

# A Break in the Brake Mechanism in Diabetes

## A cause of postprandial hyperglycemia

The importance of insulin and glucagon as fine regulators of glycemic excursions is well established (1). Alterations in gastric emptying are generally not considered important contributors to postprandial hyperglycemia until late complications of diabetes such as gastroparesis have occurred (2,3). It is now emerging that the rate of gastric emptying may be a major determinant of postprandial glycemic excursions in healthy subjects, as well as in type 1 and type 2 diabetic patients (4).

Gastroparesis is a relatively rare complication that occurs late in diabetes because of irreversible intestinal nerve damage (4); it must be distinguished from the physiological inhibitory effects of acute hyperglycemia on gastric motility (5,6). The latter has been proposed as a defense mechanism existing to minimize postprandial hyperglycemia by reducing the rate of efflux of glucose into the circulation from the gut (7). This may be of special importance for people with type 1 diabetes who have a reduced ability to delay gastric emptying in response to hyperglycemia (8). Cross-sectional studies suggest that an inverse relationship between the rate of gastric emptying and blood glucose concentration also exists in type 2 diabetic patients (4) and, thus, that similar regulatory mechanisms may exist in both conditions.

### Regulation of gastric emptying

**Extrinsic pathway.** Normally, the rate of gastric emptying is tightly regulated as a result of neural and hormonal feedback triggered by the interaction of nutrients within the small intestine known as the ileal brake mechanism or “extrinsic pathway” of control. This feedback is caloric-load dependent, relates to the length of small intestine exposed to nutrient, and regulates the overall rate of emptying to about 2–3 kcal/min (9,10). When food reaches the intestine, L- and K-cells in the distal small bowel are stimulated to produce glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic

peptide (GIP), respectively, both of which exert their effects on different targets (11). In the brain, they act on the hypothalamus, reducing appetite; they also send signals via cholinergic and peptidergic neurotransmission in the vagus nerve directly to the stomach, inhibiting antral motility and stimulating pyloric motility, both of which contribute to inhibition of gastric emptying (12). GLP-1 and GIP stimulate glucose-dependent insulin release from pancreatic islet  $\beta$ -cells, as well as human islet amyloid pancreatic peptide (hIAPP), and simultaneously inhibit glucagon secretion from pancreatic  $\alpha$ -cells. Insulin plays a role in the reduction of food intake through an action in the satiety center in the hypothalamus, whereas hIAPP slows gastric emptying, an action mediated by the central nervous system requiring an intact vagus nerve and area postrema (13). In contrast, nitric oxide (NO) is an important neurotransmitter in the gut and has been demonstrated to be a key physiological mediator of nonadrenergic noncholinergic (NANC) relaxation of gastrointestinal smooth muscle (14) of the stomach, pylorus, and the duodenum, thereby facilitating gastric emptying by partially inhibiting pyloric and proximal duodenal contractions (15). The final outcome on the rate of gastric emptying and the prevention of postprandial hyperglycemia is clearly dictated by a delicate balance between these opposing forces.

**Intrinsic pathway.** The intrinsic pathway is dependent upon the action of hyper- or hypoglycemia on gastric emptying. Hyperglycemia stimulates secretion of insulin and hIAPP and inhibits the secretion of glucagon from the pancreas and ghrelin from the stomach (16). The increase in hIAPP and decrease in ghrelin both slow the gastric emptying rate by producing a parasympathetic signal (17). Ghrelin secretion is stimulated by cholecystokinin and gastrin, and it in turn enhances antropyloric coordination, a signal transmitted via the vagus nerve (18), which acceler-

ates gastric emptying (19). Ghrelin, in addition, acts on the satiety center in the hypothalamus to enhance food intake (20). Hypo- and hyperglycemia can act directly in the hypothalamus, increasing or decreasing appetite respectively (21), but they also activate the parasympathetic system and send signals to increase (hypoglycemia) (22) or decrease (hyperglycemia) (23) the gastric emptying rate.

