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Taste of glucose elicits cephalic-phase insulin release in mice

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ABSTRACT

We reported previously that when C57BL/6 (B6) mice ingest glucose, plasma insulin levels rise above baseline before blood glucose levels do so. This observation led us to speculate that the taste of glucose elicits cephalic-phase insulin release (CPIR) in mice. Here, we examined the specific contributions of taste and glucose to CPIR. In Experiment 1, we bypassed the mouth and delivered glucose directly to the stomach. We found that plasma insulin levels did not rise above baseline until after blood glucose levels did so. This revealed that taste stimulation is necessary for rapid insulin release (i.e., CPIR) in mice. In Experiment 2, we examined the observation that sucrose, maltose and Polycose (a maltodextrin) all elicit CPIR. We proposed in a prior study that these carbohydrates did not directly elicit CPIR; instead, they were digested by oral amylases and alpha-glucosidases, and that it was the enzymatically liberated glucose that elicited CPIR. In support of this possibility, we reported that acarbose (an alpha-glucosidase inhibitor) prevented sucrose, maltose and Polycose from eliciting CPIR. Here, we sought to confirm that glucose alone could elicit CPIR in the presence of acarbose. Indeed, we found that glucose alone and glucose + acarbose each elicited equally robust CPIR. Taken together, these results provide further support for the hypothesis that mice possess a glucose-specific taste transduction pathway that triggers rapid insulin release.

1. Introduction

Most studies of the sense of taste focus on its role in identifying foods and motivating consumption [42,57]. Taste serves another essential but less-appreciated role. Together with olfaction, somatosensation and vision, taste activates a panoply of physiological responses (called cephalic-phase responses, or CPRs) which facilitate the digestion, transport, and storage of ingested nutrients [40]. The best-studied CPR is cephalic-phase insulin release (CPIR). It is elicited by taste, olfactory, and tactile input from foods, and markedly reduces the postprandial surge in blood glucose in humans [49], macaques [7], rats [19,28,38] and mice [16]. We illustrate the benefit of CPIR in Fig. 1, where mice were administered the same dose of glucose either orally (via licking) or intragastrically (IG) (via gavage). The figure shows time-dependent changes in plasma insulin and blood glucose relative to baseline. As compared with IG administration, oral administration caused plasma insulin levels to rise more robustly, and glucose to be cleared more rapidly from the blood.

The available evidence indicates that oral sensory input from food activates preganglionic parasympathetic neurons in the dorsal motor nucleus of the vagus (DMNV) in the brainstem [13,14,43]. This input to the DMNV, in turn, activates descending parasympathetic fibers, which release acetylcholine (ACh) onto pancreatic beta cells and induce insulin secretion [5,47,55,59]. What remains to be clarified is the nature of the afferent pathway that triggers CPIR. Here, we focus on the transduction mechanisms in sugar-sensitive taste cells, which mediate the initial stages of taste processing in this afferent pathway in mice.

Sweeteners are generally effective elicitors of CPIR [50], although this idea is disputed in the literature. For example, in humans, there are reports that CPIR is elicited by sugars [56], low calorie sweeteners (LCSs) [6], sugars and LCSs [8,23], sugars but not LCSs [10,20,39] or neither [1,48]. In rats, one study reported that CPIR is elicited by glucose alone [19], whereas others indicated that it is elicited by multiple types of sugar and LCS [4,36,37,50,51]. In mice, we found that CPIR is elicited by glucose and other glucose-containing carbohydrates (sucrose, maltose and a maltodextrin), but not fructose, alpha-methyl-d-glucopyranoside (a non-metabolizable sugar analog) or LCSs (Fig. 2). These inconsistencies likely reflect species differences and disparities in the duration, intensity and method of oral stimulation.

