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Gut hormones and the treatment of disease cachexia

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Advances in the understanding of appetite are leading to a refined concept of disease cachexia and point to novel therapeutic strategies based on the manipulation of appetite. The complex social and psychological short-term influences on appetite obscure the fact that over the longer term appetite is tightly regulated by physiological considerations; the homeostatic control of energy balance. Like obesity, which is now viewed as a disorder of homeostasis, cachexia can be seen as an adaptive response to the disease state that becomes harmful when prolonged. Several lines of evidence implicate a disorder of appetite regulation in the pathogenesis of cachexia. As the only known circulating mediator of increased appetite the peptide hormone ghrelin has attracted attention as a potential therapy. Trials in patients with various chronic illnesses, including cancer and kidney failure, have demonstrated short-term increases in energy intake. Trials in patients with emphysema and heart failure have also shown benefits in clinical outcomes such as lean body mass and exercise capacity, and longer-term trials using oral analogues are being undertaken. As well as improving nutrition, ghrelin has a number of other actions that may be useful, including an anti-inflammatory effect; of interest since many cachexias are associated with inappropriate immune activation. The manipulation of appetite, in particular by ghrelin agonism, is emerging as an exciting potential therapy for disease cachexia. Future research should focus on the ascertainment of clinically-relevant outcomes, and further characterisation of the non-nutritional effects of this pathway.

Disease cachexia: Appetite manipulation: Ghrelin

Advances in the understanding of energy homeostasis have led to the realisation that a number of conditions are caused by a disorder of appetite regulation. Many gut hormones are circulating mediators of appetite control and can be used therapeutically to manipulate appetite. This developing field, which is largely driven by the need to understand obesity, is also of relevance to cachexia, which as a result is undergoing a change in concept from unavoidable symptom to treatable complication.

Cachexia

Cachexia refers to the decline in nutritional state that is a common feature of many chronic diseases, including cancer, heart failure and chronic kidney disease. It involves

the loss of both the fat and protein stores (the latter coming largely from skeletal muscle) leading to weight loss and weakness, and even at an early stage it is associated with increased mortality. Although the hallmark of cachexia is weight loss, this outcome may be difficult to detect in the early stages or may be masked by other factors such as fluid retention, but cachexia can be said to exist when there is a persistent state of negative energy or protein balance. It therefore becomes most apparent as the disease progresses and is often thought to be a feature of ‘end-stage’ disease. However, in reality it has been present since very early in the patient’s illness and may have been amongst the presenting features when the disease was first diagnosed. Chronic kidney disease is no exception, with cachexia beginning early and progressing along with the

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decline in function of the kidneys. It is most evident therefore in those requiring dialysis treatment and becomes more common with increasing duration on dialysis^(1–4).

Cachexia in chronic diseases has profound survival implications. In relation to kidney disease, studies of patients treated in French dialysis units in the 1970s first revealed a link between poor nutritional state and mortality⁽⁵⁾, and since then a number of large studies have confirmed higher mortality associated with low albumin, low BMI or low creatinine^(6–8). This link has been confirmed with a wide variety of indicators of energy balance, including appetite, protein intake and energy expenditure^(9–11), as well as specialised measures of body composition including bioimpedance analysis and dual-energy X-ray absorption^(12,13). Baseline levels of biochemical variables such as albumin and cholesterol are the most powerful prognostic indicators in patients undergoing dialysis and have been shown to predict survival far in advance, with follow-up periods in some studies as long as 10 years^(14,15).

Poor nutrition has also been found to predict high mortality in other chronic illnesses. Weight loss or low BMI are poor prognostic factors in heart failure^(16–21), emphysema^(22–24), cirrhosis of the liver⁽²⁵⁾ and rheumatoid arthritis^(26,27). Similar findings have been made in many cancers^(28–32), with the possible exception of breast cancer, for which low BMI is not associated with increased mortality, unlike low albumin^(33,34).

The fact that nutritional indices predict mortality far in advance, independent of and better than other prognostic variables, suggests that cachexia in itself has a detrimental effect on survival. It is therefore not merely a symptom with no importance beyond being unpleasant for patients, but a complication with its own adverse outcomes and a legitimate object of life-prolonging (as opposed to palliative) treatment. Although obvious, this issue is important, since it is frequently doubted or overlooked by clinicians. Evidence resolving this issue is lacking however; the question of whether a sustained improvement in nutritional state alone leads to a survival benefit would be best addressed with interventional studies, but for the most part remains unanswered because of the difficulty of achieving sustained nutritional improvement.

