Shedding pounds after going under the knife

Losing weight can pose a challenge, but how to avoid putting those pounds back on can be a real struggle. A major health problem for obese people is that diseases linked to obesity, such as type 2 diabetes and cardiovascular disease, put their lives at risk, even in young individuals. Although bariatric surgery—a surgical method to reduce or modify the gastrointestinal tract—was originally envisioned for the most severe cases of obesity, evidence suggests that the benefit of this procedure may not be limited to the staggering weight loss it causes. Endogenous factors released from the gut, and modified after surgery, may explain why bariatric surgery can be beneficial for obesity-related diseases and why operated individuals successfully maintain the weight loss. In 'Bedside to Bench,' Rachel Larder and Stephen O'Rahilly peruse a human study with dieters who regained weight despite a successful diet. Appetite-regulating hormones in the gut may be responsible for this relapse in the long term. In 'Bench to Bedside,' Keval Chandarana and Rachel Batterham examine how two different methods of bariatric surgery highlight the relevance of gut-derived hormones not only in inducing sustained weight loss but also in improving glucose homeostasis. These insights may open new avenues to bypass the surgery and obtain the same results with targeted drugs.

■ BEDSIDE TO BENCH

Guts over glory—why diets fail

Rachel Larder & Stephen O'Rahilly

The epidemic of obesity is now a major public health concern in many parts of the world, given its impact on diabetes, heart disease, stroke and cancer[1]. Whereas genetics play a part in determining an individual's propensity to gain weight[2], the increased prevalence of obesity is likely to be attributable to a global increase in the consumption of energy-dense foods alongside a substantial decrease in physical activity levels. Although surgical methods such as gastric banding, sleeve gastrectomy and Roux-en-Y gastric bypass offer an effective treatment for weight loss (average weight loss of 62.1% 2 years after surgery[3]), they are generally recommended only for the morbidly obese, owing to the risk of postoperative mortality. For most obese individuals, the simplest way to reduce adiposity is to enact lifestyle changes that will result in weight loss, including increasing exercise levels and decreasing caloric intake. Although most dieters will initially see promising results within the first few months of embarking on a weight-loss program, the majority of them will have regained almost all of their original weight loss within 5 years[4]. A recent study in *The New England Journal of Medicine*[5] helps shed light on why this high 'relapse' rate occurs and suggests that appetite-regulating hormones produced by the gut may sabotage the good intentions of long-term dieters.

Regulation of body weight is a highly complex process centrally regulated within the brain[6]. Multiple hormonal signals from the gut, pancreas and fat are secreted in response to caloric intake and signal to the hypothalamus via neuronal or endocrine pathways to either promote or inhibit appetite[6]. Satiation signals such as glucagon-like peptide-1 (GLP-1), cholescystokinin (CCK) and peptide YY (PYY) are secreted by the intestine in response to food, with the aim of inhibiting appetite. In contrast, ghrelin secretion from the stomach is decreased after a meal, when appetite no longer needs to be stimulated. In addition, the adipocyte hormone leptin provides a longer-term signal to the brain regarding the status of energy stores within fat cells, whereas gastric inhibitory polypeptide (GIP) release from the intestine controls post-prandial insulin secretion and promotes energy storage[7].

When an individual's calorie intake is substantially reduced, the immediate response of the body is to defend against potential weight loss to ensure that reproductive integrity and survival will not be compromised—by dramatically increasing ghrelin and GIP secretion while decreasing PYY, CCK and GLP-1 levels in the circulation. The resulting increased appetite should initiate the immediate intake of calories so that energy homeostasis, and therefore fat deposits, can be maintained (**Fig. 1**).

Given the poor long-term success of many diets[4], Sumithran *et al.*[5] hypothesized that these appetite-driving hormonal changes are more than just a transient compensatory response and might persist beyond the initial 'defensive' response period. This would result in a continued increase in appetite and may explain the high relapse rate seen in many long-term dieters. The study reports the findings in 36 compliant obese participants in a weight-loss study involving an initial 8-week period of meal replacement with a very-low-calorie meal-replacement diet. During weeks 9 and 10, these participants, all of whom had lost 10% or more of their initial body weight, were gradually reintroduced to ordinary foods, and weight was stabilized. At the end of week 10, participants received individual counseling and written advice from a dietician on a dietary intake that would be consistent with their calculated energy expenditure, with the aim of weight maintenance. Satiety and hunger hormones were measured at three time points: before weight loss, after 10 weeks of weight loss and 1 year after the initial 10% reduction in weight.

Although the study was able to recapitulate

Rachel Larder and Stephen O'Rahilly are at Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK.
e-mail: so104@medschl.cam.ac.uk

