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An Absorbing Sense of Sweetness

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COMMENTARY

Over half the insulin we produce after a meal depends on the release of incretin hormones from the gut. Most notable among these are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Indeed, the action of GLP-1 on pancreatic islet cells is responsible for the underlying success of GLP-1 mimetics and dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes (1). Modulating the secretion of GLP-1 from the gut offers an exciting alternative strategy for treating diabetes. Release of gut hormones is the first step in the incretin pathway, and it is triggered when glucose enters the small intestine. Exactly how glucose stimulates GLP-1 secretion has been the topic of hot debate, with contradictions arising from the use of different in vitro model systems and technologies. In this issue of *Diabetes*, Kuhre et al. (2) present an elegant use of an intact perfused rat intestinal model that brings clarification to this controversial field and may help in the development of future antidiabetes therapies that target the gut.

Many years of research have taught us that pancreatic β-cells sense glucose first by using glucokinase to couple glycolysis to the ambient glucose concentration, and then by using ATP-sensitive potassium (K_{ATP}) channels to link electrical activity to the metabolic rate (3). Intestinal L-cells producing GLP-1 differentiate along similar lines to pancreatic β-cells, so it is interesting to ask whether L-cells and β-cells share common glucose-sensing pathways. A number of clinical findings suggest they do not. Sulfonylureas, for example, close K_{ATP} channels in β-cells and increase insulin release, yet they do not mimic the effect of glucose ingestion on GLP-1 levels (4). Human polymorphisms in glucokinase and K_{ATP} channel subunits cause diabetes as a result of impaired insulin release, but they do not correspondingly disturb plasma incretin concentrations (5,6). These findings suggest that L-cells use a different sensor for detecting glucose.

Researchers have identified two alternative glucose-sensing pathways that might operate in gut endocrine cells. Some findings suggest that gut endocrine cells can be viewed as modified taste cells, using the same sweet taste machinery as that found in the tongue, which recognizes artificial sweeteners as well as natural sugars (7). A second line of evidence supports the view that L-cells detect the rate of glucose absorption by sodium-coupled glucose transporters (i.e., sodium-glucose cotransporter 1 [SGLT1]) by utilizing the entry of positively charged sodium ions to modulate L-cell electrical activity and secretion (8,9). In Kuhre et al. (2), perfused intestine experiments assessed the validity of each of these pathways by using a model system in which the intestine retains its natural anatomical integrity.

Kuhre et al. perfused the upper small intestine of the rat via the vasculature as well as the gut lumen and measured GLP-1 every minute in the portal effluent. These experiments showed that the addition of glucose to the luminal perfusate resulted in a rapid increase in GLP-1 release that mirrored the effect of glucose ingestion on plasma GLP-1 levels in humans. Importantly, the ileum and colon were tied off and removed at the start of the experiments, ensuring that the observed GLP-1 excursions arose from L-cells within the duodenum and jejunum.

Having established the responsiveness of the model to glucose, Kuhre et al. then applied alternative stimuli to the gut lumen. Sucralose and acesulfame K targeted sweet taste machinery, and methyl-α-D-glucopyranoside (α-MGP) was used as an alternative substrate of SGLT1. In these experiments, α-MGP mimicked the action of glucose, triggering a robust elevation of GLP-1, whereas no effect was observed with the artificial sweeteners. Pharmacological interrogation of the transport pathway using the SGLT1 inhibitor phloridzin abolished responses to both glucose and α-MGP. These findings support the idea that SGLT1 acts as a glucose sensor in the initiation of GLP-1 release and do not support a direct role for sweet taste receptors in L-cells. In humans, a similar absence of effect of artificial sweeteners on GLP-1 and GIP levels has been observed (10).

