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I eat, therefore I am: the gut-brain axis and appetite control

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Abstract

Traditionally, obesity has been viewed as a simple disease of excess calorific intake in the context of a sedentary lifestyle. However, while an increase in energy consumption without corresponding expenditure is a key force in the initial development of obesity, a number of homeostatic mechanisms conspire to maintain high adiposity in individuals who are already overweight. Both central neuronal mechanisms and peripheral endocrine signals drive increased appetite and reduced metabolic rate in the obese. This prevents weight loss from occurring as quickly as one would expect, and makes sustained weight loss of more than 15% almost impossible. Currently, the most effective therapy for obesity is bariatric surgery. While previously believed to effect weight loss through malabsorption, restriction of stomach capacity or both, it is now shown that these operations fundamentally change the internal milieu of obese individuals, favouring weight loss and a reduction in appetite via cumulative changes in neuroendocrine signalling. This has led to some exploration of methods to directly affect the final common pathways in the brain and more efficiently produce weight loss.

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Introduction

Obesity is fast becoming a global epidemic. For the first time in human history, more people are dying as a result of relative calorie excess than of calorie deficit.¹ In developing nations, obesity and malnutrition coexist to create a 'double burden' of disease on already stretched health systems.² The traditional medical approach of prescribing increased exercise and reduced calorie intake, although shown to produce modest, clinically significant weight loss (usually around 5-10%), is often difficult for patients to adhere to in the first instance³ and is prone to recidivism. The interest this creates in pharmacological and surgical means of treating obesity has resulted in greater understanding of how our appetite is regulated.

Acquisition of calories and nutrients necessary for survival creates a powerful selection pressure on an organism. Evolution has thereby resulted in a complex homeostatic network in individual organisms to regulate appetite and prevent acute changes in adiposity.⁴ In humans, powerful neuroendocrine interplay exists between the digestive system, which initially receives and absorbs nutrients ingested by the organism, the adipose organ, a large endocrine organ involved in both energy storage and anorexigenic signalling, and the brain, the centre of behaviour.⁵ Greater understanding of the crosstalk between these three systems is required in order to facilitate the treatment of the obese patient, and ultimately to reduce the level of obesity and its concomitant complications in the future.

The lipostat hypothesis

Despite our general tendency to get bigger when calories are no object, individually mammals tend to 'guard' their weight. A number of experiments illustrate this: animals were either overfed or underfed for a relatively short time frame, then allowed an *ad libitum* diet. The animals exhibited compensatory behavioural and metabolic changes to restore their original weight, suggesting that there is a sliding set point, which internally monitors weight gain and loss and prevents drastic changes. This 'lipostat' is situated – like many homeostatic regulatory centres – in the hypothalamus.⁶

The lipostat purposefully integrates the peripheral signals of dietary intake and the central signals of satiety, and translates them into appropriate behavioural, metabolic and appetite changes, which maintain weight at its typical level. This is important from a homeostatic perspective: a 1% miscalculation of calorific intake or expenditure (around 20kcal a day, equivalent to a single serving of cabbage) would result in the accumulation

of an extra 1kg a year or >50kg over the average adult lifespan.⁴ It also means that once the set point has been driven upwards (as in obesity), the lipostat modifies energy expenditure and calorie intake to maintain our internally determined weight. Therefore, the traditional medical mantra of 'eat less, move more' may not be sufficient for long-term, meaningful weight loss in those who are clinically overweight/obese.

Peripheral signals: signs of dietary intake

Three separate organs act as peripheral nutrient sensors to the hypothalamic centres involved in appetite: the stomach/small intestine, the pancreas and the adipose organ. Each contributes either to acute appetite regulation (satiety following a meal) or the long-term control of eating. Signals may be endocrine, neural or neuroendocrine in nature, and can be produced by direct sensing of the relevant constituents of food (e.g., fatty acids) or by mechanotransduction (stretch of the viscera leading to relevant hormone release or neural afferent firing).⁷ This gives the central integrating regions of the brain a sense of the volume and type of meal that has been ingested.

