Obesity is a global epidemic that has proven daunting to prevent and treat. The prevalences of obesity (body mass index [BMI] >30) and morbid obesity (BMI >40) among American adults are about 30% and 5%, respectively. Obesity is so strongly associated with medical comorbidities and mortality that it has begun to overtake infectious diseases as the most significant contributor to ill health worldwide. Overweight persons are also frequently stigmatized and consequently suffer from low self-esteem. Their motivation to achieve and maintain weight loss is often Herculean. In 1 study of 47 patients who had durably lost 45 kg or more after bariatric surgery, 100% preferred to be deaf, dyslexic, diabetic, or have heart disease rather than be obese again; leg amputation and blindness were preferred by 91.5% and 89.4%, respectively. The traditional treatment paradigm of diet, exercise, and medication generally achieves no more than a 5% to 10% reduction in body weight, and recidivism after such weight loss exceeds 90% within 5 years. This failure arises because a robust homeostatic system of body weight regulation compensates for weight loss with increased hunger and decreased energy expenditure. The molecular mediators of these compensatory responses to weight loss are potential targets for antiobesity treatments. Ghrelin is a potent orexigenic (appetite-stimulating) peptide that seems to participate in the adaptive response to weight loss. Therefore, ghrelin holds promise as a target for both medical and surgical approaches to obesity.

FUNDAMENTALS OF APPETITE AND BODY WEIGHT REGULATION

Body weight is regulated within a narrow, individualized range by a process known as “energy homeostasis.” This process precisely matches overall energy intake and expenditure over long periods—to within 1% of the more than 1 million kilocalories typically consumed per year—despite large daily caloric mismatches. Deviations from the defended level of body weight engage adaptive, reciprocal alterations in appetite and energy expenditure that resist weight change, rendering behavioral and medicinal interventions for obesity relatively ineffective.
Researchers are attempting to elucidate and recontrol, and exerts long-acting catabolic effects by decreasing hypothalamic and brainstem centers of body weight control, whereas insulin agonists that preferentially partition into the brain exert the opposite actions to cause weight gain (anabolic neuropeptides). 19 Some such agents might act downstream of the mechanisms dictating obesity-related resistance to leptin and insulin. 20 Alternatively, CNS sensitization to leptin and insulin action might be achieved by increasing the rate of hormone transport across the blood-brain barrier 27 or enhancing intracellular signaling events triggered by leptin and/or insulin receptor activation. 31 The intracellular actions of leptin and insulin in the brain may converge at the level of a signaling enzyme called "phosphatidylinositol-3-OH kinase." 23 If this is confirmed, phosphatidylinositol-3-OH kinase would be a logical target for antiobesity medications that could increase CNS sensitivity to both leptin and insulin.

To regulate overall food intake, long-acting adiposity signals ultimately affect the number and size of individual meals. They, therefore, influence decisions regarding when to start and stop eating. The sense of fullness that contributes to meal termination results from mechanical, neural, and humoral signals that arise from the gut and are relayed to the brain primarily via the brainstem. Meal-stimulated, short-acting satiety factors include cholecystokinin, amylin, glucagon, glucagonlike peptide-1, apolipoprotein A-IV, bombesin-related peptides, and possibly enterostatin. 34,35 Although these factors limit meal size, their repeated administration typically does not alter body weight because of reciprocal increases in meal frequency. Thus, most are not regarded as primary regulators of long-term energy homeostasis. 36 Hormones that govern energy homeostasis—leptin and insulin—increase responsiveness to short-acting satiety signals. 10 Consequently, when fat stores diminish and leptin and insulin levels decrease, sensitivity to meal-related satiety signals is blunted, promoting increased meal size. Body adiposity indirectly modulates the efficacy of meal-related satiety signals from the gut, thereby influencing meal size.

Compared with the well-defined systems that mediate postprandial satiety and promote meal termination, those that trigger preprandial hunger and promote meal initiation remain enigmatic. Although several hypotheses regarding meal initiation have been articulated, none has garnered wide consensual support among body weight researchers. One theory asserts that individual meals are prompted by small (about 11%), transient decreases in blood glucose levels occurring shortly before the onset of meals in free-feeding conditions. 37 Despite considerable evidence supporting this glucostatic model, the phenomenon may not be physiologically important in humans. 38

Figure 1. Model to explain compensatory adjustments of caloric intake and expenditure in response to changes in body fat content. Leptin and insulin are peripheral adiposity signals that circulate in proportion to the amount of body fat and act in the hypothalamus to stimulate catabolic effector pathways while inhibiting anabolic pathways. These pathways exert opposing effects on energy balance (the difference between calories consumed and expended), which, in turn, determines the amount of body fat. CNS indicates central nervous system. Reprinted with permission from Nature (Schwartz et al 2000, Macmillan Publishers Ltd.)

