OBSERVATIONS

Effects of Proximal Gut Bypass on Glucose Tolerance and Insulin Sensitivity in Humans

Roux-en-Y gastric bypass (RYGB) surgery produces a significant improvement in glucose metabolism prior to substantial weight loss; this is proposed to result from an enhanced incretin effect secondary to bypass of the duodenum and proximal jejunum. However, the caloric restriction that occurs early after surgery also has beneficial metabolic effects. To dissect the contribution of nutrient bypass of the proximal gut to improved glucose tolerance after RYGB surgery from caloric restriction, we induced a "non-surgical, proximal gut bypass" by directly administering a glucose load to the jejunum via a nasally inserted feeding tube.

We studied 10 obese participants (BMI = 41.3 ± 7.4 kg/m^2; 36 ± 9 years; 60% female; HbA_{1c} = 5.5 ± 0.5%) on two occasions. At each visit, a 50-g glucose load was administered to either the stomach or proximal jejunum in random order. Blood was sampled −10, 0, 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, and 180 min relative to glucose administration. The following day, plasma glucose excursions from the enteral glucose load were replicated with isoglycemic intravenous glucose infusions. Data were compared with Wilcoxon signed rank tests.

Jejunal delivery of glucose produced a left-shift in the glucose curve relative to gastric delivery with a faster time to peak glucose levels (~Δ20 min, $P = 0.008$) and lower plasma glucose levels at 120 min (94 vs. 128 mg/dL, $P = 0.01$). The plasma glucose peak level and incremental area under the curve (iAUC) were not different between delivery routes ($P \geq 0.17$). By comparing the amount of intravenous glucose required to match the plasma glucose curves from the gastric and jejunal delivery routes (1), we determined that the gastrointestinal (GI) tract accounted for 19% of glucose disposal after gastric glucose delivery and increased ~twofold to 40% with jejunal delivery ($P = 0.01$). These data suggest that direct delivery of glucose to the jejunum increases the contribution of the splanchnic bed (consisting of the GI tract, mesenteric fat, and liver) to glucose disposal.

The GI incretin hormones, glucagon-like peptide 1 and gastric inhibitory peptide, contribute to glucose disposal by enhancing insulin secretion. Peak levels of both incretins were increased with jejunal compared with gastric delivery of glucose (intact glucagon-like peptide 1, 316 vs. 54 pg/mL, $P = 0.005$; gastric inhibitory peptide, 236 vs. 171 pg/mL, $P = 0.02$). The peak insulin response to jejunal glucose delivery was faster (~Δ20 min, $P = 0.04$) and higher (220 vs. 134 μU/mL, $P = 0.005$) than gastric glucose delivery. The insulin incremental area under the curve was also increased after jejunal glucose administration ($P = 0.04$). The incretin effect on insulin secretion (2) was increased ~20% with jejunal compared with gastric delivery (54 vs. 32%, $P = 0.02$). Model-derived indices of insulin sensitivity (3,4) were not different between gastric and jejunal delivery of glucose ($P \geq 0.37$).

Our data indicate that a single, direct glucose administration to the proximal jejunum is sufficient to potentiate the entero-insular axis and alter glucose homeostasis without alterations in insulin sensitivity. This suggests that the enhanced glucose tolerance and incretin effect that occur after RYGB surgery can be attributed to increased glucose utilization by the splanchnic tissue resulting from the bypass of nutrient exposure to the proximal gut and not to caloric restriction or weight loss.

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