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Ileal interposition improves glucose tolerance and insulin sensitivity in the obese Zucker rat

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Culnan DM, Albaugh V, Sun M, Lynch CJ, Lang CH, Cooney RN. Ileal interposition improves glucose tolerance and insulin sensitivity in the obese Zucker rat. Am J Physiol Gastrointest Liver Physiol 299: G751–G760, 2010. First published July 15, 2010; doi:10.1152/ajpgi.00525.2009.—The hindgut hypothesis posits improvements in glucose homeostasis after the IT procedure. In the present study, we investigated the effect of ileal interposition (IT), surgically relocating a segment of distal ileum to the proximal jejunum, on glucose tolerance, insulin sensitivity, and glucose transport in the obese Zucker rat. Two groups of obese Zucker rats were studied: IT and sham surgery ad libitum fed (controls). Changes in food intake, body weight and composition, glucose tolerance, insulin sensitivity and tissue glucose uptake, and insulin signaling as well as plasma concentrations of glucagon-like peptide-1 and glucose-dependent insulino tropic peptide were measured. The IT procedure did not significantly alter food intake, body weight, or composition. Obese Zucker rats demonstrated improved glucose tolerance 3 wk after IT compared with the control group (P < 0.05). Euglycemic, hyperinsulinemic clamp and 1-[14C]-2-deoxyglucose tracer studies indicate that IT improves whole body glucose disposal, insulin-stimulated glucose uptake, and the ratio of phospho- to total Akt (P < 0.01 vs. control) in striated muscle. After oral glucose, the plasma concentration of glucagon-like peptide-1 was increased, whereas GIP was decreased following IT. Enhanced nutrient delivery to the ileum after IT improves glucose tolerance, insulin sensitivity and muscle glucose uptake without altering food intake, body weight, or composition. These findings support the concept that anatomic and endocrine alterations in gut function play a role in the improvements in glucose homeostasis after the IT procedure.

Obesity in the ZR is an autosomal recessive trait (fa/fa) caused by defective leptin receptors. Heterozygous lean ZRs are normal, whereas the homozygous obese ZR develops progressive insulin resistance, glucose intolerance, hyperlipidemia, and hypertension (15). The obese ZR has been used extensively to study obesity-related insulin resistance and is therefore an excellent model for investigating how IT improves glucose homeostasis (4). In the ZR model peripheral insulin resistance is characterized by moderately elevated circulating glucose levels, hyperinsulinemia, abnormal glucose tolerance, and increased pancreatic β-cell mass (15). Insulin resistance in this model is due to defective insulin signaling, minor reductions in basal insulin-sensitive glucose transporter (GLUT-4) expression, and defective insulin-stimulated GLUT-4 membrane translocation (3, 27).

Alterations in the secretion or activity of enteric hormones have been implicated in the resolution of T2DM after RYGB surgery (1, 11). Incretins are peptides secreted by the gut that augment insulin secretion and glycemic control in response to oral (vs. intravenous) glucose, protein, and fat intake (1). Glucose-dependent insulino tropic peptide (GIP) is secreted by K cells in the duodenum and jejunum whereas glucagon-like peptide-1 (GLP-1) is secreted by L cells in the distal small bowel and colon (1). Both GIP and GLP-1 bind specific receptors on pancreatic β-cells to increase islet cell mass and stimulate insulin secretion (1). Extrapancreatic effects of GLP-1 include the stimulation of glucose metabolism in liver and muscle (23, 33). GIP levels are not altered in T2DM, but reductions in β-cell GIP receptors and postreceptor defects in GIP signaling have been identified (17). Impaired GLP-1 release and action have also been reported in T2DM (12). Thus alterations in incretin synthesis or activity represent a potential...