Signals from the periphery are almost all stimulated by dietary intake. A variety of mechanisms highlight the complexity of appetite regulation; the major determinants of satiety from the periphery, however, are anorexigenic (stimulate feelings of fullness).⁸

Anorexigenic (appetite-suppressing) signals

Simple neuronal mechanisms act via the vagus nerve. Stretch of the stomach increases the rate of vagal afferent firing, which is processed initially in the nucleus tractus solitarius before projecting to the hypothalamus. As the stomach stretches and mechanotransduction increases, the feeling of fullness increases proportionally.⁸

Neuroendocrine mechanisms also increase the activity of the vagus nerve, either via receptors (e.g., CCK1 receptors responding to cholecystokinin and leading to increased vagal afferent firing) or by increasing gastric stretch, such as the reduction of intestinal motility by peptide tyrosine tyrosine (PYY). The central role of the vagus nerve in communicating satiety signals from the gut is underlined by evidence that vagotomies in animal models often result in a loss of anorexigenic hormone signalling, resulting in overfeeding and weight gain.⁹ Hormones also act centrally to produce feelings of satiety. Glucagon-like peptide 1 (GLP-1), perhaps better known as an incretin since the addition of exenatide to the pharmacopoeia for

diabetes, has an important role in generating central satiety. Delivery of GLP-1 antagonists centrally promoted overeating in experimental rodent models;¹⁰ additionally, the SCALE study recently illustrated that the GLP-1 analogue 'liraglutide' produced meaningful weight loss as an adjunct to diet and exercise.¹¹ Pancreatic peptide (PP) also acts centrally via Y4 receptors and increases proportionally with the calorie content of ingested food boluses.⁷

Two hormones increase proportionally with fat mass: insulin, a pancreatic hormone secreted in response to food ingestion, and leptin, an adipokine directly secreted from adipose tissue. These hormones act as acute and chronic negative feedback loops.⁷ Mice lacking leptin (*ob/ob*) are indistinguishable from their heterozygote littermates at birth, but quickly gain weight through massive overeating. Rarely, human obesity has been shown to be associated with a loss of leptin function; however, in the vast majority of patients leptin is massively oversecreted.¹² This has important implications for how the hormone is sensed centrally and reduces the lipostat's ability to appreciate total fat mass.

Orexigenic signals

There is a single orexigenic signal secreted in the periphery: ghrelin, a peptide secreted from the stomach, acts on its receptor (GHS-R) to stimulate appetite. Ghrelin levels are highest while fasting and are higher in individuals who are chronically fasted (such as those with anorexia nervosa and people on weight loss diets). Ghrelin acts throughout the gut-brain axis to increase gastric motility, gastric acid secretion and calorific intake.⁷

Central signals: our hedonistic brain

The brain is the integrative centre of the whole organism, allowing appropriate responses to both external and internal stimuli. Two important groups of neurons have been identified: an orexigenic group, Agouti-related peptide/neuropeptide Y neurons (AgRP/NPY); and, an anorexigenic group, pro-opiomelanocortin neurons (POMC). AgRP neurons are stimulated by ghrelin and inhibited by PYY, leptin and insulin. In POMC neurons the inverse is true.¹³ This bimodal system of antagonistic neurons integrates peripheral signals, producing an appropriate feeling of hunger or fullness. The result is a sensitive homeostatic sensor, which monitors input and modulates output by multiple efferent pathways, such as the paraventricular hypothalamus, dorsomedial hypothalamic nucleus and the limbic system.¹⁴

This acts via a second order set of neurons to alter metabolism by

regulating thyroid hormone signalling, and behaviour via efferents to higher cortical centres.^{15,16} The cortex also plays a role, with modifications in taste, smell and memory, all driven by activity in the arcuate nucleus and circulating appetite-regulating hormones.¹⁷

Alterations in signalling in the obese patient

So why, in spite of such overwhelmingly complex homeostatic machinery, do people become obese? As individuals gain fat mass, levels of insulin and leptin secretion increase. As is seen in type II diabetes mellitus (T2DM), high circulating levels of insulin result in tissue becoming resistant to its effects, and failure of peripheral tissues to uptake glucose.¹⁸ A similar process occurs in the central nervous system in regards to leptin: as higher levels accumulate in the blood, the brain ceases to respond appropriately, negating leptin's influence as a satiety signal.¹² Subsequently, as patients increase their energy expenditure (exercise) or reduce calorie intake (diet) in order to lose weight, GLP-1, PYY and other anorexigenic hormones are suppressed in favour of ghrelin secretion.³ This acts via central mechanisms, resulting in changes in behaviour and metabolism that prevent effective weight loss, making it difficult for patients to attain sustained and clinically meaningful changes in fat mass.

