3 in taste papillae. These findings are consistent with the immunohistochemistry data. Mean impulse frequencies to glucose with or without NaCl were larger in mixed-type than in glucose-type fibers in WT mice [2**]. This implies that

the combined activation of TAS1Rs and transporters by sugars may enhance responses to glucose over those achieved by either mechanism alone.

Extra-oral glucose sensing by TAS1Rs and glucose transporters

Similar to glucose sensing in the oral tissues, both TAS1Rs and glucose transporters function to sense glucose in the intestine, pancreas, and brain (Fig. 1). In the intestine, TAS1R2, TAS1R3, and gustducin are expressed in enteroendocrine cells [5]. These components play an important role in sensing luminal sugars to increase SGLT1 expression and glucose absorptive capacity. Like *Tas1r3*$^{-/-}$ and *Gnat3*(gustducin)$^{-/-}$ mice, mice lacking glucagon-like peptide-2 (GLP-2) do not show a sugar-induced increase in SGLT1 expression [6]. GLP-2 is secreted from the small intestine in response to glucose and sucralose, and the GLP-2 receptor is expressed in enteric neurons but not in absorptive enterocytes [6]. Thus, luminal sugar sensing in enteroendocrine cells by TAS1R3-dependent mechanisms induces GLP-2 secretion, which stimulates enteric neurons to increase SGLT1 expression and glucose absorption in the intestine. Similar mechanisms also contribute to the regulation of GLUT2 transporter trafficking to the apical membrane of enterocytes to increase glucose absorption [7*]. In addition, mice exposed to sucralose for 12 weeks show increases in sweet taste receptors, glucose transporters, and glucose absorption [8]. All these reports suggest that TAS1Rs and glucose transporters function to enhance glucose absorption in the intestine in a coordinated manner.

In pancreatic β-cells, TAS1Rs contribute to insulin secretion. Glucose sensing by TAS1R3-dependent mechanisms enhances glucose-induced insulin secretion and GLUT2-mediated ATP production, which leads to closure of $K_{ATP}$ channels and thus

depolarization [9]. In the presence of glucose at concentrations below those that stimulate insulin release (3~5 mM glucose), activation of the TAS1R3-dependent receptor exerts an excitatory effect on β-cell bioelectrical activity [10, 11*]. These reports suggest that TAS1R3-dependent mechanisms amplify insulin secretion from β-cells in cooperation with glucose transporters. In addition, TAS1R3-dependent mechanisms may activate TRPM5 (transient receptor potential cation channel subfamily M member 5) to depolarize pancreatic β-cells and enhance glucose-stimulated insulin secretion [12]. In either case, TAS1R3-dependent mechanisms collaborate with glucose transporters to enhance insulin secretion from pancreatic β-cells.

TAS1Rs and glucose transporters are expressed and sense glucose in the brain [13]. For example, neurons in the hypothalamus possess several mechanisms for glucose sensing, including GLUT2/3-$K_{ATP}$, SGLT, and TAS1R-dependent mechanisms [14]. Among them, sucralose-responsive neurons with a TAS1R-dependent mechanism primarily consist of non-pro-opiomelanocortin (POMC) neurons, and activation of these neurons by intracerebroventricular injection of sucralose suppresses food intake [15]. This suggests that TAS1R-dependent mechanisms in the hypothalamus, together with glucose transporters, contribute to regulation of food intake by sensing the glucose level in the brain.

Leptin-$K_{ATP}$ channel pathway in glucose-sensitive cells

Certain hormones have a pivotal role in maintaining energy homeostasis in our body. Leptin, an adipocyte-derived hormone, regulates food intake and energy expenditure to suppress weight gain by acting on central and peripheral organs. Leptin is a unique hormone, inducing either excitation or suppression on target cells. Leptin's excitation is

observed in vagal afferent neurons and POMC neurons of the hypothalamus and the nucleus of solitary tract (NST), while hypothalamic neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, pancreatic β-cells, and sweet taste receptor cells are suppressed by leptin [16-19]. These effects reduce food consumption and suppress energy storage, which prevents excess caloric intake/storage. This consonant, cooperative regulation by leptin may be responsible for maintaining adequate energy states of our body.