[Image of Figure 1: Model to explain compensatory adjustments of caloric intake and expenditure in response to changes in body fat content. Leptin and insulin are peripheral adiposity signals that circulate in proportion to the amount of body fat and act in the hypothalamus to stimulate catabolic effector pathways while inhibiting anabolic pathways. These pathways exert opposing effects on energy balance (the difference between calories consumed and expended), which, in turn, determines the amount of body fat. CNS indicates central nervous system. Reprinted with permission from Nature (Schwartz et al 2000, Macmillan Publishers Ltd.)]
and even if it is, this knowledge does not translate easily into clinical applications.

In contrast, if a circulating hormone plays a critical role in meal initiation, this moiety might be amenable to pharmacologic manipulation for clinical purposes. Recent evidence suggests that the newly discovered enteric hormone, ghrelin, may be a physiologic meal initiator that also contributes to long-term energy homeostasis. Ghrelin is interesting because it is the only known circulating orexigen and also because it is a potential link between the short- and long-term regulation of appetite and body weight.

**Ghrelin: The Only Known Orexigenic Hormone**

Ghrelin, a peptide first identified as an endogenous growth hormone secretagogue, 39 is a powerful orexigen, stimulating food intake through growth hormone–independent mechanisms. 40–43 The name ghrelin is derived from the Proto-Indo-European root ghe- for growth and the suffix –relin for releasing substance. 39 The mature, 28–amino acid peptide is cleaved from the precursor preproghrelin, which contains a signal sequence dictating secretion in blood. The receptor-binding sequence at the N-terminus is almost 100% conserved among primates, 39 rods, 39,44 fish, 45 dogs, 46 amphibians, 47 and birds, 48 suggesting an important physiologic role. Ghrelin undergoes an entirely unique posttranslational modification in which an 8-carbon fatty acid group is covalently linked to the serine-3 residue. 39 This process, known as n-octanoylation, is essential for bioactivity. Moreover, full receptor binding and activation can be achieved with as few as 4 N-terminal amino acids, as long as the octanoyl group is attached. 49 Although the function of this modification is yet unknown, its requisite nature and uniqueness to ghrelin have potential therapeutic implications for ghrelin blockade. An antagonist to the putative transacylation enzyme that octanoylates ghrelin should inactivate the hormone in a highly selective manner.

**Anatomy of Ghrelin Production**

The stomach is the principal site of ghrelin synthesis, although significant production occurs in the small intestine and minor amounts are present elsewhere in the body. 39,50–52 The gastric fundus contains 10 to 20 times more ghrelin per gram of tissue than the duodenum, the next richest source. 30,52,53 Lesser concentrations of ghrelin are present in the jejunum and ileum, generally diminishing with increasing distance from the stomach. 31–53 This pattern of expression is qualitatively conserved in all species examined to date. 45–48 Gastric ghrelin-producing cells reside in the oxyntic glands, in contact with the basolateral membrane adjacent to the bloodstream, and most do not have direct contact with the stomach lumen. 30,53 Changes in ghrelin levels following either gastrectomy or small-bowel resection suggest that roughly two thirds of circulating human ghrelin comes from the stomach and one third from the small intestine. 31,54

**Potential Roles for Ghrelin in the Regulation of Appetite and Body Weight**

Peripheral or central administration of ghrelin to rodents stimulates short-term food intake as potently as any known compound. 49 This orexigenic action is mediated, at least in part, via activation of neurons in the hypothalamic arcuate nucleus that coexpress neuropeptide Y (NPY) and agouti-related protein (AgRP)—both prototypic anabolic neuropeptides. Almost all arcuate NPY/AgRP neurons express the ghrelin receptor and can be stimulated by ghrelin, as judged by increases in the firing rate and the expression of c-Fos, NPY, and AgRP in these cells. 41,43,60 Pharmacologic blockade of either NPY or AgRP attenuates the orexigenic actions of ghrelin. 41,43,59 The standard hormonal model of ghrelin action asserts that circulating ghrelin derived primarily from the gut accesses the medial arcuate nucleus through a leaky blood-brain barrier at that location and increases food intake by activating NPY/AgRP neurons. Recent evidence indicates that another important neurocrine mode of ghrelin action involves suppression of visceral afferent vagal nerve activity. 33,64 The physiologic importance of very small quantities of CNS-derived ghrelin is also being actively investigated. 60

