# Gut feelings about appetite

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The obesity epidemic is now widely recognized as a major threat to health in many different countries. Some surgical therapies for obesity are efficacious and indicate that signals from the gastrointestinal tract are capable of exerting beneficial long-term effects on food intake and body weight. The development of non-surgical therapies targeting this system depends on understanding how food, and the absence of food, in the gastrointestinal tract signals to those parts of the brain that regulate feeding behaviour. What can be called gastrointestinal surveillance systems include both nervous pathways linking the gut and brain, and some gut hormones. Nutrient sensing mechanisms within the gastrointestinal tract determine the release of satiety hormones such as *cholecystokinin* (CCK), or appetite stimulating hormones such as *ghrelin*, and offer potential therapeutic targets. It seems that CCK and *ghrelin* both act on the vagus nerve that links the gut to the brain. Examples of interactions between different factors regulating this pathway are discussed. It is argued that sufficient is now known to indicate that this signalling system can provide new targets for the treatment of obesity.

## Introduction

Obesity has developed in Western societies so much that it can be regarded now as an epidemic that is a major threat to health, and this is the case in a growing number of developing countries as well.[1] The origins of this epidemic are not clear, but they include influences at the interface of genetic inheritance, culture, life style, economics and physiology. The implications are beyond aesthetics since obesity is linked to many common, important diseases including Type-2 diabetes, high blood pressure, coronary artery disease, osteoarthritis and cancer. Whilst changes in life style and diet directed at increasing energy expenditure and decreasing energy intake are important primary objectives in preventing obesity, these strategies do not prove especially useful in reducing obesity in individuals who are already obese or in long term maintenance of weight loss.[2] For the growing number of people in this group, therefore, other therapeutic approaches are necessary.

The overall balance between energy intake and expenditure determines body weight over relatively long periods, and understanding the relevant control mechanisms within the body is important. Possible therapeutic targets based on this knowledge have started to emerge.[3] In the brain, mechanisms controlling food intake and metabolism are concentrated in the hypothalamic region. This region receives signals from the stomach and intestines via the vagus nerve and also through the blood stream via hormonal influences from fat cells (adipose tissue)[3] and from the gut. An emerging body of evidence now suggests that it is timely to reconsider whether these signals might also provide opportunities to develop treatments for obesity.

### Long versus short term: obesity therapy by modulating visceral signals?

One of the main signals from fat cells is the polypeptide hormone *leptin*, which is released into the blood and conveyed to the brain where it regulates nervous pathways leading to inhibition of food intake and stimulation of energy expenditure. Animals with mutations in the gene responsible for the synthesis of the *leptin*, and also those very rare humans with *leptin* gene mutations, exhibit excessive eating (hyperphagia) and obesity. Administration of *leptin* to individuals with a mutant *leptin* gene dramatically reduces their hyperphagia and obesity.[4] However, it has not so far proved possible to develop more widely applicable treatments for obesity based on *leptin* administration.

In contrast to *leptin*, signals from the gastrointestinal tract are generally thought to be involved in terminating an individual meal, i.e. they determine meal size. For this reason they have often been considered as primarily concerned with relatively short-term control of food intake, which may account for their neglect as potential therapeutic targets in obesity.[5] An approach to restricting food intake could be through operations that reduce the volume of the stomach or one of several forms of gastric bypass (food passing directly to more distal parts of the gut thereby avoiding digestion and absorption), or combinations of the two.[6] A recent review of the efficacy of these operations concluded that they produce sustained loss of body weight in excessively obese subjects, and that the treatment is cost-effective. Is it obvious that because a smaller stomach is more readily filled there should be reduced food intake leading to weight loss, or do the results with gastric surgery suggest there are interesting things to learn about the mechanisms regulating food intake, that might be useful in developing new, non-surgical, treatments of obesity?