Bariatric surgery: anatomical or biochemical intervention?

An emerging therapy for obesity is bariatric surgery, particularly the Roux-en-Y gastric bypass. This procedure was developed to produce weight loss through restriction of total stomach volume (producing earlier vagal stimulation by stretch) and malabsorption.³ However, it has since come to light that this mechanism alone is unlikely to result in the sustained weight loss seen in patients postoperatively. Some 85% of patients with T2DM became normoglycaemic following the procedure, independent of weight loss. This suggests that some change is elicited in hormonal signalling and, ultimately, the gut-brain axis.¹⁹

Weight loss following a Roux-en-Y gastric bypass is dissimilar physiologically from weight loss due to starvation, exercise or dieting. With the traditional 'eat less, move more' paradigm, ghrelin increases and GLP-1 and PYY decrease to create an appetite-stimulating hormonal milieu. Following Roux-en-Y the inverse is true.²⁰ The chance of a person having a significant response to Roux-en-Y bypass, or losing a clinically significant amount of weight following surgery, can be predicted with some

accuracy by measuring these hormones. Leptin is reduced to levels comparable to lean subjects, indicating a return to a non-obese hormone profile.¹⁷ Finally, non-specific inhibition of hormone signalling with somatostatin allows for an increase in appetite as tested by an *ad libitum* meal.²¹

Unfortunately, this surgery also carries the risk of developing malabsorption and dumping syndromes; thus, it is only reserved for individuals with very high BMIs (40kg/m² without comorbidities or 35kg/m² with comorbidities).^{22,23} Evidence is beginning to accumulate for a less drastic operation, the sleeve gastrectomy, which carries a lower risk of mortality and morbidity but also has a reduced chance of producing sustained weight loss and a change in obesity-related disease.²⁴

Deep brain stimulation: neuromodulation of a final common pathway

While the hormonal control elicited by gastric bypass is impressive, researchers are now considering how best to manipulate the final common pathway of satiety. Deep brain stimulation (DBS) is currently indicated for a number of diseases (notably Parkinson's disease) with impressive reductions in symptoms.²⁵ This intervention requires stereotactic placement of electrodes in the brain (around the lateral hypothalamus), but eliminates the risk of malabsorption.²⁶ It is arguably more precise than the Roux-en-Y by consistently affecting the final common pathway.

Although research is only beginning in this intriguing approach to a common illness, results are reasonably promising. A 2013 pilot study of bilateral implantation of DBS electrodes (developed for Parkinson's disease) into the lateral hypothalamic nuclei of three patients with intractable obesity was performed safely and had some evidence of efficacy. A major limiting factor of this study was that the electrodes that are produced for Parkinson's neuromodulation are too large to target the specific areas of the lateral hypothalamus associated with appetite;²⁷ however, as the technology develops, more success may emerge from this approach to the treatment of obesity. Additionally, a wide range of alternative targets is being explored – such as elements of the brain's reward circuitry (nucleus accumbens) – suggesting new directions for the future of bariatric surgery.²⁸

Conclusions

Obesity has historically been associated with poor health. Hippocrates reportedly stated: "Corpulence is not only a disease itself, but the harbinger of others". In the modern era of energy-



(and calorie-) sparing devices for work and easy availability of calorie-dense foods, a veritable epidemic of 'corpulence' has emerged.^{29,30} While the best solution to this problem is prevention, there will inevitably be individuals who gain enough weight to endanger their health.

Medical treatment of obesity has historically been simplistic and has neglected the complexity of human biology and the powerful homeostatic mechanisms to prevent sudden changes in physiology. Prescription of diet and exercise will continue to be the mainstay of treatment in the overweight, but an awareness of the limitations of this strategy is an important consideration for clinicians.

Understanding the gut-brain axis also allows for tailoring treatment of the obese patient in novel ways, by using GLP-1 agonists as an adjunct for weight loss or utilising surgery (bariatric or neurological) to fundamentally alter the communication pathways between these organs, as discussed above. Ultimately, this will produce a range of therapies that are: a) effective; and, b) enduring in the fight against obesity, reducing patient morbidity and mortality, and allowing individuals to lead healthier, happier and longer lives.

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