Leptin's inhibitory effects are linked to $K_{ATP}$ channels (Fig. 2). In hypothalamic NPY/AgRP neurons, leptin activates $K_{ATP}$ channels via a phosphatidylinositol-3 kinase (PI3K)-dependent mechanism [16]. Leptin's inhibition of pancreatic β-cells is mediated by $K_{ATP}$ channel opening and trafficking to the plasma membrane [16, 20]. The sweet-suppressive effect of leptin also arises from activation of the $K_{ATP}$ channel in TAS1R3-positive taste cells [21]. Furthermore, sweet responses of secretin tumor cell line (STC-1) enteroendocrine cells and their sweet-induced GLP-1 secretion are suppressed by leptin via activation of $K_{ATP}$ channels [22]. Thus, most inhibitory effects of leptin on target cells may rely on activation of $K_{ATP}$ channels. The leptin-$K_{ATP}$ channel pathway may reduce the sweet (glucose or sugars) sensitivity of target cells having orexigenic or energy-storage functions, thereby reducing energy intake and storage to maintain an appropriate energy state for the whole body.

In taste cells, $K_{ATP}$ channels are coupled with glucose transporters (Fig. 2). Although leptin's effects have been investigated only in TAS1R3-positive taste cells [21] and artificial-sweetener-responding taste cells [23], leptin may also affect TAS1R3-negative, glucose transporter-positive taste cells in taste buds [2**], since they also possess $K_{ATP}$ channels. Leptin would inhibit both mixed-type cells and sugar/calorie-sensing cells in

taste buds, thereby regulating food intake and energy homeostasis via signaling pathways to the brain, pancreas, and/or other organs. However, this should be verified by further studies.

Glucose and metabolic sensors for cephalic-phase insulin release (CPIR)

Oral stimulation with food elicits CPIR prior to nutrient absorption, which lasts for 3-6 min and limits hyperglycemia for hours after the meal to maintain glucose homeostasis [24]. Neural pathways for CPIR initiate from food-related sensory inputs that activate parasympathetic neurons in the dorsal motor nucleus of the vagus. The activated efferent fibers terminating in the pancreas enhances insulin secretion via a cholinergic system [25*]. Application of the M3 muscarinic receptor agonist carbachol to murine isolated pancreatic β-cells increases depolarizing waves and insulin secretion in a glucose-dependent manner, including substimulatory glucose concentrations [26-28].

In mice, CPIR is triggered by oral stimulation with glucose and glucose-containing sugars, but not with noncaloric sweeteners, whereas in humans and rats some sweeteners also elicit CPIR [25*]. Recent studies using global knockout mouse models for molecules involved in sweet taste signal transduction demonstrated that $K_{ATP}$ channels play a pivotal role in glucose-mediated CPIR [25*, 29, 30]. TAS1R3, SGLT1, calcium homeostasis modulator 1 (CALHM1) ATP-release channels [31], and P2X2+P2X3 ATP receptors [32] on taste afferent fibers are not necessary for CPIR, since mice with genetic deletions of these molecules, but not deletion of SUR1, a component of $K_{ATP}$, exhibited normal CPIR [29, 30]. Curiously, isolated pancreatic islets of *Tas1r3*$^{-/-}$ [9], *Slc5a1*(SGLT1)$^{-/-}$ [33], and *Abcc8*(SUR1)$^{-/-}$ [34] mice commonly lacked first-phase (2-7 min) and exhibited largely reduced second-phase insulin secretion in response to glucose stimulation. This implies

that decreased glucose-stimulated insulin secretion does not explain the strain differences between *Abcc8*$^{-/-}$ vs *Tas1r3*$^{-/-}$ or *Slc5a1*$^{-/-}$ mice in CPIR triggered before a major glucose rise.

Glucose sensors in taste cells and their selective signaling pathways to the brain/pancreas may be involved in glucose-mediated CPIR. Our recent studies [2**; Yasumatsu et al., unpublished data] suggest that taste cells can take up glucose from the apical membrane via SGLTs and/or GLUTs and may be depolarized by the dual mechanisms of early $Na^+$ entry with glucose and/or later $K_{ATP}$ channel closure by glucose metabolism. The early phase was initiated immediately, and the later phase started ~30 s after stimulation [Yasumatsu et al., unpublished data]. *Slc5a1*$^{-/-}$ mice could use the GLUT pathway for glucose uptake in taste cells, followed by cell depolarization via $K_{ATP}$ closure and signal transmission to the brain/pancreas, which leads to CPIR. *P2rx2*$^{-/-}$*P2rx3*$^{-/-}$ mice are reported to show no residual taste nerve responses to sugars [32] but exhibit clear CPIR [30]. However, nerve response analyses were limited to within 20 s after stimulation [32], which might not fully cover potential later-phase glucose responses via $K_{ATP}$ closure. This should be verified by further studies.