Several observations from human and animal studies suggest that ghrelin has the unique capacity to influence both individual meal initiation and long-term body weight control. The following evidence is consistent with a role for ghrelin in meal initiation. (1) Ghrelin is produced primarily by the stomach, 39 an organ sensitive to short-term nutrient fluxes. (2) Circulating levels in rodents increase with fasting and rapidly decrease with refeeding or gastric infusion of nutrients (but not water), as would be predicted for a meal initiator. 40,43,62–65 (3) Exogenous ghrelin triggers eating in rodents when administered at times of minimal spontaneous food intake. 31–45 (4) The orexigenic effects of ghrelin are rapid and short lived, as required for a signal governing individual meals. 40–43,66 (5) Ghrelin may stimulate gastric motility and acid secretion, which are known to increase in anticipation of meals. 43,67 (6) Hypothalamic NPY/AgRP neurons—targets of ghrelin’s orexigenic actions—are implicated in the CNS control of meal initiation. 60

Orexigenic effects of ghrelin occur in rodents administered low-dose peripheral injections that produce blood levels within the physiologic range. 60 Similarly, the effects on appetite of modest intravenous doses of ghrelin generating near-physiologic blood levels have been investigated in a blinded, crossover study in humans. 70 Subjects receiving ghrelin reported a 46% increase in the perception of hunger and ate an average of 28% more calories at a subsequent buffet meal compared with another occasion when they received vehicle. The response was universal and, despite overeating, subjects experienced no nausea, vomiting, or excessive sensation of satiety. The observation that peripheral administration of ghrelin at approximately physiologic doses stimulates hunger and food intake in humans and rodents strengthens the hypothesis that natural fluctuations of endogenous circulating ghrelin levels affect appetite. Human plasma ghrelin levels sharply increase before and decrease after...
caloric restriction (Figure 2), cancer anorexia, cardiac cachexia, anorexia nervosa, and bulimia nervosa. A trend toward decreased ghrelin levels was found in subjects who gained weight through overfeeding, a finding that suggests bidirectional regulation. Obese individuals who lose even 5% of body weight manifest significantly increased circulating ghrelin levels. Because reduced food intake accompanies all of the above conditions of weight loss, it is theoretically possible that ghrelin levels increase in these settings because of decreased inhibitory input from ingested nutrients rather than from weight loss per se. We have found, however, that weight loss achieved by chronic exercise without hypophagia in humans also increases plasma ghrelin levels (Karen E. Foster, MD, Anne McTiernan, MD, and D.E.C., unpublished data, 2002). Moreover, mice subjected to mild caloric restriction, insufficient to reduce body weight, show no alteration in plasma ghrelin levels (Eugene N. Bush, PhD, and D.E.C., unpublished data, 2002). Together, these findings suggest that circulating ghrelin levels fluctuate in response to changes in body weight. This phenomenon is consistent with a role for ghrelin in the adaptive response to body weight changes, and thus, in long-term energy homeostasis. The important implications are that an increase in ghrelin levels caused by weight loss may contribute to weight regain and, therefore, pharmacologic ghrelin blockade may help maintain voluntary weight loss.

Steady-state ghrelin levels correlate negatively with measures of adiposity and are low in overweight individuals, this observation is consistent with a compensatory rather than causal role for ghrelin in common obesity. The only known overweight condition associated with high ghrelin levels is the Prader-Willi syndrome. The most common form of human syndromic obesity, Prader-Willi syndrome, results from defective expression of several imprinted genes on chromosome 15. Extreme hyperphagia and juvenile-onset obesity are hallmark features—so severe that untreated individuals may die of obesity-related complications before the age of 30 years. Humans with Prader-Willi syndrome have plasma ghrelin levels that are 4 1/2 times higher than those of equally obese controls. These levels are comparable to or higher than those that stimulate appetite and food intake during peripheral ghrelin administration in humans and rodents. Therefore, hyperghrelinemia may play a primary causal role in the hyperphagia and obesity of Prader-Willi syndrome.

