Sweet taste receptor signaling in beta cells mediates fructose-induced potentiation of glucose-stimulated insulin secretion

George A. Kyriazis, Mangala M. Soundarapandian, and Björn Tyrberg
Metabolic Signaling and Disease, Diabetes and Obesity Research Center, Sanford-Burnham Medical Research Institute, Orlando, FL 32827

AUTHOR SUMMARY

The increase in circulating glucose levels that occurs after a meal is the primary stimulus of insulin release from beta cells (i.e., endocrine cells residing in the pancreatic islets of Langerhans). In turn, circulating insulin facilitates glucose clearance, restoring levels of glucose in the blood to premeal levels and preventing further insulin secretion. Although glucose is indispensable for this insulin release, numerous other molecules, including the major dietary sugar fructose, can help stimulate insulin secretion in vitro (1). Here, we describe a pathway for the regulation of postmeal insulin release in which fructose leads to improved glucose-stimulated insulin secretion mediated by sweet taste receptors on the surface of beta cells.

Considering that fructose induces insulin secretion despite the documented poor metabolism of fructose in islets (2), we hypothesized that the effects of fructose on insulin release may be mediated by sweet taste receptors on beta cells. These are molecules on the cell’s surface that bind and respond to sugars and other sweeteners, best known for their role in mediating sweetness in the taste buds of the tongue. The three members of the T1R family of taste receptors form heterodimers (two-part structures) to confer umami (T1R1–T1R3) and sweet (T1R2–T1R3) sensing. Consequently, removal (ablation) of T1R1 or T1R2 will obliterate umami or sweet taste, respectively, whereas removal of T1R3 eliminates both taste responses (3). Therefore, we used mice lacking the T1R2 gene (i.e., T1R2−/− mice) to assess the direct role of sweet taste receptors in the regulation of insulin release.

We found that the in vitro delivery of 10 mM fructose increased insulin release in the presence of 8.3 mM glucose, but not 3.0 mM glucose, in isolated islets from unmutated (i.e., WT), mice, but failed to induce similar effects in T1R2−/− islets. This finding highlights the essential role of sweet taste receptors in fructose-mediated insulin release. It also highlights that fructose has no effect on insulin secretion unless significant levels of glucose are present, suggesting that fructose cannot induce hypoglycemia, a life-threatening condition. We also found that phosphodiesterase C, intracellular calcium, and the ion channel TRPM5 were required for fructose-mediated insulin release, just as they are required for sweet perception in the taste buds.

Interestingly, we found that sweet TRs are also present in human islets. Similar to the case in mouse cells, fructose and saccharin (an artificial sweetener) stimulated insulin release in the presence of a sufficient amount of glucose. To assess the direct role of taste receptors, we used lactisole, a molecule known to specifically inhibit human sweet taste receptors (3). Lactisole, indeed, abolished fructose-induced insulin release in human cells, confirming the significance of taste receptor signaling in human islet function. Our findings in isolated mouse and human islets led us to speculate that postmeal fructose could rapidly and directly induce insulin release via beta cell taste receptors. To address this hypothesis, we used an i.v. dose of fructose (1.0 g/kg) in catheterized, conscious mice and monitored blood glucose and insulin levels. We found that fructose induced an early, transient increase of plasma insulin in WT mice, whereas T1R2−/− mice showed no insulin response. Glucose levels, however, remained unaltered immediately after the injection, suggesting that the rapid increase in plasma insulin in WT mice comes not from changes in blood glucose, but rather from the direct effects of fructose on sweet taste receptors on the beta cells.

During a meal of both glucose and fructose, the two sugars will be proportionally absorbed by the gut, entering the systemic blood circulation simultaneously. We hypothesized that postmeal circulating nutrients, such as fructose, may synergize with glucose to potentiate (i.e., amplify) insulin release. Thus, we assessed whether low levels of fructose, similar to those found in postmeal blood circulation, could potentiate glucose-stimulated insulin secretion. We showed that 3.0 mM fructose was indeed adequate to potentiate insulin release in WT mouse islets, but not in T1R2−/− islets, given that we simultaneously also increased the glucose concentration (Fig. P1A). This low concentration of fructose was, however, ineffective at inducing insulin secretion by itself if glucose was not increased. Similarly, in human islets, low levels


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1To whom correspondence should be addressed. E-mail: btyberg@sanfordburnham.org.

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of fructose also potentiated glucose-stimulated insulin release, which we could block with lactisole. Finally, to test the physiological relevance of fructose-induced potentiation of insulin secretion in vivo, we used a single dose of a low amount of fructose (0.3 g/kg) that had no effect on insulin release by itself, along with glucose (0.5 g/kg). The addition of fructose potentiated insulin release in conscious, catheterized WT mice compared with glucose only (Fig. P1B). Consistent with our in vitro data, these effects were absent in T1R2−/− mice (Fig. P1C). We conclude that sweet TR signaling potentiates glucose-stimulated insulin secretion in mouse and human cells and in mice in vivo.

The mechanism by which fructose stimulates insulin release in the presence of glucose was unknown for decades. Our data, together with previous reports showing that sweet taste receptors in the gut stimulate glucose uptake and GLP-1 secretion (4, 5), suggest a taste receptor-dependent “intestinopancreatic” axis that participates in the regulation of postmeal insulin release by sugars. It is intriguing to speculate that dietary fructose, typically consumed as sucrose (i.e., cane sugar) or high-fructose corn syrup, might target both the gut and pancreatic beta cell taste receptor machineries to establish mechanisms for the regulation of insulin release and glucose delivery to the tissues. Such a scenario requires further investigation, as it may be part of the link between the possible adverse effects of high fructose consumption and metabolic diseases. Given that other similar so-called G protein-coupled receptors are important targets for approved diabetes drugs (exenatide and liraglutide), taste receptors may also have therapeutic potential worth exploring in the future.