Gut-brain axis for sugar signals

Rodents show a conditioned preference for glucose over fructose. For this conditioning, both orosensory and postingestive signals are required [35, 36]. TAS1R2+TAS1R3 and $K_{ATP}$-dependent mechanisms are not necessary to acquire and express conditioned preference for the orosensory properties of glucose, but olfactory cues contribute [36, 37]. Although still not tested, SGLT- and/or GLUT-dependent taste signals may also be involved in the conditioned preference to glucose. In long-term testing, taste-blind *P2rx2*$^{-}$

*$^{-/-}$P2rx3$^{-/-}$* mice prefer caloric sugars and develop metabolic syndrome, suggesting sugar preference involves postingestive mechanisms [38].

Postingestive signals for glucose may be derived from the gut and transduced via the vagus nerve to the brain. In the intestine, faster (within seconds) neuronal signaling could be accomplished by "neuropod cells" – enteroendocrine cells with glutamatergic excitatory synapses with vagal neurons [39**]. Luminal nutrients such as glucose and sucrose, but not fructose, activate neuropod cells (cholecystokinin-enteroendocrine cells) via SGLT1, leading to glutamate release to induce excitatory postsynaptic potentials in nodose ganglion neurons within 1 s. Indeed, neurons in the nodose ganglion are activated by intestinal infusion of glucose within several seconds, and this is blocked by phlorizin [40]. From nodose ganglion neurons, sugar signals are transmitted to the NST, the parabrachial region, and dopaminergic neurons in the substantia nigra [41], involved in the neural reward pathway, which may be important for developing sugar preference. Although SGLT1 is mentioned as a gut sensor for glucose, some enteroendocrine cells possess TAS1R-dependent mechanisms and $K_{ATP}$ channels [5, 42]. Similar to insulin release from β-cells, interaction among TAS1Rs, glucose transporters, and $K_{ATP}$ channels in enteroendocrine cells may enhance transmitter release, reinforcing sugar signals to the vagus nerve.

## Conclusion

TAS1Rs, glucose transporters, and $K_{ATP}$ channels play critical roles in detecting sugars throughout our body. These mechanisms function solely or cooperatively and are regulated by hormonal and neuronal factors to produce sugar (caloric) signals that are indispensable for maintaining energy homeostasis. Unknown mechanisms and neural

pathways still underlie sugar signaling; however, collectively the evidence suggests the existence of an exquisite system for sugar detection/signaling to regulate energy homeostasis of our body.

Acknowledgments

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By using *Tas1r3*$^{-/-}$ mice and SGLT1 blocker phlorizin, the report demonstrated the existence of 3 types of glucose sensitive fibers in the gustatory nerves. Also, the report showed the glucose entry into some taste cells from the receptor membrane by using fluorescent glucose analog, 2-NBDG, which is blocked by phlorizin and phloretin. Thus, SGLTs and GLUTs are involved in oral detection of glucose.

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The enteroendocrine cells release hormones, which enter the bloodstream and/or activate the vagal nerve minutes to hour after ingesting a meal. This report showed faster (within second) signal transduction from the enteroendocirine cells to nerve fibers. Such enteroendocrine cells named 'neuropod cells' make glutamatergic synapse with vagal nerve fibers, thereby transmit sugar signals in the gut within second to the brain.

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*: special interest

**: outstanding interest

Figure legends

Fig.1. Sugar sensing systems of the tongue and other organs. Glucose transporters (SGLTs, GLUTs) and G-protein coupled receptor TAS1R2+TAS1R3 play key roles in sugar detection in many organ such as the tongue, gut, pancreas and brain. Sugar signals are transmitted to various organs via the nervous system and/or humoral factors and helps maintain energy homeostasis.

Fig.2. Mechanisms for transducing and signaling the presence of sugars and leptin's suppression of sugar responses. The $K_{ATP}$ channel plays key roles in both SGLT/GLUT signaling and leptin signaling. TAS1R2+TAS1R3: taste receptor family 1 members 2 + 3, SGLTs: sodium-glucose cotransporters, GLUTs: glucose transporters, PLCβ2: phospholipase β2, TRPM5: transient receptor potential cation channel subfamily M member 5, Ob-Rb: functional leptin receptor, PI3K: phosphatidylinositol-3 kinase

Fig.1 Yoshida et al.