### The gut surveillance systems

The transmission of information from the gastrointestinal tract to the brain

depends on what can be called the surveillance systems of the gut. These are involved in sensing changes in the environment of the digestive tract and in directing the appropriate responses. The nervous pathways connecting the digestive tract and brain provide one part of the system. During normal digestion, the vagus nerve is an important route for signalling both from gut to brain, and from brain to gut. Vagal nerve fibres serving the stomach are activated by gastric distension and changes in their activity are likely to occur in patients after the gastric surgery mentioned above. Importantly however, signalling by vagal nerve fibres running from gut to brain is also closely linked to a second surveillance system, the hormonal (or endocrine) system of the gut.

It is just over 100 years since the first gut hormone (*secretin*) was discovered. It is responsible for the secretion of bicarbonate and water from the pancreas in response to the arrival of stomach acid in the duodenum. It was assumed that the gut hormones were released after a meal by the presence of food in the gut. This was supported by the anatomical observation that enteroendocrine cells in many cases project into the lumen of the intestine and so appear specialized for sampling the contents.

The gut hormones are released from the digestive tract into the bloodstream and trigger effects elsewhere in the body. Taken as a whole, the endocrine surveillance system is made up of about a dozen different hormones each produced in specialized cell types collectively known as enteroendocrine cells.[7] The system can be loosely grouped into three functional domains concerned with regulating digestion in one or other of the stomach, upper small intestine or ileum/colon. Most gut hormones appear to have roles directed at controlling digestion within their own domain of the gut, and with regulating nutrient entry to, or exit from, that region. The control of food intake, i.e. nutrient delivery, by gastrointestinal surveillance mechanisms therefore provides one component of a system directed at optimizing nutrient digestion and absorption.

It has recently come as a surprise that at least three hormones produced in enteroendocrine cells might be released not by food, but by the absence of food in the gut, i.e. during fasting. Two of these, *ghrelin* and *orexin-A*, stimulate food intake. Interestingly, *ghrelin* release is reported to be suppressed after gastric surgery for obesity treatment.[8] This means the efficacy of gastric restriction and bypass surgery in obesity subjects is not just mechanical. Clearly, it now becomes important to know whether inhibiting the release of hormones such as *ghrelin* is sufficient on its own to decrease appetite.

### Tasting the gut contents

The way that some enteroendocrine cells sense the absence of food is still largely unknown. The factors may be physical (e.g. mechanical stretching of the stomach

wall by its contents) or chemical (including both nutrient and non-nutrient chemicals). In addition, infectious agents, particularly bacteria, influence gut hormone secretion. At a cellular level there is now growing evidence that nutrient sensing in the gut may depend on mechanisms similar to those involved in tasting food in the mouth, although for the most part conscious sensations of taste are not generated.

One encouraging development is the identification of specific sensing mechanisms in enteroendocrine cells that involve a class of molecule known as G-protein-coupled receptors, or GPCRs.[9] These mediate the action of many different types of cell–cell signalling in the body; they are also involved in sensing an extraordinary range of odours in the nose and in sensing sweet and bitter tastes in the mouth.[10] Very many different GPCRs have been identified. What makes them important is that they are targets of many common drugs, and the knowledge required to generate novel compounds acting at GPCRs is relatively well developed. Very little has been done so far to exploit systems of nutrient sensing by enteroendocrine cells as therapeutic targets. However, just as there are chemical compounds that taste sweet and can be used as sugar replacements without adding appreciably to the calories in the diet, it should, in principle, be possible to produce compounds that have no nutrient value but target nutrient receptors on enteroendocrine cells to stimulate or inhibit selectively the release of gut hormones. Therapeutically useful compounds might therefore inhibit the release of appetite stimulants such as *ghrelin* or stimulate the release of satiety factors.

## CCK: key regulator of gut–brain signalling

Of the several gut hormones that evoke sensations of satiety, *cholecystokinin* (CCK) has been studied the longest and most intensively. It is produced in the first part of the small intestine and can be viewed as a regulator of fat and protein digestion in this part of the gut. It works by balancing the capacity for digestion with the delivery of food to be digested. On the one hand, this is achieved by stimulating pancreatic enzyme secretion and gall bladder contraction, both of which increase the capacity for digesting fat and protein into forms suitable for absorption. On the other hand, CCK also inhibits the delivery of food to the small intestine and it does this both by reducing the rate of emptying of the gastric contents into the intestine, and by inhibiting food intake.[11,12] The latter effects have provided an important model for understanding the control of food intake by gut hormones.