The cause of malnutrition in these conditions is poorly understood. Energy expenditure has been found to be increased by most investigators and there is sometimes a small quantity of abnormal nutrient loss, e.g. during the dialysis procedure, but the predominant finding is of reduced appetite. Occasionally this anorexia is a result of secondary complications that are known to influence appetite such as gastritis or a concurrent infection, but for the most part the reduction in appetite occurs when no reversible factor can be identified. The frequent observation of increased levels of inflammatory cytokines in the plasma has led some investigators to the conclusion that cachexia is caused by inflammation, and the pathogenesis of cachexia and inflammation are undoubtedly linked⁽³⁵⁾. However, the predominant direction of this association is far from clear and neither mechanism is well understood.

Cachexia therefore appears to be an intrinsic part of the primary disease, for which the pathogenesis is unclear.

In order to understand this process it is necessary to focus on appetite and how it is normally regulated, because despite the influence of numerous external factors appetite is surprisingly tightly controlled.

Appetite

Like the fact that objects fall to the ground, the fact that man has the desire to eat is such a fundamental part of his existence that it is sometimes difficult to appreciate the underlying mechanism.

In the short term, appetite depends on an enormous number of factors, which doubtless include the body's need for energy but more frequently are dominated by other considerations: 'this food is really nice, but I should leave some for my friend, plus I want to look good on the beach this summer, although it is still only February ...' 'Which is most important right now?' It appears to be a choice that is dependent on values and personality.

However, the long-term picture is quite different, and this position can be appreciated with a simple calculation. Although body weight tends to increase slightly during much of adult life, it is remarkable for its stability, with a yearly weight change of <1 kg in most of the population⁽³⁶⁾. The excess energy needed to induce this weight gain has been variably estimated, but is approximately 30 MJ⁽³⁷⁾, whilst the yearly energy intake is >3000 MJ. Consequently, most individuals manage to match energy intake to equal energy expenditure, with an error of <1%. It was long suspected, therefore, that a regulatory system existed to control appetite in order to maintain energy homeostasis⁽³⁸⁾, and this theory was confirmed by the subsequent discovery of some of the elements of this system, beginning with the discovery of the adipose tissue hormone leptin⁽³⁹⁾, which gives feedback to the brain about the adequacy of energy stored in the form of fat. Obesity is now firmly accepted to be a disorder of this homeostatic system.

That energy balance is homeostatically controlled suggests that cachexia, as another condition in which energy is imbalanced, is also a disorder of this homeostatic system. If an external factor arises that influences appetite or energy expenditure in some way, then the regulatory system should adjust to restore energy balance. A persistent state of imbalance is maintained when the system itself is disordered or adjusted.

This outcome explains the difficulty encountered in increasing long-term energy intake in clinical trials, which is seen even when energy supplements are administered parenterally. For example, in a randomised trial of intradialytic parenteral nutrition in patients undergoing haemodialysis both groups received an oral supplement, but the intervention group also received an intravenous supplement of approximately 25 kJ/kg at each dialysis session (three times per week) for 12 months. Modest improvements in albumin and body weight were found for both groups, but no benefit in clinical outcomes and no differences between the two groups. One striking finding was that spontaneous energy intake (i.e. what the patients were eating at home between dialysis sessions) gradually

declined over the first 6 months of the trial in both groups, and even more so in the intervention group, so that the total energy intake was found to be little changed in either group during most of the trial⁽⁴⁰⁾. To compensate for the supplements being taken appetite was subconsciously being down-regulated, restoring the total energy intake to its previous level.

It has thus far been reasoned on theoretical grounds that cachexia is likely to be a result of some change in appetite regulation, but no direct evidence has been considered. However, different lines of evidence are beginning to emerge that firmly implicate appetite control in the pathophysiology of cachexia.

First, human observational studies have suggested that negative regulators of appetite are elevated in cachexia. Most attention has focused on leptin, which is higher than expected in heart failure^(41,42) as well as in chronic kidney disease^(43,44), although other hormones are also involved, such as peptide YY, which is also elevated in these conditions⁽⁴⁵⁾. Although many of these studies are merely highlighting a cross-sectional association, longitudinal studies have also shown that raised baseline leptin predicts weight loss over the next 17 months in patients undergoing dialysis, strengthening the likelihood that this association is indeed causal⁽⁴⁶⁾.

Second, a number of animal studies have shown prevention or reversal of cachexia by deletion or blockade of specific appetite pathways. For example, in the melanocortin-4 receptor-knock-out mouse, which lacks a key part of the brain's appetite circuitry⁽⁴⁷⁾, the cachexia that usually follows the induction of kidney failure or cancer in mice, induces very little change in body weight in leptin receptor-deficient mice⁽⁴⁸⁾. In addition, injection of a melanocortin antagonist into the brain, which therefore blocks part of the appetite circuit, reverses the weight loss in cancer-bearing mice⁽⁴⁹⁾, and in other experiments the loss of appetite and lean body mass are prevented by peripheral injection of similar agents^(50,51).