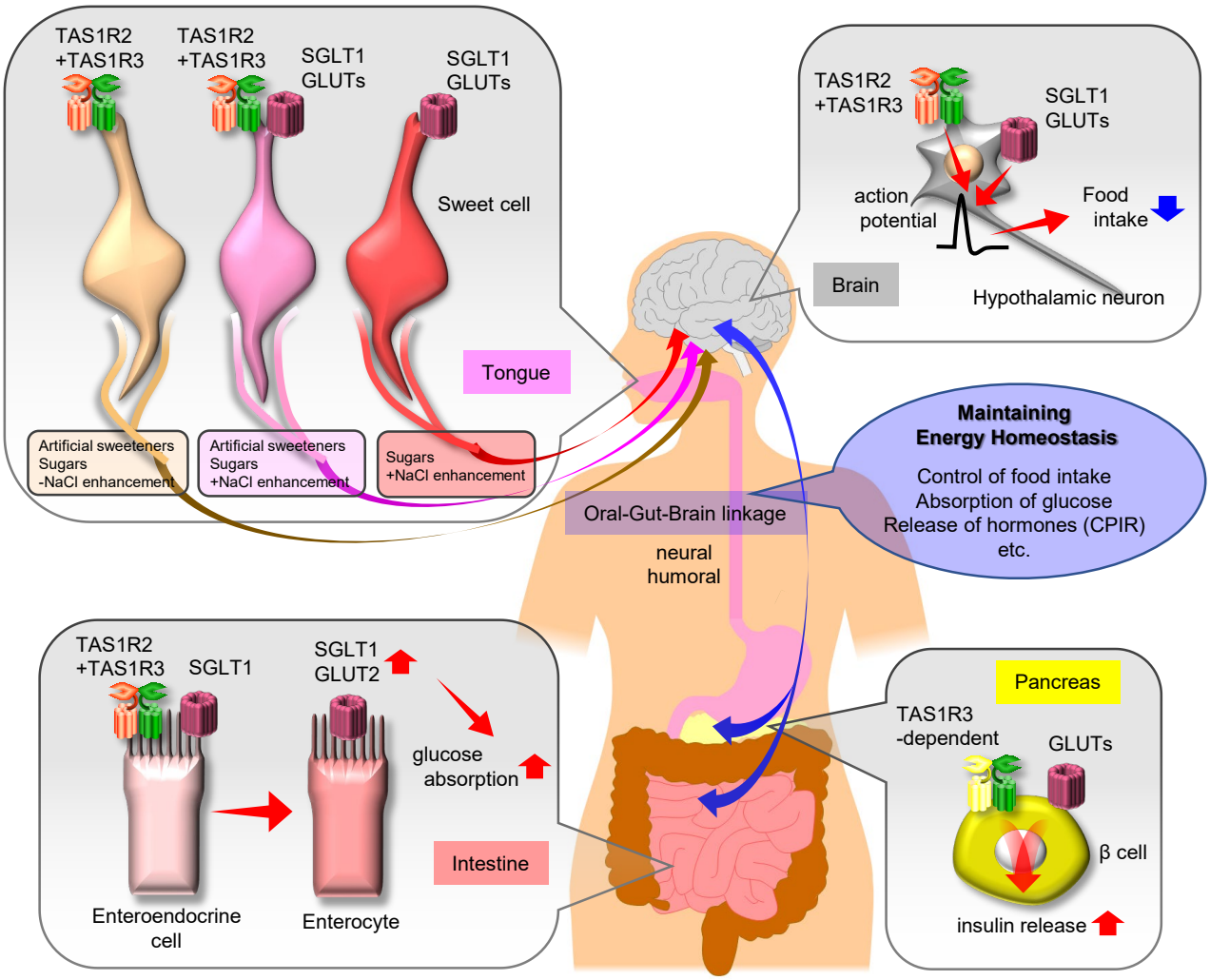


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Fig.2 Yoshida et al.