Digestion of dietary fat (triglycerides) yields fatty acids and it is these that stimulate CCK release. Inhibiting this digestion has, in fact, already provided one compound for treating obesity, namely, *tetrahydrolipstatin* and the principle

underlying its action is to deprive the body of fatty acids by inhibiting triglyceride digestion.[2] This approach has not been very successful, mainly owing to a range of unpleasant side effects. Moreover, ironically, it actually leads to a reduction in CCK secretion (i.e. loss of a satiety factor).[13] The human diet typically contains a wide range of different fatty acids that vary in the number of carbon atoms they contain. The release of CCK appears particularly sensitive to the number of carbon atoms in the fatty acid chain. Those fatty acids with a chain length greater than 12 carbon atoms are effective releasers of CCK (and increasing chain length further has little additional effect), while those with a chain length of 11 carbons or shorter are ineffective.[14] Currently, there is great interest in diets high in fat and protein (the Atkin's diet) which seem to be effective in treating obesity. This paradoxical effect of increased fat intake promoting the disposal of body fat could possibly be explained through this effect on CCK. Taken together with recent work suggesting there may be a GPCR that responds to dietary fatty acids[15,16] it no longer seems idle to suppose that drugs might be developed that lack the calories of fatty acids, but retain the special property of mimicking fatty acids in releasing CCK and so exerting satiety effects.

## Modulation of CCK and vagal nerve signalling

Although most areas of the brain exclude peptide hormones (like those released from the gut) by means of a barrier (the blood–brain barrier), this is not the case for the hypothalamus which is therefore thought to be a direct target for some hormones controlling appetite. Alternatively, however, hormones can influence behaviour by acting on nervous pathways leading into the brain and the vagus nerve turns out to be an important route for mediating hormonal signals influencing food intake.

CCK acts on specific receptors (known as CCK-A or CCK-1 receptors) that are found on the vagal neurons running from gut to brain (called afferent neurons in contrast to those running from brain to gut, the efferent neurons). The vagal afferent neurons serving the stomach also work as mechanoreceptors[17] and probably include those responding to gastric distension. Mimicking or enhancing the effects of CCK on this system would therefore be expected to increase sensations of satiety.

Several different ways in which the activity of the CCK-vagal signalling system may be modulated are now recognized. For instance, the sensitivity of this system changes during infection and inflammation, specifically in the small intestine. One example is infection with *Giardia* which occurs in the part of the intestine that produces CCK and is associated with increased CCK release.[18] In contrast, infections that are mainly restricted to lower parts of the gastrointestinal tract such as the colon (leading for example to diarrhoea) are not associated with increased

CCK release. Infection of the small intestine is also associated with loss of appetite, as well as sensations of nausea and bloating. It is unlikely that there is a single factor responsible for these sensations. Even so, the increased release of CCK can plausibly be supposed to play a role in loss of appetite. In adults, and in economically advanced societies, this type of infection may often be little more than an inconvenience. But in children, particularly in the developing world, recurrent infections of this type, associated with loss of appetite where calories may be restricted in any case, may well have longer lasting implications for normal growth, development and health.