Cachexia therefore appears to be a result of an adaptation of appetite to the diseased state. However, if reduced appetite in these conditions has such adverse consequences, then why should such an adaptive mechanism exist? Although speculative, the answer is perhaps obvious when it is considered that short-term illnesses are a more powerful evolutionary pressure than modern chronic diseases, which occur largely in later life. During a short-term illness such as an infection or injury it would be advantageous for appetite to be diminished, so that food-seeking behaviours, e.g. hunting, that would be more hazardous than usual are postponed until after recovery from the illness. Reduced appetite and cachexia may well be consequences of an adaptive mechanism that is of no advantage in the modern setting.

Ghrelin

Ghrelin is a gut hormone involved in appetite regulation that has attracted attention as a possible means of

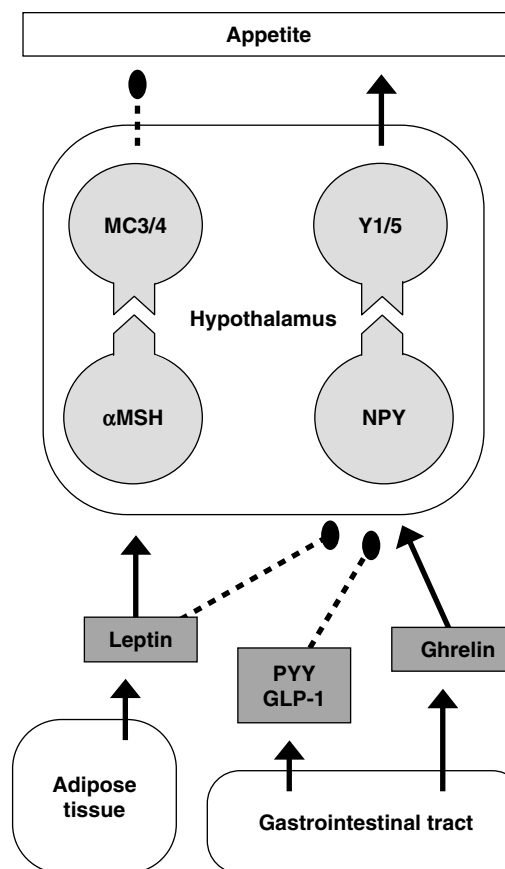


Fig. 1. Simplified model of homeostatic appetite control. Appetite is largely governed by the opposing actions of two populations of neurons within the hypothalamus: those releasing melanocortin (MC)-stimulating hormone (α MSH), which act via the MC3 and MC4 receptors and reduce appetite; those releasing neuropeptide Y (NPY), which act via the Y1 and Y5 receptors to increase appetite. A number of circulating hormones affect appetite largely through their action on these hypothalamic neurones. Leptin from adipose tissue reduces appetite, whereas ghrelin from the stomach increases appetite. The gastrointestinal tract also releases a number of 'satiety' hormones after a meal that, amongst other actions, reduce appetite; these hormones include peptide YY (PYY) and glucagon-like peptide 1 (GLP-1). —, Stimulates; ..., inhibits.

increasing appetite in the treatment of cachexia. It will be helpful to review the relevant physiology briefly.

Integration of the peripheral signals controlling appetite takes place within the hypothalamus. For a detailed consideration of appetite control, which is beyond the scope of the present article, excellent reviews are available^(52,53). Very briefly, there are two types of neurons within the arcuate nucleus (located at the base of the hypothalamus) that have opposing effects on ingestive behaviour and respond differently to a number of circulating hormones (Fig. 1). Neuropeptide Y-releasing neurons are orexigenic (increasing food intake), whereas melanocortin-releasing neurons are anorexigenic. Anorexigenic signals from the periphery include leptin from adipose tissue and a number of satiety signals from the gut that are released following a meal, e.g. peptide YY and oxyntomodulin. The only known orexigenic signal from the periphery is ghrelin.

Ghrelin was originally discovered as the endogenous ligand for a receptor known to cause the release of growth hormone⁽⁵⁴⁾, and increased growth hormone after ghrelin injection has been demonstrated in rodents⁽⁵⁵⁾ and man⁽⁵⁶⁾. Of greater interest was the subsequent appreciation of its role in appetite generation. Through its action on neuropeptide-releasing neurons in the hypothalamus^(57–59) ghrelin leads to increased food intake and weight gain in rodents^(60–62) and has been shown to increase food intake, as well as the feeling of hunger in healthy volunteers, when given by intravenous infusion or subcutaneously^(63,64).

Levels of ghrelin rise progressively during the day when not eating, reaching a peak before a meal, after which there is an abrupt drop in levels, suggesting a short-term role in the initiation of each meal. In addition, this daily pattern is superimposed on a basal level that is increased following weight loss by dieting, which suggests involvement also in the longer-term regulation of appetite^(65,66).