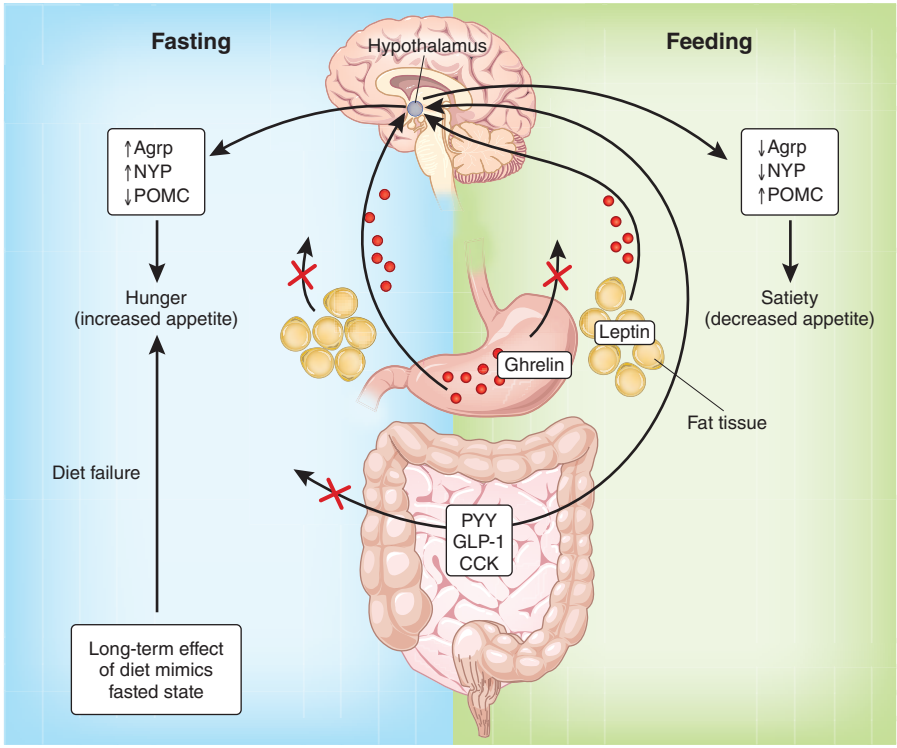

Figure 1 Effect of feeding and fasting on hunger hormones. During and after regular feeding, there is a reduction in the production of ghrelin by the stomach. In contrast, production of PYY, GLP-1 and CCK from the gut is increased, and serum leptin levels also rise. These changes are detected by the brain, resulting in modulation of gene expression of orexigenic (Agouti-related protein (AGRP) and neuropeptide Y (NPY)) and anorexigenic (pro-opiomelanocortin (POMC)) proteins, which result in decreased appetite and a feeling of satiety such that caloric intake is stopped. During fasting, decreased food intake suppresses the release of PYY, GLP-1 and CCK from the gut while stimulating the secretion of ghrelin by the stomach. Fasting also decreases serum leptin levels. These changes are detected by the brain, resulting in upregulation of orexigenic and downregulation of anorexigenic gene expression within the hypothalamus, leading to hunger. Dieting results in a gut hormone profile that mimics the fasted state. These changes can persist for 12 months after initial weight loss and may explain why the majority of obese dieters fail to maintain a reduced body weight.

previously published data showing the expected short-term changes in various appetite-regulating hormones after 10 weeks of weight loss (**Fig. 1**), the data obtained 1 year after weight loss also showed that circulating mediators of appetite never returned to pre-intervention levels. At the last time point measured, the subjects continued to show substantially decreased levels of leptin, PYY and CCK and increased levels of ghrelin and GIP, coupled with a regain of about 30% of the weight they had lost a year before. The decreased leptin levels observed in the subjects were not unexpected, as some fat loss was maintained. Yet, the persistent changes in circulating gut hormone levels and increased hunger 12 months after initial weight loss were unexpected. Taken together with recent data showing that the reduction in energy expenditure seen immediately after weight loss can also endure for more than 12 months[8], these data present a strong physiological basis for the high rate of recidivism to obesity after nonsurgical approaches to weight loss.

Currently, bariatric surgery incorporating gastrointestinal bypass is the only obesity treatment that routinely achieves substantial and permanent weight loss[9]. Interestingly, recent research focusing on this success has shown that, unlike dieting, bariatric surgery is associated with marked appetite-suppressing changes in ghrelin, PYY and GLP-1 abundance, which presumably dominate over the weight-gain–promoting effects of lowered plasma leptin concentrations[10]. Although the mechanisms of these changes are not fully understood, it is thought that by bypassing a substantial portion of the small bowel, and thus increasing delivery of unabsorbed nutrients to the PYY- and GLP-1–producing cells of the distal bowel, an amplified gut-hormone response to food is achieved, resulting in increased satiety after surgery.

Given that rodent studies suggest that increased PYY levels are crucial for the maintenance of weight loss after gastric bypass surgery[11,12], studies of gut hormone profiles in the small percentage of subjects that fail to maintain weight after gastric bypass would be helpful in determining whether increased ghrelin and decreased PYY and GLP-1 levels contributed to their relapse and whether they are really essential for weight loss. More research is also warranted into how changes in these gut hormones after bypass surgery contribute to the rapid resolution of type 2 diabetes, often before substantial weight loss is observed. GLP-1 receptor antagonists blocked improvements in oral glucose tolerance tests in rats that underwent bypass surgery, suggesting that post-operative increases in GLP-1 are key for improving glucose homeostasis after bariatric surgery[13].

The report by Sumithran *et al.*[5] highlights the importance of afferent signals from the gastrointestinal tract to the brain in the maintenance of energy homeostasis and suggests that a potential therapy for obesity might be developed if one can replicate the hormonal milieu seen after gastric bypass surgery. With both leptin and ghrelin failing to show great promise as antiobesity drug targets, current focus has shifted to the development of drugs based on the function of specific gut hormones such as GLP-1 and PYY[14]. With nausea proving to be a common adverse effect during clinical trials of these drugs, the successful achievement of an anorectic effect with these drugs will probably depend on developing sustained-release formulations of a low-dose cocktail of multiple gut hormones that can be dispensed together to match the benefits of gastric bypass surgery without having to go under the knife.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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