It is commonly assumed that T1r2 + T1r3 is the only sweet taste receptor in mammals [9,57]. If so, then it would follow logically that T1r2 + T1r3 and its associated IP_3 signaling pathway [9,12] mediate CPIR. Two lines of evidence contract this inference. First, mice that are "blind" to sweeteners (i.e., that exhibit no preference for sweeteners over water in brief-access lick tests) still exhibit a normal CPIR to 1 M glucose [15,16]. These mice were rendered "blind" to sweeteners by

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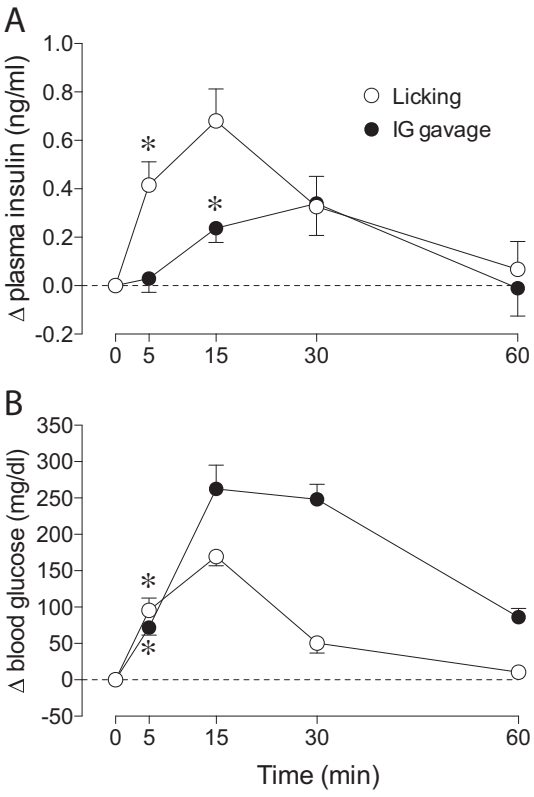

Fig. 1. Changes in (A) plasma insulin levels and (B) blood glucose levels (relative to baseline) over a 60-min period in B6 mice following oral (i.e., licking) or intragastric (IG gavage) administration of 2.8 M (50%) glucose (dosage = 2 mg/g mouse). For oral administration, each mouse took a mass-specific number of licks (4.3/g mouse) for the glucose solution; whereas for IG administration, the same volume of glucose solution was gavaged (e.g., 0.1 ml/25 g mouse). We indicate when plasma insulin and blood glucose levels first rose significantly (*P < 0.01; one-sample *t*-test) above baseline following the glucose challenge, separately for each administration method. Symbols represent mean ± S.E.; N = 6 mice per mouse group and administration technique. These data are from a prior report [16]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

deletion of the gene(s) for components of the sweet taste transduction cascade, including the T1r3 subunit of T1r2 + T1r3, the calcium homeostasis modulator 1 (Calhm1) or the ATP receptor (P2X2 + P2X3). Second, because fructose, glucose, sucrose, maltose and LCSs are all ligands for T1r2 + T1r3 [27,34], they would all be expected to elicit CPIR. However, this is not the case in mice (Fig. 2).

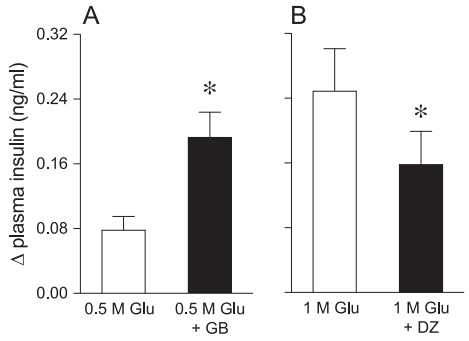

Fig. 3. Oral stimulation with pharmacological agents that either increase (glyburide) or decrease (diazoxide) K_{ATP} channel activity produced corresponding changes in CPIR magnitude. Each test involved two sessions with a given mouse—one session was conducted with a control solution and the other session with an experimental solution. (A) In the glyburide test, the control solution was 0.5 M glucose (Glu) and the experimental solution was 0.5 M glucose + 0.15 mM glyburide (GB). (B) In the diazoxide test, the control solution was 1 M glucose and the experimental solution was 1 M glucose + 0.25 mM diazoxide (DZ). The Δ plasma insulin concentration reflects the change in plasma insulin between measurements obtained at baseline and 5-min after each mouse initiated licking for the experimental or control solution. Each mouse completed 200 licks for a solution during each session. Within a panel, we compare the Δ plasma insulin concentration elicited by the control versus experimental solutions, using a paired *t*-test (*P < 0.03). We show mean ± S.E.; N = 9 mice per panel. These data are from a prior study [15].

