



Is Bariatric Surgery Brain Surgery?

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Roux-en-Y gastric bypass (RYGB) reliably produces sustained weight losses, reduces circulating blood glucose, and lowers risk of type 2 diabetes (1). Accompanying these benefits, however, is symptomatic hypoglycemia, reported by up to one-third of post-bariatric surgery patients (2,3). In an estimated <1% of RYGB patients (4), postprandial hyperinsulinemic hypoglycemia causes severe symptoms including neuroglycopenia with significant morbidity. New mechanistic insights and treatment options for these patients are needed. Potential contributors include rapid glucose delivery into the bloodstream, improved β -cell function, and gut adaptations, but the role of the central nervous system (CNS) is an important and underdeveloped area of research (3). In their article in this issue of *Diabetes*, Almby et al. (5) investigate whether RYGB alters the brain response to hypoglycemia in humans—a topic with further relevance to the CNS contribution to RYGB's modification of overall glucose homeostasis.

Human neuroimaging studies document RYGB-induced changes in brain function and suggest reversibility of obesity-associated findings (6–8). Studies of cerebral metabolism measuring [18 F]-fluorodeoxyglucose uptake by positron emission tomography (FDG-PET) show that brain glucose uptake is elevated in participants with obesity and partially reversed post-RYGB (6,7), but controlled studies of the cerebral metabolic response to insulin-induced hypoglycemia are lacking. Cerebral blood flow response to insulin-induced hypoglycemia assessed by arterial spin labeling (ASL) showed increased regional blood flow (vs. euglycemia) in the cortex, thalamus (9), and hypothalamus (10) in healthy adults. Almby et al. provide novel data on the effect of RYGB on brain response to hypoglycemia (5).

Almby et al. included 11 participants that underwent, before and 4 months after RYGB, a comprehensive assessment of brain glucose metabolism and function, cognitive performance, and hormonal responses during a two-stage, normo- and hypoglycemic hyperinsulinemic clamp (5). During normoglycemia, global tracer influx rate (K_i) and

estimated total brain glucose uptake (MR_{glu}) by FDG-PET decreased postoperatively, an indirect measure indicating lower metabolic demand, whereas global cerebral blood flow increased. During hypoglycemia, RYGB attenuated counterregulatory responses by glucagon and cortisol. Glucose influx was greater during hypoglycemia (vs. normoglycemia) in diffuse brain regions but lower in the hypothalamus, a finding that was present both pre- and post-RYGB. As seen for normoglycemia, global cerebral blood flow increased from pre- to post-RYGB during hypoglycemia, positively correlating with cognitive function. Post-RYGB changes by functional magnetic resonance imaging (fMRI) were found only during the glucose-lowering phase of the clamp and consisted of 1) increased activity within a functional network that included the thalamus, hypothalamus, and right frontal regions, and 2) changes in functional connectivity between a region of interest in the lateral hypothalamus and the hippocampus and cerebellum.

Strengths of this intensive study include simultaneous blood sampling, clamped control of blood glucose, and multimodal neuroimaging providing complementary data on brain glucose metabolism, cerebral blood flow, and functional networks (5). The most significant limitation is small sample size, requiring cautious conclusions particularly regarding fMRI outcomes (11). The lack of a control group limits conclusions about RYGB versus the effects of weight loss itself, and numerous other physiologic and behavioral changes resulting from RYGB (Fig. 1A) are also potential confounders or mediators of the observed CNS effects of surgery. Finally, CNS mediators of postbariatric postprandial hypoglycemia might only become apparent years after RYGB or once individuals are symptomatic. Nonetheless, the complex protocol will make larger studies challenging, so identifying takeaways and next directions informed by the unique approach of Almby et al. is worthwhile (5).

As previously observed (12), the counterregulatory hormone response to hypoglycemia was dampened post-RYGB (5). Were CNS responses similarly altered?

