Weight loss produced by gastric bypass surgery: more gut feelings hit the brain¹,²

Arne Astrup

Weight loss after gastric bypass surgery can typically amount to 30–50 kg the first year and is generally well maintained, with only slight regain over several years. Gastric bypass started to replace jejunoileal bypass procedure in the 1970s (1), as the latter caused too many serious adverse events. At that time, weight loss was attributed to the restriction of food intake caused by the reduced gastric pouch size, the limited diameter of the gastroenterostomy, and malabsorption of the energy-containing macronutrients. Almost 50 years ago, a surprising improvement in glycemic control after gastric bypass in patients with type 2 diabetes was observed before any weight loss occurred (1), but it took decades of research before the discovery that the intestinal hormones play a role both for an improvement in glycemic control in obese patients with type 2 diabetes independent of weight loss and for the weight loss and reduction in food intake.

The hormone glucagon-like peptide-1 (GLP-1) is predominantly secreted from enteroendocrine L cells of the distal small intestine and is partly responsible for the “incretin effect,” ie, the phenomenon that glucose administered orally leads to a substantially greater insulin response than does glucose administered intravenously. One of GLP-1’s physiologic roles is to amplify glucose-induced insulin secretion in the postprandial phase; thus, it is an important player in glucose homeostasis. In 1998 it was shown that GLP-1 is also a satiety hormone in human subjects (2), and today it is known that GLP-1 possesses multiple physiologic functions, including inhibition of glucagon secretion, improved β cell function and survival, and reduced rates of gastric emptying.

Today it is well recognized that the improvement and remission in patients with type 2 diabetes that occur after gastric bypass must be attributed to an immediately improved β cell function with an exaggerated postprandial GLP-1 secretion resulting from a more rapid gastric emptying and reduced transit time of nutrients, and to a later improvement in insulin resistance brought about by the reduced energy intake and reduction in fat mass size (3).

The understanding of the mechanisms behind the dramatic weight loss and how it is sustained over time have also evolved, and a number of studies from le Roux’s group (4) have linked the exaggerated postprandial response of the satiety hormones GLP-1, peptide YY, and oxyntomodulin to the weight loss in obese patients after gastric bypass. The causal involvement of these hormones has been established by studies showing increased food intake following blockade. These hormones, particularly in concert, act as satiety signals to the brain after food ingestion, but recent studies suggest that they may also change food selection in a healthier direction. Gastric bypass has been found to reduce meal size, increase the number of meals, decrease emotional and uncontrolled eating (5), reduce the intake of energy-dense sweet and fatty foods, and increase the consumption of vegetables (6). It is, however, difficult to ascertain whether the changes in food preference and avoidance are a result of the hormonal metabolic changes caused by gastric bypass or of changes imposed as part of a healthier diet to sustain the weight loss.

In this issue of the Journal, another study from le Roux’s group by Miras et al (7) examines obese patients before and after gastric bypass and compares them with normal-weight control subjects. This group has used a methodology in which subjects had to work progressively harder to obtain a food reward (reinforcer) until they stopped clicking (breakpoint)—a measure of the reinforcing value (7). Breakpoints were assessed by the number of mouse clicks in the last completed ratio. The major results were that gastric bypass seems to induce an alteration in the reinforcing effects of sweet and fatty candy but not of vegetables. The breakpoint for candies, but not vegetables, was reduced by 50% in the obese patients after gastric bypass. Patients with the largest reduction in breakpoint also demonstrated the greatest weight loss. In conclusion, it is very likely that gastric bypass surgery resulted in the selective reduction of the reward value of a sweet/fat taste and in turn a reduction in intake of foods with these properties.

An elucidation of the effect of GLP-1 and other gut hormones on food selection may be important for our nutritional and physiologic understanding and also for development of pharmacologic and bariatric strategies of management of obesity. But how can we get more insight? Future studies need to separate the effects of hormonal alterations on taste perception from their effects on the rewarding and hedonic qualities of foods. Although regulation of ingestive behavior can be compartmentalized as homeostatic

¹ From the Department of Nutrition, Exercise, and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark.
² Address correspondence to A Astrup, Rolighedsvej 30, DK-1958 Frederiksberg, Denmark. E-mail: ast@life.ku.dk.
First published online August 8, 2012; doi: 10.3945/ajcn.112.045179.
or hedonic, on the basis of neuroanatomical and functional parameters, communication between these 2 integrated “compartments” is believed to determine when, what, and how much we eat (8). Our ability to study the neural networks that influence ingestive behavior in humans has improved with the advances in functional brain imaging technology (ie, blood oxygen level–dependent signal response from fMRI) and the developments in psychobiological concepts within this research area, providing us with new opportunities to demonstrate a potential effect of gut hormones on food preferences, aversions, and rewarding effects. Several such studies are ongoing.

Gastric bypass surgery exerts complex alterations that affect several hormones and afferent neural pathways, and despite all efforts to design optimal studies, there is a need for controlled studies, preferably double blinded. This can be achieved by infusion of the gut hormones separately and in combination to study short-term effects in humans, whereas long-term effects can be studied with the use of GLP-1 agonists, such as exenatide and liraglutide. Liraglutide has been shown to produce sustained weight loss for up to 2 y in nondiabetic obese patients (9), and there are preliminary reports that indicate that obese patients treated with GLP-1 analog experience “healthy” alterations in food preference and diet composition similar to those observed in gastric bypass patients (10). One can hope that such mechanistic insights into the hormonal systems that influence our diet selection may contribute to improving the prevention and management of obesity and type 2 diabetes.

AA is a member of the Advisory Board for Novo Nordisk and has been Principal Investigator of clinical trials (funded by Novo Nordisk) of liraglutide, a long-acting GLP-1 agonist, for the management of obesity, marketed by Novo Nordisk for the treatment of type 2 diabetes mellitus.

REFERENCES