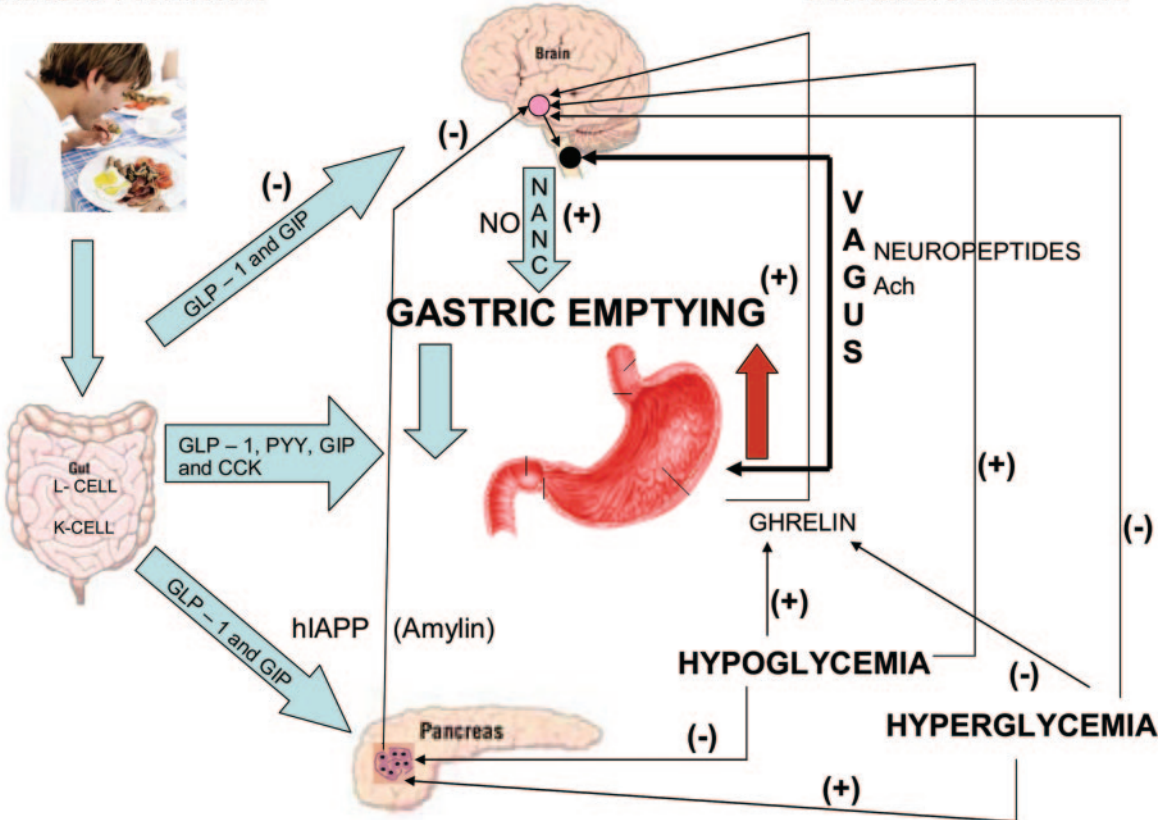
### Regulation of gastric emptying in diabetes

Before the advent of autonomic neuropathy, rapid gastric emptying is seen in subgroups of patients in the early stages of non-insulin-dependent diabetes (type 2 diabetes), and neuropathy-free, insulin-dependent diabetes (type 1 diabetes) (19). Solid gastric emptying is accelerated in obese type 2 diabetic patients without overt autonomic neuropathy when compared with obese nondiabetic patients (24). In diabetes, there is impaired meal-induced relaxation of the gastric fundus, increased pyloric motor activity, fewer antral contractions, and impaired antroduodenal coordination. Disturbances of the gastric electrical rhythm, measured by electrogastrography, also occur frequently (9). Hence, the extrinsic ileal brake mechanism may be impaired in diabetes.

In this issue, Woerle et al. (25) examine the intrinsic brake mechanism and report that slowing of gastric emptying by hyperglycemia may be impaired in patients with type 1 diabetes. In this study, consequences of euglycemia- and hyperglycemia-induced changes in gastric emptying on postprandial glucose fluxes and excursions were seen in 10 healthy subjects and 15 type 1 diabetic subjects after ingestion of a mixed meal using the double isotope approach ( $[6,6-^2\text{H}_2]$  and  $[1-^{13}\text{C}]$  glucose) and scintigraphic measurements of gastric emptying. It was found that gastric emptying was greater in type 1 diabetic subjects

# EXTRINSIC PATHWAY

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**Figure 1**—Regulation of gastric emptying.

than in healthy subjects. Hyperglycemia markedly delayed gastric emptying in healthy subjects but did not alter it in type 1 diabetic subjects. Plasma IAPP increased approximately fourfold in healthy subjects, whereas it was undetectable in type 1 diabetic subjects. IAPP replacement using the analogue of IAPP, pramlintide, in type 1 diabetic subjects slowed gastric emptying to a comparable extent—as did hyperglycemia in healthy subjects—and greatly reduced postprandial hyperglycemia. Meal-derived glucose appearance in plasma was reduced and splanchnic glucose sequestration increased.

Woerle et al. concluded that in patients with type 1 diabetes, the ability to delay gastric emptying in response to hyperglycemia is impaired. This impairment contributes to exaggerated rates of meal-derived glucose appearance and, ultimately, postprandial glucose excursions.