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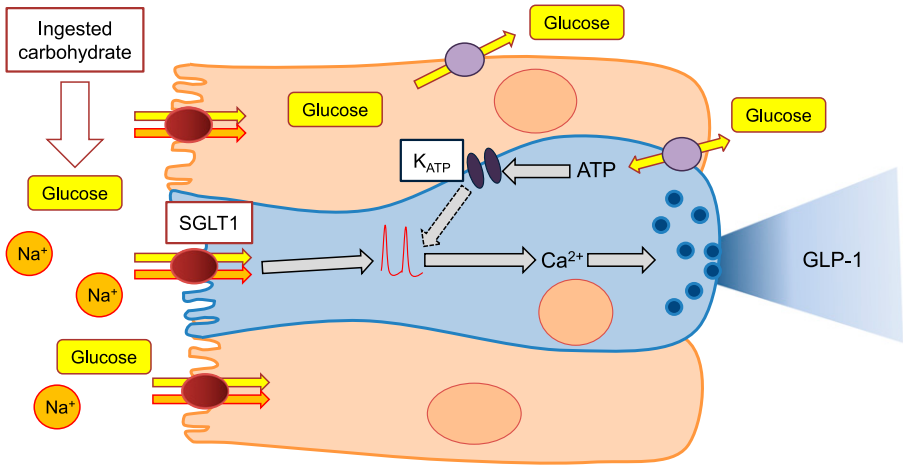

Figure 1—SGLT1 is responsible for glucose absorption across the small intestinal brush border, and on the apical membrane of L-cells, it acts as the primary sensor of ingested glucose, triggering electrical activity and GLP-1 secretion. K_{ATP} channels modulate some control over GLP-1 release but are not responsible for peak postprandial GLP-1 levels.

Historically, the role of metabolism and K_{ATP} channels in L-cells has been difficult to establish using in vitro systems. The results of Kuhre et al. have addressed this gap by showing that blocking K_{ATP} channels with sulfonylureas led to enhanced GLP-1 release, whereas opening the channels with diazoxide suppressed secretion. In this respect, L-cells resemble pancreatic β-cells. The intriguing findings leave us with a dilemma: Given that glucokinase and K_{ATP} channels are highly expressed in L-cells (11), and sulfonylureas triggered GLP-1 secretion in the perfused rat intestine, why have no effects of sulfonylureas on GLP-1 levels been observed in human studies? A simple answer may be that SGLT1 activity, not K_{ATP} channel closure, dominates peak GLP-1 responses to ingested carbohydrate. However, K_{ATP} channels might regulate the background electrical tone in L-cells, thereby modulating their responsiveness to other stimuli. Whereas SGLT1 wins out in the short term, the effects of sulfonylureas might become evident after a meal when peak glucose-triggered GLP-1 levels have subsided.

One fascinating take-home message from these findings is that the body uses different glucose sensors in different tissues to match ambient glucose levels. In healthy β-cells, the use of glucokinase as a link between metabolic rate and glucose concentration regulates insulin secretion over a glucose range that is high enough to protect us from neuroglycopenia but not so high that we experience long-term complications related to hyperglycemia. L-cells, by contrast, have hijacked SGLT1—the intestinal brush-border glucose absorption machinery—to act as their primary glucose sensor. GLP-1 secretion thereby mirrors the rate of glucose absorption from the gastrointestinal tract—sending a perfectly matched signal to the β-cell that it is time to step up the rate of insulin secretion to compensate for the imminent glucose load (Fig. 1).

Clinical data emerging from people treated with therapeutic SGLT2 and combined SGLT1/2 inhibitors may prove decisive in our understanding of the role of SGLT1 in human physiology. Early results, including those from animal models, have suggested that SGLT1 inhibition impairs early peaks of GLP-1 and GIP secretion and slows glucose absorption in the upper small intestine (9). The consequence, however, is the delivery of large nutrient loads to the lower gastrointestinal tract, recruitment of the large reserve of distal L-cells, and a delayed but exaggerated peak in GLP-1 release (12,13). In some ways, these consequences resemble the effects of gastric bypass surgery, which also results in enhanced nutrient delivery to the jejunum and ileum as well as increased GLP-1 secretion (14). Modulating rates of nutrient absorption to achieve an optimal balance between glucose excursions, gut hormone release, and insulin secretion is an exciting prospect for the design of new antidiabetes therapies.

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