In animal models of disease-induced cachexia ghrelin has been shown to increase food intake and prevent the loss of body weight. This effect has been seen in rats with wasting induced by repeated lipopolysaccharide injections⁽⁶⁷⁾, rats with cardiac cachexia induced by coronary artery ligation⁽⁶⁸⁾ and in rats and mice with tumours^(69,70). A few studies have examined the potential for ghrelin to improve nutritional status in human cachexia.

In a randomised cross-over study of a single dose of ghrelin given by infusion, increased appetite has been demonstrated in patients with metastatic cancer and anorexia and weight loss⁽⁷¹⁾. On separate days patients who were unaware of their treatment allocation were given ghrelin or saline (9 g NaCl/l) by infusion after an overnight fast and then served an excessive quantity of a preselected meal. All seven patients increased their energy intake by an average of 31% following ghrelin infusion, and reported greater appreciation of the meal.

A similar study conducted on nine patients with kidney failure treated by peritoneal dialysis has shown a doubling of energy intake immediately following subcutaneous administration and a 27% increase over the first 24 h period⁽⁷²⁾. Importantly, food intake over the next 48 h period was unchanged, demonstrating the lack of a compensatory underswing.

The longer-term anabolic effects of ghrelin have also been demonstrated in non-randomised studies involving twice daily infusions. In ten patients with heart failure, left ventricular ejection fraction, exercise capacity and lean body mass were all shown to increase after 3 weeks of treatment, whilst no change was observed in a control group of patients hospitalised for diagnostic testing⁽⁷³⁾. The same investigators have reported similar results in seven patients with chronic obstructive pulmonary disease in whom respiratory muscle strength, lean body mass and functional capacity were found to be improved after a 3-week period of treatment⁽⁷⁴⁾.

It seems likely therefore that the acute effect on appetite translates into a medium-term improvement in nutritional state, but ghrelin is thought to possess a number of other actions that are not obviously nutritional and may prove to be relevant to the cachexia of chronic diseases.

Ghrelin lowers blood pressure by vasodilation in rodents and man by an effect that appears to be independent of NO^(75–77), and this process leads to an increase in stroke volume and cardiac output without a marked change in heart rate in healthy volunteers as well as patients with heart failure^(78–80). This effect may underlie some of the benefit seen after 3 weeks in patients with heart failure⁽⁷³⁾, and might also be particularly useful in heart failure caused by pulmonary hypertension. In a rat model of pulmonary hypertension induced by monocrotaline injection, repeated administration attenuates a number of features of disease, including the increase in right ventricular pressures, myocyte hypertrophy and vascular remodelling⁽⁸¹⁾.

Ghrelin is also thought to possess an anti-inflammatory effect. Many cells of the immune system have been found to express receptors for ghrelin⁽⁸²⁾ and *in vitro* experiments have clearly demonstrated that ghrelin suppresses the release of inflammatory cytokines by stimulated monocytes and lymphocytes^(83,84). *In vivo* studies have confirmed this effect in a number of rodent models of inflammation, including chemically-induced colitis, pancreatitis or arthritis and acute lung injury induced by sepsis^(85–89). Circulating inflammatory markers and histological grade are reduced by ghrelin, as is the overall clinical severity and mortality. These findings are of particular interest since cachexia is frequently accompanied by inappropriate low-grade inflammation.

Finally, vascular calcification has been shown to be reduced by ghrelin in a rodent model induced by excessive vitamin D⁽⁹⁰⁾. This effect is of interest largely to patients undergoing dialysis in whom vascular calcification commonly accompanies cachexia. There are therefore a number of actions of ghrelin beyond appetite regulation that may be of therapeutic benefit in cachexia, but there are as yet only limited data in this area. Much further work will be needed to establish the place of ghrelin in clinical use and there are important practical problems that will need to be solved.

One major limitation of treatments based on natural hormones is the need for parenteral administration because of the large size of the molecule. It is therefore of interest that a number of small-molecule analogues are available that are orally absorbed and are currently being investigated for therapeutic potential. RC-1291 (amorelin) in particular has shown efficacy in terms of growth hormone secretion as well as appetite stimulation and weight gain in phase 1 studies^(91,92); the results of future trials are eagerly awaited.

Conclusion

Cachexia begins early in the course of many chronic diseases and shortens survival. It is caused by a down-regulation in appetite, which makes it resistant to long-term treatment with nutritional supplements. Appetite can be increased, however, using the natural appetite regulatory hormone ghrelin, and this pathway shows early promise in clinical trials as an appetite-stimulating and anabolic treatment. The extent to which a long-term increase in energy intake will improve the clinical features

and survival of cachexia remains unknown, but the ability to achieve the former may soon be a reality, allowing this important question to be answered.

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