**EFFECT OF BARIATRIC SURGERY ON CIRCULATING GHERLIN LEVELS**

Roux-en-Y gastric bypass (RYGB) is the most effective, commonly accepted method to achieve major weight loss, and it is the treatment of choice for persons with morbid obesity. The procedure restricts the gastric volume that is capable of storing food, bypassing most of the stomach and all of the duodenum with a gastrojejunostomy. Patients who have undergone RYGB often shed hundreds of pounds, and these effects have been documented to persist for at least 14 years. Gastric bypass seems to circumvent or over-
The mechanisms underlying this dramatic effect are enigmatic. Clearly, the small size of both the residual gastric pouch and the stoma between it and the jejunum should limit the amount of food consumed at one sitting. Indeed, gastric restriction after RYGB unequivocally causes early satiety and reduced meal size.\(^9\)\(^0\),\(^9\)\(^1\) If this were the only mechanism constraining food intake, however, postoperative patients would be predicted to increase the frequency and caloric density of their meals, especially in response to massive weight loss. In contrast, individuals who have undergone RYGB typically eat fewer meals and snacks per day.\(^9\)\(^0\),\(^9\)\(^1\) They also voluntarily restrict consumption of calorie-dense foods, such as fats, high-calorie carbohydrates, ice cream, and high-calorie beverages.\(^9\)\(^0\),\(^9\)\(^1\) These alterations arise in part from the generalized loss of hunger that extends beyond postprandial satiety and occurs despite a lack of change in the perception of high-calorie carbohydrates (ie, sweets) as being delicious or in the overall enjoyment of food.\(^9\)\(^0\),\(^9\)\(^3\),\(^9\)\(^4\)

The unexpected loss of appetite and paradoxical changes in eating behavior that typically follow RYGB may help explain why this procedure causes greater and more durable weight loss than does vertical banded gastroplasty (VBG) (Figure 3). The degree of gastric restriction from VBG is at least as great as that from RYGB, in terms of the size of both the residual gastric pouch (9-20 vs 15-30 mL, respectively) and the distal gastric stoma (0.9-1.2 cm for both procedures).\(^9\)\(^2\),\(^9\)\(^5\),\(^9\)\(^6\) Yet prospective, randomized, and sequential comparative studies consistently show that RYGB is more effective than VBG at decreasing caloric intake, reducing excess body weight (50%-80% reduction for RYGB vs 30%-55% for VBG), and maintaining satisfactory weight loss.\(^7\)\(^5\),\(^9\)\(^7\)-\(^1\)\(^0\) Dumping and malabsorption are possible explanations for the greater efficacy of RYGB; but the severity of dumping does not correlate well with the amount of weight loss, and clinically significant malabsorption does not occur after the standard proximal RYGB.\(^1\)\(^0\)\(^5\) Moreover, randomized, prospective trials indicate that the weight loss following RYGB is comparable to that achieved with the radical, malabsorptive jejunoileal bypass (Figure 3),\(^1\)\(^0\)\(^4\),\(^1\)\(^0\)\(^5\) even though only about 0.9 m (3 ft) of small intestine is bypassed with RYGB, compared with 3.6 to 5.5 m (12-18 ft) with jejunoileal bypass.\(^9\)\(^5\)

Together, these findings suggest that cryptic mechanisms beyond gastric restriction and malabsorption may play important roles in the loss of appetite and body weight caused by RYGB. One hypothesis is that the procedure affects gut-derived factors involved in appetite regulation.\(^1\)\(^0\) Cholecystokinin, serotonin, and vasoactive intestinal polypeptide have been investigated as potential candidates but were found to be unaltered by the operation.\(^1\)\(^0\)\(^6\),\(^1\)\(^0\)\(^7\) Because most ghrelin production occurs in the anatomical region affected by RYGB, we investigated the effect of this operation on circulating ghrelin levels.

Persons who had undergone RYGB had markedly lower ghrelin levels than did lean or matched-obese controls (Figure 4).\(^7\)\(^5\) The integrated area-under-the-curve plasma ghrelin value obtained from 24-hour profiles measured (mean [SE]) 1.4 (0.4) years after RYGB was 77% lower than that in lean controls and 72% lower than that in matched-obese controls. Ghrelin levels were low in the RYGB group despite an average 36% loss of body weight, which should have increased ghrelin levels if it had been achieved by other means (vide supra). Furthermore, subjects who underwent RYGB displayed none of the meal-related oscillations found in lean and obese controls. These findings suggest that ghrelin suppression can be considered as one potential mechanism by which RYGB reduces hunger and causes weight loss. This hypothesis offers a plausible explanation for the seemingly paradoxical reduction of interimal hunger that occurs after RYGB, as well as for the greater weight-reducing efficacy of RYGB compared with the equally re-

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Figure 3. Diagrams of a proximal Roux-en-Y gastric bypass (A), vertical banded gastroplasty (B), and jejunoileal bypass (C). Reprinted with permission from the American Society for Bariatric Surgery. Available at: http://www.asbs.org.