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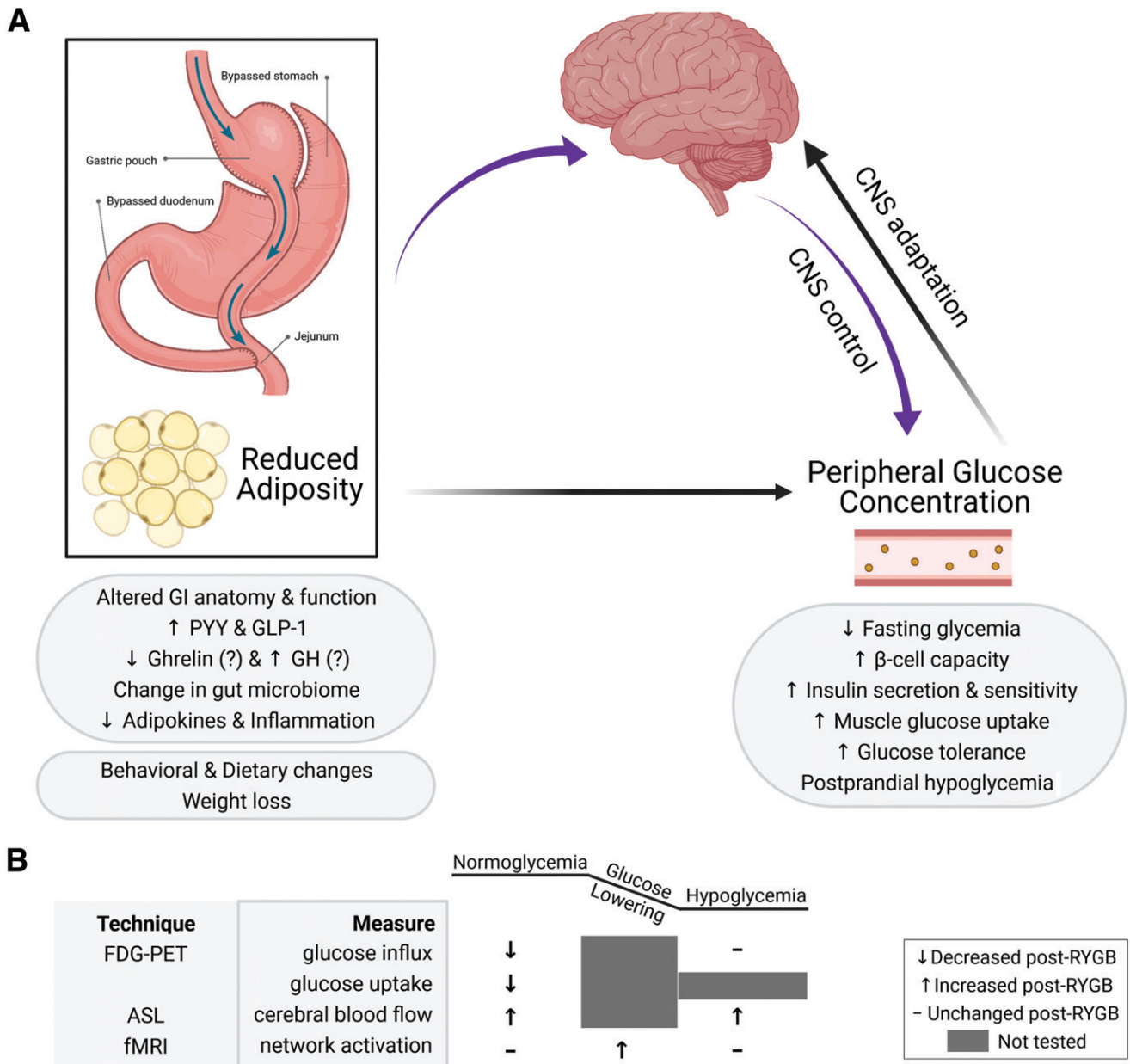