There are at least two other potential taste transduction mechanisms for glucose. One is the Na^+/glucose co-transporter 1 (SGLT1), which transports Na^+ ions together with glucose. This produces an intracellular electrogenic signal that increases in proportion to glucose transport [18]. Second, the K_{ATP} channel is part of a glucosensor in pancreatic beta cells [2]. It consists of an inwardly rectifying K^+ channel (Kir6) and a regulatory sulfonylurea receptor (Sur1). Given that both SGLT1 and the K_{ATP} channel are expressed in T1r3-positive taste cells of mice [32,52,58], either mechanism could function as part of a glucose-specific taste transduction pathway. We recently reported several lines of evidence that contradict a role of SGLT1, but support a role of the K_{ATP} channel in CPIR [15]. For example, we demonstrated that Sur1 (but not SGLT1) was necessary for glucose-stimulated CPIR. We also discovered when mice take a mere 200 licks from a solution containing glucose plus pharmacological agents that either increase (glyburide) or decrease (diazoxide) K_{ATP} signaling, they exhibit corresponding changes in glucose-stimulated CPIR (Fig. 3). The fact that such small quantities of glyburide or diazoxide were able to reliably modulate plasma insulin levels within 5 min indicates that they acted selectively on K_{ATP} channels in taste cells.

If the K_{ATP} transduction pathway in taste cells responds selectively

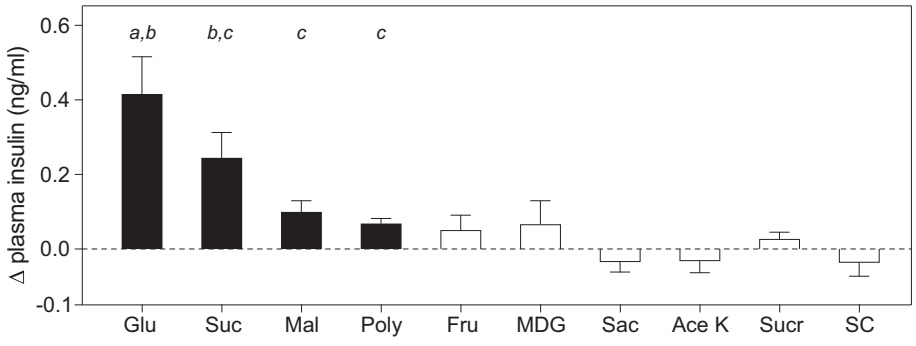

Fig. 2. Some but not all sweeteners elicit CPIR in B6 mice. CPIR was defined as a significant increase in plasma insulin concentration (i.e., Δ plasma insulin concentration) within 5 min of initiating licking for the taste stimulus, based on a one-sample *t*-test (P < 0.05). We use closed bars for taste stimuli that elicited CPIR (i.e., glucose, sucrose, maltose and Polycose), and open bars for taste stimuli that did not elicit CPIR. We compare mean (± S.E.) CPIR magnitude across glucose, sucrose, maltose and Polycose with a Tukey-type multiple comparison test. The means that differ significantly from one another lack a shared letter (i.e., a, b or c) above them (P < 0.05). We use the following abbreviations for each taste stimulus: glucose (Glu), sucrose (Suc), maltose (Mal), Polycose (Poly), fructose (Fru), alpha-methyl-d-glucopyranoside (MDG), saccharin (Sac), acesulfame potassium (Ace K), sucralose (Sucr) and SC45647 (SC). These data are from a prior study [15].