Figure 4. Mean (SE) 24-hour plasma ghrelin profiles from subjects who undertook gastric bypass and nonoperated on controls. Study groups include obese subjects who had undergone a proximal Roux-en-Y gastric bypass (n=5), normal-weight controls (n=10), and obese subjects matched to the gastric bypass group with regard to final body mass index (calculated as weight in kilograms divided by height in meters squared), age, and sex (n=5). Breakfast (B), lunch (L), and dinner (D) were provided at the times indicated. To convert ghrelin values to picomoles per liter, multiply by 0.296. Reprinted with permission from Cummings et al.\(^7\)\(^5\)

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restrictive VBG. If more definitive interventional studies confirm that ghrelin suppression contributes to weight loss after RYGB, this finding would imply that pharmacologic blockade of ghrelin signaling may achieve some of the profound weight loss that results from RYGB.

The mechanism by which RYGB may decrease circulating ghrelin levels is unknown. Cyclical fluxes in enteral nutrients are a dominant regulatory influence on ghrelin.65 We speculate that the condition of an empty stomach and duodenum, which normally stimulates ghrelin production, paradoxically inhibits it when present continuously after RYGB. This process, known as "override inhibition," would resemble the paradoxical suppression of gonadotropins or growth hormone by continuous signaling from gonadotropin-releasing hormone or growth hormone–releasing hormone, respectively.108,109 The possibility that ghrelin-producing cells are subject to override inhibition when persistently deprived of contact with enteral nutrients is suggested by our data showing a progressive decrease of circulating levels during an overnight fast (Figures 2 and 4).65,75 Similarly, we found that human 24-hour plasma ghrelin profiles obtained during the last day of a 56-hour fast showed no mealtime oscillations and had lower area-under-the-curve values than did those obtained in the fed state (D.E.C., Mary H. Samuels, MD, and Jonathan Q. Purnell, MD, unpublished data, 2002). Finally, we have observed that plasma ghrelin levels were nearly 5 times lower in individuals fed only with intravenous total parenteral nutrition (TPN) than in free-feeding controls (mean [SE] fasting plasma ghrelin levels, 107 [17] vs 513 [52] pg/mL, in 6 patients who received only TPN vs 20 controls, respectively, P<.001). It is tempting to speculate that low ghrelin levels in these patients might contribute to the loss of appetite associated with TPN.110,111

If ghrelin-producing cells in the stomach and duodenum are, indeed, silenced after RYGB because they are permanently isolated from direct contact with enteral nutrients, other forms of bariatric surgery that do not involve gastrointestinal bypass should not suppress ghrelin levels. Consistent with this model, we have found that plasma ghrelin levels increase significantly for at least 1 year following adjustable Silastic gastric banding, to a degree commensurate with the amount of weight loss achieved (D.E.C. and Karine Clément, MD, PhD, unpublished data, 2002). It is possible that RYGB suppresses hunger and causes weight loss more effectively than does adjustable Silastic gastric banding partly because only RYGB reduces circulating ghrelin levels.

Although extant data implicate ghrelin in both the short- and long-term regulation of appetite and body weight, much of the available evidence supporting these hypotheses is circumstantial. Many of the critical experiments required to prove whether ghrelin is important in energy homeostasis require the use of ghrelin antagonists, which several pharmaceutical agencies are developing. Interventional studies using either ghrelin blockers or physiologic ghrelin restitution will also be required to determine if a decrease in plasma ghrelin levels after RYGB contributes significantly to the weight-reducing efficacy of this operation.

If it were ultimately proven that ghrelin suppression plays a significant role in RYGB-induced weight loss, the finding would have potentially important clinical implications for surgical design. Our study was small and it is entirely possible that a larger trial would have revealed that some people who undergo RYGB do not have unusually low ghrelin levels. If this is the case, a compelling question is whether the degree of ghrelin suppression influences the efficacy of the procedure. It is also important to determine the mechanism by which ghrelin suppression occurs, so that the effect can be expressly sought in bariatric surgery. We have speculated that ghrelin levels decrease after RYGB because most ghrelin-producing cells, isolated from direct contact with enteral nutrients, experience override inhibition. If this conjecture is valid, the position of the staple-line partitioning the stomach may be a critical determinant for the effect.

Accepted for publication December 18, 2002.

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