The pancreatic  $\beta$ -cell hormone hIAPP is cosecreted with insulin in a fixed molar ratio (26) and has potent inhibitory effects on gastric emptying (27). Thus, patients with type 1 diabetes, even if they are without concomitant enteric neuropathy, should have increased rather than de-

layed rates of gastric emptying because they are hIAPP deficient (28). This may also apply in type 2 diabetes, wherein secretion of hIAPP is impaired before insulin secretion (29).

Hyperglycemia has been reported to cause profound inhibition of vagal activity accompanied by substantial hIAPP secretion (30). In contrast, in IAPP-deficient patients with type 1 diabetes, hyperglycemia did not affect vagal activity (8). Because the inhibitory effect of IAPP on gastric emptying seems to be mediated via inhibition of vagal nerve activity (30), the observations of Woerle et al. are consistent with the concept that a hyperglycemia-induced delay in gastric emptying may be at least partially regulated via an IAPP-mediated inhibitory effect on vagal nerve activity (27).

Teleologically, the slowing of gastric emptying during hyperglycemia can be seen as an important defense mechanism preventing hyperglycemia. hIAPP secretion is linked to insulin release (26). As a response to hyperglycemia, the pancreatic  $\beta$ -cell, with its glucose sensor, increases insulin and IAPP secretion. Insulin suppresses hepatic glucose output

and increases peripheral glucose uptake (31).

Taking this into consideration, hIAPP deficiency may be seen as one cause for the unresponsiveness to delayed gastric emptying. To prove that IAPP deficiency is the sole reason for unresponsiveness to a hyperglycemia-induced delay in gastric emptying, direct inhibition of the IAPP effects using a specific antagonist would be required to fulfill Koch's postulates.

As indicated above, there are other candidates for the regulator role of the brake mechanisms. Ghrelin levels rise in the circulation before and decrease after a meal (32). The postprandial suppression of ghrelin levels 30–60 min after a meal were significantly lower in obese patients than in normal-weight patients. Plasma ghrelin levels are, hence, elevated in diabetes. Elevated endogenous ghrelin enhances antropyloric coordination, which accelerates gastric emptying in the early stages of diabetes (19). This, together with the role of NO as an accelerator of gastric emptying, suggests that defining the complexity of loss of the brake mechanism will require studies with combinations of agents or at least control of their

levels that also manipulate the dose of administered hIAPP.

In addition to the above candidates, GLP-1 inhibits gastric emptying (33). Its secretion, however, is stimulated by the intestinal nutrient content and flow rather than by plasma glucose concentrations themselves (34). Insulin and GLP1 secretion in diabetes are impaired, and this could also contribute to loss of the brake mechanism (36). Insulin itself may be another regulator of gastric emptying in healthy subjects (36); however, the effects of hyperinsulinemia on gastric emptying were found to be marginal (36).

Taken together, these studies highlight the importance of a delay in gastric emptying response to hyperglycemia to minimizing postprandial glucose excursions, a defense mechanism not operative in patients with type 1 and 2 diabetes that may be at least partially explained by hIAPP (27) and/or GLP1 deficiency (32) or impaired suppression of ghrelin (18). Perhaps a more sobering thought is what would transpire if pramlintide or exenatide were given to patients with autonomic nerve dysfunction with reduction in vagal activity. Would this lead to obstruction and bezoar formation, or would the loss of vagal function be a failsafe device on which the actions of hIAPP and GLP1 to slow gastric emptying are lost? According to a case study report, a patient with type 1 diabetes and long-term complications (retinopathy, neuropathy, and end-stage renal disease) who had undergone a recent islet-after-kidney transplant and was put on exenatide for improving glycemic control developed severe gastroparesis and food content bezoar 11 months later. Exenatide was stopped and restarted after removing the bezoar endoscopically, but this was followed by recurrence of gastrointestinal symptoms and another gastric bezoar. Exenatide was discontinued, and the patient's condition remained stable after intrapyloric botulinum injection (37).

Clearly, this is a very complex arena, and further studies on the effects of inhibition of hIAPP (if and when an antagonist becomes available) and the impact of autonomic dysfunction might serve to resolve some of these issues. Whatever the case, the authors have shed new light on the role of hyperglycemia per se on vagal function and the implications of hIAPP deficiency on the brittle diabetes control of the patient with type 1 diabetes. We can only conjecture now on what the impact of a loss in the

brake mechanism would mean to the action of hIAPP in diabetes (26).

One caveat is that the slowing of gastric emptying seems to be of cardinal importance in regulating postprandial glycemia. However, there is another side to the coin. The presence of autonomic neuropathy slows gastric emptying and, thus, the use of agents that embrace this mechanism are fraught with the possibility of causing complications like obstruction and gastric bezoar formation. We therefore conclude that if there is no break in the brake mechanism, don't fix it. Beware of overzealous attempts to slow gastric emptying when the mechanism is broken.

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