EDITORIAL (SEE PENNANT ET AL., P. 2183)

Prandial Insulin and the Systemic Appearance of Meal-Derived Glucose in People With Type 1 Diabetes

The rate of appearance of meal-derived glucose is determined by a variety of factors. Ingested complex carbohydrates require enzymatic digestion into monosaccharides before absorption. Although this step per se is not rate limiting, the rate of gastric emptying and orocecal transit time may affect the rapidity with which such carbohydrates are exposed to the appropriate digestive enzymes (1). The resulting monosaccharides are then transported into the enterocyte and then into the portal vein where, ultimately, a fraction is extracted by the liver. The remainder is released into systemic circulation via the hepatic venous system. Hepatic extraction of meal-derived glucose is largely dependent on the prevailing glucose and, to a lesser extent, insulin concentrations.

Intriguingly, in this issue of *Diabetes Care*, Pennant et al. (2) report that the rate of meal-derived glucose appearance in people with type 1 diabetes is unchanged by administration of prandial insulin 20 min before meal ingestion. This is a finding that at face value might have profound implications for affected patients treated with intensive insulin therapy.

There is limited information on splanchnic extraction in type 1 diabetes. Nuclear magnetic resonance spectroscopy has demonstrated that in people with poorly controlled type 1 diabetes, glycogen synthesis is markedly impaired after ingestion of a mixed meal (3). On the other hand, a similar series of experiments under hyperinsulinemic-euglycemic conditions concluded that there was no difference in hepatic glycogen synthesis between people with well-controlled type 1 diabetes and healthy control subjects (4).

The applicability of these experiments to the splanchnic extraction of enterally delivered glucose is uncertain. However, in a series of experiments designed to determine whether splanchnic glucose metabolism is altered in people with type 1 diabetes, we used a dual-tracer approach to measure splanchnic extraction of intraduodenally infused glucose. In addition, flux through the uridyldiphospho-glucose pool (an index of hepatic glycogen synthesis) was measured using the acetaminophen glucuronide method (5) in type 1 diabetic and nondiabetic subjects. Portal venous hormone concentrations were kept constant and equal in both groups by using somatostatin and replacement amounts of glucagon. Insulin concentrations were increased to ~550 pmol/l, whereas glucose concentrations were clamped at ~8.5 mmol/l by means of a supplemental intravenous glucose infusion (6).

In this situation, wherein glucose, insulin, and glucagon concentrations in people with type 1 diabetes are matched to those in healthy control subjects, initial splanchnic glucose extraction, uridyldiphospho-glucose flux, and total body glucose disappearance do not differ in diabetic and nondiabetic subjects during enteral glucose administration. These data imply that relative insulin deficiency and/or glucagon excess, rather than an intrinsic defect in splanchnic glucose metabolism, are the primary causes of postprandial hyperglycemia in people with poorly controlled type 1 diabetes. Of note is the fact that insulin concentrations were far higher than those present in the current study.

Basal-bolus insulin regimens have become the cornerstone of therapy for people with type 1 diabetes in part because of their effectiveness in mimicking normal postprandial insulin secretion, and thereby achieving good glycemic control, while avoiding the hypoglycemia that inevitably accompanied simpler insulin regimens (7). The pattern of postprandial insulin secretion and the prevailing degree of insulin action (defined as the ability of insulin to stimulate glucose uptake and suppress endogenous glucose production) interact to alter postprandial glycemic excursion (8). Similar to what is observed in the current study, an appropriate rise in postprandial insulin concentrations led to higher peak glucose concentrations and increased glycemic excursion. To a certain extent, these differences were attributable to increased suppression of endogenous glucose production (as observed in the study by Pennant et al. when an insulin bolus was administered preprandially), at least over the first 180 min after meal ingestion (2).

Absence of meal-induced suppression of glucagon secretion is also a potential contributor to postprandial glucose concentrations in situations wherein the postprandial rise in insulin is delayed and decreased or absent (9). Unfortunately, in the current study we are unable to determine if glucagon concentrations differed between study days and perhaps contributed to the observed differences in postprandial glucose concentrations.

Another consideration when examining the systemic appearance of meal-derived glucose is the methodology used to measure this parameter. The dual-isotope method pioneered by Steele et al. (10) enabled simultaneous measurement of both the systemic rate of appearance of ingested glucose ($R_{a\ meal}$) and postprandial endogenous glucose production. This method utilizes an infused and an ingested tracer to trace glucose fluxes. The appearance of ingested glucose is calculated by multiplying the rate of appearance of the ingested tracer by the tracer-to-tracee ratio of the ingested meal. Initial splanchnic glucose uptake can be calculated by subtracting the portion of the ingested glucose that reaches the circulation from the total amount of glucose ingested. Endogenous glucose production is calculated by subtracting $R_{a\ meal}$ from the total glucose appearance. Although the model-calculated appearance of glucose is reliable in a steady state, it is inaccurate when the ratio of tracer to tracee changes from infinity during the first 15–30 min after meal ingestion.

This experimental approach has been used by a large number of investigators to study postprandial glucose metabolism in a wide variety of species. However, results have been inconsistent. Estimates of initial splanchnic glucose uptake made by this method have varied widely, as has the pattern of endogenous glucose pro-

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duction, which has ranged from rapid near-complete suppression to an initial paradoxical rise followed by a subsequent fall in endogenous glucose production (11). These discrepancies are likely to arise from inadequacies of the model used to calculate turnover in the rapidly changing conditions occurring after carbohydrate ingestion.

In an effort to overcome the marked changes in the ratio of glucose to tracer concentrations that occur after meal ingestion, we developed and validated a novel triple-tracer approach to minimize changes in both meal and endogenous plasma tracer-to-tracee ratios, thereby allowing simultaneous measurement of $R_{a\ meal}$ and endogenous glucose production. We minimized changes in plasma ratios of infused and ingested tracers by infusing [6-^{3}H]-glucose in a manner anticipated to mimic the systemic R_a of the [1-^{13}C]-glucose contained in a mixed meal. At the same time, [6,6-$^{2}H_2$]-glucose was infused in a pattern that mimicked the anticipated pattern of change of endogenous glucose production after meal ingestion (12).

This approach is virtually model independent, yielding essentially the same results when interpreted using steady state or nonsteady state assumptions and either a one- or two-compartment model (13). As emphasized by Pennant et al. (2), in comparison, a dual-tracer approach underestimates systemic glucose appearance by 16%. This systematic underestimation of meal glucose appearance may potentially miss a small effect of prandial insulin on $R_{a\ meal}$. Another consideration when designing experiments is the sample size necessary to detect a significant change in $R_{a\ meal}$. Given the degree of variance in $R_{a\ meal}$ observed in this experiment and, indeed, in other experiments using a triple-tracer design (14), eight subjects would be too small a sample size to reliably detect a 20% change in $R_{a\ meal}$, let alone a subtler magnitude of change produced by prandial insulin.

When analyzing the results of this study, it is important to keep sight of the fact that prandial insulin administration dramatically decreases postprandial glycemic excursion. Although this study does not completely exclude the possibility that a basal-bolus insulin regimen improves postprandial glycemic control in part by altering $R_{a\ meal}$ as a consequence of increased splanchnic extraction of meal-derived glucose, it reemphasizes the importance of suppression of endogenous glucose production in decreasing postprandial glucose concentrations.

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