The increased release of CCK in intestinal infections gives rise to the question of whether counter-balancing or restraining influences might exist. Two new candidates have emerged in this regard, and both – as might be expected – are associated with stimulation of appetite. *Ghrelin* is produced in the stomach and, as has already been mentioned, stimulates food intake and this action requires the vagus nerve,[19] perhaps by decreasing the discharge of vagal afferent neurons that stimulate appetite, leading to satiety.[20] The other appetite-stimulating hormone, *orexin-A*, also acts on vagal afferent neurons and has been shown to reverse the effect of CCK on the discharge of these neurons.[21]

The development of drugs targeting the vagal/satiety pathway is a possibility. It has long been known that cannabis stimulates appetite. The active agent in cannabis, $\Delta^9$-tetrahydrocannabinol, acts at CB1 receptors, which are widely distributed in the central and peripheral nervous systems. They normally respond to the body's own cannabis compounds, the *endocannabinoids*, of which *anandamide* and *2-arachidonylglycerol* are good examples. *Anandamide* stimulates food intake and increases in concentration in the intestine during food restriction.[22] Remarkably, a related compound, *oleoylethanolamide*, inhibits food intake probably via a mechanism that does not include cannabinoid receptors.[23] While the effects of *anandamide* and *oleoylethanolamide* on food intake are in opposite directions, in both cases it appears that the vagus nerve is a target for their effects. Moreover, it seems that there are interactions between CCK-1 and CB1 receptors in controlling signalling by the vagal afferent pathway (unpublished observations). Manipulation of this system through the development of compounds targeted at decreasing appetite or evoking satiety, can therefore be expected to offer therapeutic benefits.

### Evolutionary perspective

Biologically important signalling systems frequently exhibit redundancy, so that if one component of a signalling network is lost another compensates. For something as fundamental to survival as the control of food intake, it should not therefore be a surprise that there is a multiplicity of regulatory molecules with

many complex interactions. However, one of the fascinating features of the systems controlling food intake is that many of the primary regulatory molecules are deployed in more than just one part of the body. For example, the same receptors and signalling molecules that work in regions of the brain like the hypothalamus are also found in the gut and vagus nerve, and in each case are involved in control of food intake. This seems to be a remarkable example of conservation of function during evolution, by which a common set of regulatory molecules has been selected for the control of body weight at multiple physiological levels. The pressure of evolution, at least for the most part, has been directed at fitting organisms to face the challenge of survival in periods of food shortage, interspersed with periods of abundance. Shortage of food is no longer a day-to-day challenge to the survival of a growing proportion of the world's population, and obesity is one result. Impressive progress has been made in the identification of neurochemical signalling pathways that determine the way that body weight is regulated. The new challenge is to identify those components that can most readily be targeted to redress the imbalance in obesity. Sufficient is now known to indicate that signals from the gut might provide new approaches to meet this challenge.

## References

1. WHO Technical Report Series 916 (2002) Diet, Nutrition and the prevention of chronic diseases.
2. S. Klein, T. Wadden and H. J. Sugerman (2002) AGA technical review on obesity. *Gastroenterology*, **123**, 882–932.
3. J. C. Clapham, J. R. Arch and M. Tadayyon (2001) Anti-obesity drugs: a critical review of current therapies and future opportunities. *Pharmacol. Ther.*, **89**, 81–121.
4. S. O'Rahilly, I. S. Farooqi, G. S. Yeo and B. G. Challis (2003). Minireview: human obesity-lessons from monogenic disorders. *Endocrinology*, **144**, 3757–3764.
5. S. C. Woods, R. J. Seeley, D. Porte, Jr. and M. W. Schwartz (1998). Signals that regulate food intake and energy homeostasis. *Science*, **280**, 1378–1383.
6. National Institute for Clinical Excellence,T.A.N.4. (2002) Full guidance on the use of surgery to aid weight reduction for people with morbid obesity.
7. G. J. Dockray (2003) Making sense of gut contents. *Scand. J. Gastroenterol.*, **38**, 451–455.
8. D. E. Cummings, D. S. Weigle, R. S. Frayo, P. A. Breen, M. K. Ma, E. P. Dellinger and J. Q. Purnell (2002) Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *New England Journal of Medicine*, **346,** 1623–1630.
9. S. V. Wu, N. Rozengurt, M. Yang, S. H. Young, J. Sinnett-Smith and E.

Rozengurt (2002) Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. *Proceedings of the National Academy of Science USA*, **99**, 2392–2397.