Figure 1—Model describing the relationship between RYGB surgery, peripheral glucose concentration, and the CNS. *A*: RYGB surgery reconstructs gastrointestinal (GI) anatomy impacting nutrient absorption, gastric emptying, enervation, and gut microbiome, among other factors. RYGB surgery and accompanying weight loss also change circulating hormones and adipokines such as, but not limited to, increased levels of polypeptide YY (PYY), glucagon-like peptide 1 (GLP-1), and amylin; potential relative deficiencies of ghrelin and increases in growth hormone (GH); and reduction in proinflammatory markers. These established multifactorial contributors act to modify peripheral glucose concentration, which could then lead to CNS adaptations (black arrows). Purple arrows show areas for further investigation with an alternative model that proposes RYGB surgery and/or accompanying reduced adiposity impacts the CNS regulation of glucose metabolism, likely at the level of the hypothalamus, thereby contributing to postsurgical improvements in peripheral glucose concentrations in a bidirectional manner. *B*: CNS changes after RYGB surgery and weight loss as described by Almby et al. (5) during normoglycemia (5.0 mmol/L), glucose-lowering, and hypoglycemia (2.7 mmol/L). Figure created with BioRender (biorender.com).

While hypoglycemia induced an increase in global brain glucose influx rate relative to normoglycemia, the magnitude of this response did not differ from pre- to post-RYGB, nor did ASL results (5). With the possible exception of fMRI results restricted to the glucose-lowering phase of the clamp procedure (Fig. 1*B*), the findings do not support the conclusion that RYGB specifically

impacts CNS response to hypoglycemia. Negative findings could be related to the inability of the techniques applied to spatially resolve hypothalamic nuclei involved in counterregulation (13), or to the fact that subtypes of neurons within the same region are activated while others are reciprocally inhibited by hypoglycemia (14).

Nevertheless, the observations by Almby et al. (5) join a growing literature documenting that bariatric surgery affects the brain. The brain might not only passively adapt to lower circulating glucose but also actively contribute to glucose lowering in a bidirectional manner (15,16) (Fig. 1A). For example, RYGB acts on the ventromedial hypothalamus to improve hepatic insulin sensitivity in rodents (17). Almby et al. hypothesize that the “set point” of circulating blood glucose was lowered postoperatively, explaining blunted counterregulatory response (5). What specific CNS mechanisms might lower glycemic “set point”? Could the current study’s findings be mechanistically related to the metabolic benefits of RYGB? Durable lowering of circulating blood glucose by the CNS has been demonstrated through intracerebroventricular injection of fibroblast growth-factor 1 (FGF-1) (18). Whether FGF-1’s mode of action overlaps with that of RYGB is unknown. Reductions in inflammation in the mediobasal hypothalamus after RYGB-induced weight loss (19) offer another plausible link to CNS-mediated improvements in glucose regulation (20). Finally, astrocytes govern the efficiency of systemic glucose entry into the brain and thereby influence hypothalamic glucose sensing and, consequently, homeostatic responses to glucoprivation and hyperglycemia (16), making astrocytes and neuron–glia interactions compelling and understudied areas of research for both dampened counterregulatory response and improved glucose metabolism post-RYGB.

Looking forward, it will be critical to further interrogate the brain’s role in the metabolic consequences of bariatric surgery. Delineating neuronal circuitry, identifying glial cell mechanisms, and testing causality will require preclinical models, but human studies should augment these experiments. Neuroimaging studies of patients with postbariatric hypoglycemia are needed as are investigations of the early postoperative period to determine which CNS findings precede improved glucose metabolism and might be driving—rather than adapting—to it. Although the current study (5) did not provide direct leads to ameliorate clinically significant post-RYGB hypoglycemia, it suggests that pursuing broader questions regarding the CNS role in control of peripheral blood glucose could be revealing.

