Neuro-endocrinology

BRIEFINGS

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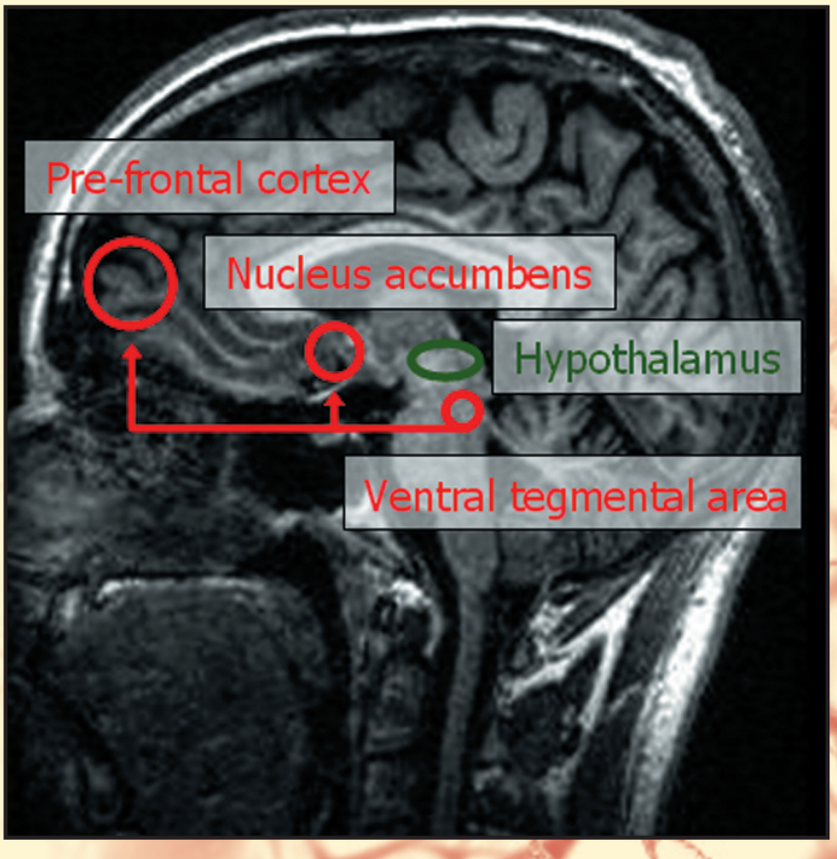
My Brain Made Me Do It, And My Gut Didn't Help

SUMMARY

Decisions about what, when and how much to eat are made by the brain but these choices can be strongly influenced by the hedonic and rewarding properties of sweet or fatty foods. The rumbling before and the fullness after eating tells us that the gut also has an important role in the initiation and termination of feeding. Gut-derived peptides continually convey homeostatic information to the brain to guide feeding. These circulating signals can also modify the pleasure and reward associated with food.

The brain drives eating

The amount and type of food we eat depends not only on energy balance and nutritional requirements, the rewarding properties of certain foods are also extremely influential. Hedonic desire for appetising foods can easily overwhelm homeostatic mechanisms that normally restrict feeding. This is problematic because palatable foods are often not nutritionally balanced - the foods we find tasty tend to be high in sugar, fat, salt and calories. Thus, reward-driven feeding encourages overeating, weight gain and obesity. Let us say that you have a fairly robust resistance to the hedonic appeal of sweet foods and you are able to limit yourself to one meagre 100 kcal bar of chocolate a day in addition to your normal diet. After a year, you will have consumed an extra 35,000 kcal, accumulated a surplus 5 kg body weight and have sufficient energy stores to survive, albeit uncomfortably, for a fortnight without food. We all know that overeating can turn us into something we do not want to be - fat, or even dead! - but cognitive restraint is easily overcome. Gaining a large amount of body weight is easy, losing it is exceptionally difficult. It is easy to see how reward-driven over-consumption of palatable food could contribute to this.



A close-to-midline saggital MRI image of the author's brain. The hypothalamus (green circle) is a complex and interconnected region involved in *homeostatic* feeding. In red are elements of the reward pathway, important in *hedonic* feeding. The ventral tegmental area is activated by sensory stimuli related to reward ("Look! Chocolate!"), the nucleus accumbens is thought to reinforce rewarding behaviour and be involved in the sensation of pleasure ("Remember? Chocolate tastes nice!"). The pre-frontal cortex guides thought and action ("Go on, eat the chocolate!").

The gut has a mind of its own

The most common approach to reverse obesity requires cognitive changes: making a conscious effort to eat differently, or more modestly, or to do (a lot) more strenuous activity. Happily, the most successful long-term treatment for obesity seems to require no willpower at all. However, nothing is ever simple, and obesity must reach a riskily morbid state and submission to the surgeon's blade is required. Bariatric surgery describes any form of surgery that reduces the volume or absorptive area of the proximal gut. Surgery results in rapid sustained weight loss and resolves type II diabetes more often than not. Originally, it was believed that the beneficial effects of bariatric surgery derived from hastening the feeling of fullness and a malabsorption syndrome. Post-operatively, patients could no longer endure large meals or absorb so many calories. However, it seems that this simplistic explanation is not true – instead, alterations in the way the gut-brain axis signals information to the brain's homeostatic and reward pathways are responsible for many of the clinical improvements after bariatric surgery. Understanding these changes fully may allow us to pharmacologically mimic post-surgical changes so obese individuals can lose weight without having to risk irreversible surgery.

Listening to the gut

At least two potential therapeutic approaches exist - to inhibit hunger or to enhance satiety. Since only one hunger-promoting gut peptide has been identified to date (ghrelin), modifying the gut-brain axis to inhibit hunger may be an unachievable, and perhaps unwanted, goal. After all, undernutrition or starvation are arguably just as hazardous as over-eating. Instead, enhancement of satiety represents a more appealing approach to fight obesity, and many gut peptides contribute to the termination of food intake by signalling satiety. Glucagon-like peptide (GLP-1) and peptide YY3-36 are co-released from the ileum and colon to act in the brain to reduce acute food intake. Obese humans have lower circulating levels of these peptides, and injection of either causes weight loss in both lean and obese humans. GLP-1 also improves glucose tolerance in diabetic patients. At present it is not clear whether beneficial changes in the gut-brain axis after bariatric surgery depend on homeostatic pathways, reward pathways or both. It is not only humans who respond to bariatric surgery, it works for obese rats too and studies using rodent models of bariatric surgery have begun to address these questions.

"Gaining body weight is easy, losing it is exceptionally difficult"

Post-operatively, rats, like humans, have a decreased desire to consume fatty foods and this aversion to fat increases as time passes. Furthermore, rats prefer less-sweet foods after surgery - a reversal of the increased preference for sweetness seen in obesity. In other words, it is possible that changes in gut-brain signalling may alter hedonic eating.

Keeping healthy in the face of the seductive drive to eat is hard, but understanding the central mechanisms of action gut-brain axis peptides may lead to the development of foods or drugs for the treatment of obesity. For example, the release pattern of certain gut peptides is dependent on the type of macronutrient consumed. Thus it is conceivable that foods could be designed to stimulate satiety either homeostatically or by enhancing the feeling of pleasure or reward. Alternatively, drugs that mimic the central effects of gut peptides are under development. Weekly injection of an analogue of GLP-1 reduces body weight and adiposity while improving glucose tolerance in rats made obese by a high-fat diet. Foods or drugs such as these have the potential to restrain hedonic feeding and simultaneously re-establish or strengthen a link between homeostatic requirements and food intake.

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