10. B. Lindemann (2001) Receptors and transduction in taste. *Nature*, **413**, 219–225.

11. J. Gibbs, R. C. Young and G. P. Smith (1973) Cholecystokinin elicits satiety in rats with open gastric fistulas. *Nature*, **245**, 323–325.

12. G. J. Dockray (1988) Regulatory peptides and the neuroendocrinology of gut-brain relations. *Q. J. Exp. Physiol.*, **73,** 703–727.

13. P. Hildebrand, C. Petrig, B. Burckhardt, S. Ketterer, H. Lengsfeld, A. Fleury, P. Hadvary and C. Beglinger (1998) Hydrolysis of dietary fat by pancreatic lipase stimulates cholecystokinin release. *Gastroenterology*, **114**, 123–129.

14. J. McLaughlin, L. M. Grazia, M. N. Jones, M. D'Amato, G. J. Dockray and D. G. Thompson (1999) Fatty acid chain length determines cholecystokinin secretion and effect on human gastric motility. *Gastroenterology*, **116**, 46–53.

15. Y. Itoh, Y. Kawamata, M. Harada, M. Kobayashi, R. Fujii, S. Fukusumi, K. Ogi, M. Hosoya, Y. Tanaka, H. Uejima, H. Tanaka, M. Maruyama, R. Satoh, S. Okubo, H. Kizawa, H. Komatsu, F. Matsumura, Y. Noguchi, T. Shinohara, S. Hinuma, Y. Fujisawa and M. Fujino (2003) Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature*, **422**, 173–176.

16. C. P. Briscoe, M. Tadayyon, J. L. Andrews, W. G. Benson, J. K. Chambers, M. M. Eilert, C. Ellis, N. A. Elshourbagy, A. S. Goetz, D. T. Minnick, P. R. Murdock, H. R. Sauls Jr., U. Shabon, L. D. Spinage, J. C. Strum, P. G. Szekeres, K. B. Tan, J. M. Way, D. M. Ignar, S. Wilson and A. I. Muir (2003) The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. *J. Biol. Chem.*, **278**, 11303–11311.

17. H. E. Raybould, R. J. Gayton and G. J. Dockray (1988) Mechanisms of action of peripherally administered cholecystokinin octapeptide on brain stem neurons in the rat. *Journal of Neuroscience*, **8,** 3018–3024.

18. F. C. Leslie, D. G. Thompson, J. T. McLaughlin, A. Varro, G. J. Dockray and B. K. Mandal (2003) Plasma cholecystokinin concentrations are elevated in acute upper gastrointestinal infections. *Quart. J. Med.*, **96**, 870–871.

19. M. Kojima, H. Hosoda, Y. Date, M. Nakazato, H., Matsuo and K. Kangawa (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*, **402**, 656–660.

20. Y. Date, N. Murakami, K. Toshinai, S. Matsukura, A. Niijima, H. Matsuo, K. Kangawa and M. Nakazato (2002) The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology*, **123**, 1120–1128.

21. G. Burdyga, S. Lal, D. Spiller, W. Jiang, D. Thompson, S. Attwood, S. Saeed, D. Grundy, A. Varro, R. Dimaline and G. J. Dockray (2003) Localization of orexin-1 receptors to vagal afferent neurons in the rat and humans. *Gastroenterology*, **124**, 129–139.

22. R. Gomez, M. Navarro, B. Ferrer, J. M. Trigo, A. Bilbao, A. I. Del, A. Cippitelli, F. Nava, D. Piomelli and D. F. Rodriguez (2002) A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *Journal of Neuroscience*, **22**, 9612–9617.

23. D. F. Rodriguez, M. Navarro, R. Gomez, L. Escuredo, F. Nava, J. Fu, E. Murillo-Rodriguez, A. Giuffrida, J. LoVerme, S. Gaetani, S. Kathuria, C. Gall and D. Piomelli (2001) An anorexic lipid mediator regulated by feeding. *Nature*, **414**, 209–212.

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