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References

- Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ* 2014;349:g3961
- Lee CJ, Clark JM, Schweitzer M, et al. Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy. *Obesity* (Silver Spring) 2015;23:1079–1084
- Salehi M, Vella A, McLaughlin T, Patti ME. Hypoglycemia after gastric bypass surgery: current concepts and controversies. *J Clin Endocrinol Metab* 2018;103:2815–2826
- Goldfine AB, Patti ME. How common is hypoglycemia after gastric bypass? *Obesity* (Silver Spring) 2016;24:1210–1211
- Almby KE, Lundqvist MH, Abrahamsson N, et al. Effects of gastric bypass surgery on the brain: simultaneous assessment of glucose uptake, blood flow, neural activity, and cognitive function during normo- and hypoglycemia. *Diabetes* 2021;70:1265–1277
- Tuulari JJ, Karlsson HK, Hirvonen J, et al. Weight loss after bariatric surgery reverses insulin-induced increases in brain glucose metabolism of the morbidly obese. *Diabetes* 2013;62:2747–2751
- Rebelos E, Immonen H, Bucci M, et al. Brain glucose uptake is associated with endogenous glucose production in obese patients before and after bariatric surgery and predicts metabolic outcome at follow-up. *Diabetes Obes Metab* 2019;21:218–226
- Olivo G, Zhou W, Sundbom M, et al. Resting-state brain connectivity changes in obese women after Roux-en-Y gastric bypass surgery: a longitudinal study. *Sci Rep* 2017;7:6616
- Arbeláez AM, Su Y, Thomas JB, Hauch AC, Hershey T, Ances BM. Comparison of regional cerebral blood flow responses to hypoglycemia using pulsed arterial spin labeling and positron emission tomography. *PLoS One* 2013;8:e60085
- Page KA, Arora J, Qiu M, Relwani R, Constable RT, Sherwin RS. Small decrements in systemic glucose provoke increases in hypothalamic blood flow prior to the release of counterregulatory hormones. *Diabetes* 2009;58:448–452
- Poldrack RA, Baker CI, Durnez J, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat Rev Neurosci* 2017;18:115–126
- Abrahamsson N, Börjesson JL, Sundbom M, Wiklund U, Karlsson FA, Eriksson JW. Gastric bypass reduces symptoms and hormonal responses in hypoglycemia. *Diabetes* 2016;65:2667–2675
- Rooijackers HMM, Wiegers EC, Tack CJ, van der Graaf M, de Galan BE. Brain glucose metabolism during hypoglycemia in type 1 diabetes: insights from functional and metabolic neuroimaging studies. *Cell Mol Life Sci* 2016;73:705–722
- Quenneville S, Labouèbe G, Basco D, et al. Hypoglycemia-sensing neurons of the ventromedial hypothalamus require AMPK-induced TXN2 expression but are dispensable for physiological counterregulation. *Diabetes* 2020;69:2253–2266
- Ruud J, Steculorum SM, Brüning JC. Neuronal control of peripheral insulin sensitivity and glucose metabolism. *Nat Commun* 2017;8:15259
- García-Cáceres C, Quarta C, Varela L, et al. Astrocytic insulin signaling couples brain glucose uptake with nutrient availability. *Cell* 2016;166:867–880
- Paranjape SA, Chan O, Zhu W, et al. Improvement in hepatic insulin sensitivity after Roux-en-Y gastric bypass in a rat model of obesity is partially mediated via hypothalamic insulin action. *Diabetologia* 2013;56:2055–2058
- Scarlett JM, Rojas JM, Matsen ME, et al. Central injection of fibroblast growth factor 1 induces sustained remission of diabetic hyperglycemia in rodents. *Nat Med* 2016;22:800–806
- van de Sande-Lee S, Melhorn SJ, Rachid B, et al. Radiologic evidence that hypothalamic gliosis is improved after bariatric surgery in obese women with type 2 diabetes. *Int J Obes* 2020;44:178–185
- Schur EA, Melhorn SJ, Oh S-K, et al. Radiologic evidence that hypothalamic gliosis is associated with obesity and insulin resistance in humans. *Obesity* (Silver Spring) 2015;23:2142–2148