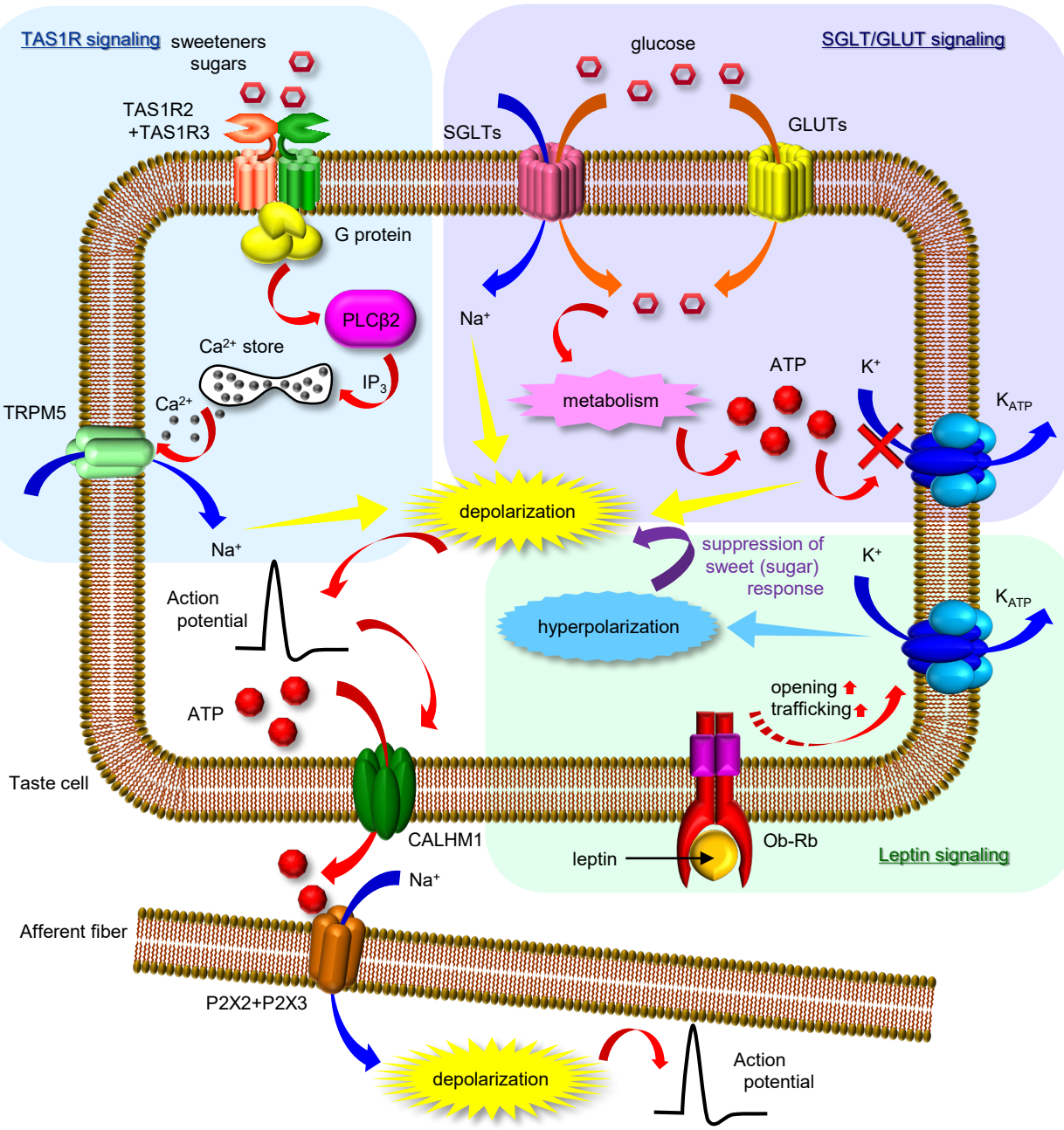


Fig.2. Mechanisms for transducing and signaling the presence of sugars and leptin's suppression of sugar responses.
The $K_{ATP}$ channel plays key roles in both SGLT/GLUT signaling and leptin signaling. T1R2+T1R3: taste receptor family 1 members 2 + 3, SGLTs:sodium-glucose cotransporters, GLUTs: glucose transporters, PLCβ2: phospholipase β2, TRPM5: transient receptor potential cation channel subfamily M member 5, Ob-Rb: functional leptin receptor, PI3K: phosphatidylinositol-3 kinase, CALHM1: calcium homeostasis modulator 1