

## Strategies to improve ingestive behaviour with reference to critical illness

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The complex interplay between neural and endocrine responses following food intake regulates ingestive behaviour and ultimately determines subsequent energy intake. These processes include cognitive, gastrointestinal-derived and metabolic mechanisms. Such physiological responses to the ingestion of food initiate short- to medium-term inhibition of intake (satiety). However, in clinical states in which systemic inflammation is evident there is a more profound satiety response and a clear absence of motivation to eat that is evident as loss of appetite. These negative influences on energy intake can contribute to poor nutritional status, and consequently poor physical function, and impact on rehabilitation and recovery. Cytokine mediators of the inflammatory response directly influence feeding behaviour at the hypothalamic nuclei and may explain the lack of motivation and desire for food. However, additional detrimental effects on appetite are brought about because of alterations in intermediary metabolism present in inflammation-induced catabolism. This process forms part of the host response to inflammation and may explain symptoms, such as early satiety, frequently reported in many patient groups. In clinical states, and cancer in particular, pharmacological strategies have been employed to ameliorate the inflammatory response in an attempt to improve energy intake. Some success of this approach has been reported following administration of substrates such as EPA. Novel strategies to improve intake through administration of anti-cytokine drugs such as thalidomide may also be of benefit. However, drugs that oppose the actions of neurotransmitter pathways involved in central induction of satiety, such as 5-hydroxytryptamine, have failed to improve intake but appear to enhance enjoyment of food. Such findings indicate that therapeutic nutritional targets can only be achieved where novel pharmacological therapies can be supported by more innovative and integrated dietary management strategies. Many of these strategies remain to be elucidated.

### **Ingestion behaviour: Critical illness: Intervention strategies: Ghrelin**

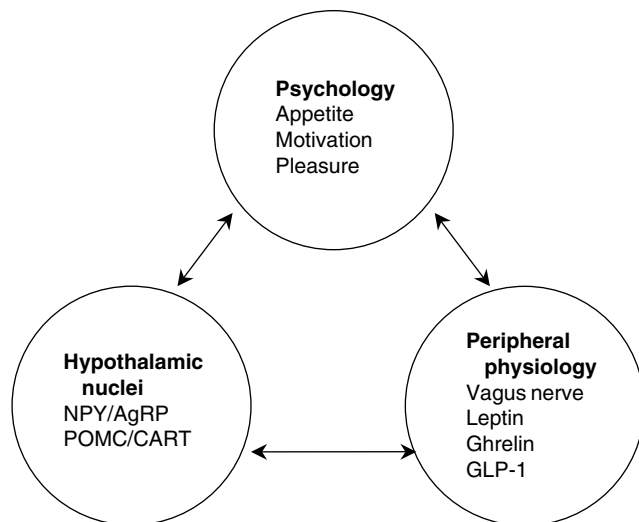
The regulation of food intake in healthy individuals has an inordinate extent of complexity that requires an understanding of the integration of appetite variables, specific food preferences, food behaviour and psychology as well as the physiological and metabolic responses to nutrient (energy) intake. The biopsychological model put forward by Blundell & Tremblay (1995) reduces this complex interplay to three key levels (Fig. 1): first, the psychological level that includes appetite sensations and pleasurable or hedonic responses to food as well as food behaviour; second, the physiological and metabolic events occurring in the periphery; third, the level of neurotransmitter, metabolic and possibly nutrient interactions in the brain. Subsequent research has expanded the complexity of the controlling neurotransmitter and peptide pathways (Kirschgessner, 2002; Morton *et al.* 2006), and more peripheral mediators have been identified as important

regulators of energy homeostasis (e.g. leptin). Currently, the literature abounds with research investigating the neural and endocrine pathways (Baynes *et al.* 2006) that determine ingestive behaviour, and has primarily been driven by the global epidemic of obesity. However, the model retains its appropriateness for the study of ingestive behaviour in both over- and undernutrition.

The elucidation of the mechanisms that dictate and influence feeding behaviour are essential to the improvement of nutritional intervention strategies in patients who are underweight or at high risk of developing disease-related malnutrition. This patient group includes those who are critically ill, for whom appropriate and targeted nutritional support can improve functional rehabilitation and outcome (Eneroth *et al.* 2006). The general metabolic response to the trauma present in critical illness brings about profound effects on the physiological regulation

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**Fig. 1.** Biological and psychological elements regulating food (energy) intake. NPY, neuropeptide Y; AgRP, Agouti-related protein; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; GLP-1, glucagon-like peptide 1. (Adapted from Blundell & Tremblay, 1995.)

of ingestive behaviour. These effects are most notable when the development of a systemic inflammation occurs, effecting the orchestration of neuroendocrine responses through pro-inflammatory cytokines that act both locally in a paracrine fashion and distally as endocrine mediators. Thus, both peripherally- and centrally-produced cytokine inflammatory mediators can influence a change in the cognitive and autonomic processing that governs the initiation and cessation of ingestion. The consequences of such a response are to provide anorexigenic signalling to inhibit motivation and desire to eat, reduce energy intake, reduce body weight and alter body composition.

The fact that nutritional demands alter in disease states generally is not in question (Richardson & Davidson, 2002). However, homeostatic control is lost during pathophysiological processes involved in the host response to trauma and critical illness, promoting a prevalence of undernutrition in patients requiring critical care. It is unclear how and where the disease process(es) *per se* and the metabolic response to injury affect the key levels of regulation of appetite variables in relation to ingestive behaviour. However, the extent of wasting and both its psychological and physical consequences are key determinants of recovery and rehabilitation. The body of literature examining the central and peripheral processing that impacts on energy intake shows considerable promise in improving ingestive behaviour in patients in whom loss of appetite and poor intake is evident. However, identification of appropriate targets for intervention in critical illness (and other wasting disorders) poses an important challenge to clinicians because of the heterogeneous nature of such a population and the paucity of research in this area.

#### Alterations in appetite variables in disease

The development of undernutrition and risk of malnutrition in critical illness (Hill, 1996) results in rapid weight loss

and overt changes in body composition. Hence, a large proportion of patients with critical illness require to be artificially fed, which can lead to both under- and over-feeding (Reid, 2005), primarily as procedures for estimating requirements are not definitive. Whilst the immediate goal is to provide adequate nutrition by whatever means (enteral nutrition, parenteral nutrition or a combination of both), ultimately most patients need to be weaned to resume oral intake. The barriers to resumption are often self reported (and include taste changes, early satiety, poor motivation to eat, no pleasure in eating and too tired to eat) or self-evident, with patients having poor mobility and low functional status. Furthermore, there is no definitive information on whether artificial nutritional support itself is a barrier to resumption and maintenance of oral intake. Research findings on the effects of parenteral feeding on appetite have revealed equivocal results (for review, see Stratton & Elia, 1999). Most recently, Murray *et al.* (2006) have reported little change in appetite variables following infusion of three isoenergetic types of feed to patients with intestinal failure predominantly associated with Crohn's disease. In contrast, patients fed entirely by total parenteral nutrition have been reported as having appetite (hunger) sensations that are distressing (33%) and most (83%) continue to have a strong desire to eat (Stratton *et al.* 1998). It is tempting to speculate that maintenance of appetitive sensations when the gut is completely by-passed represents the restoration of the normal drive to eat in the absence of inflammatory mediators. However, evidence from Bannerman *et al.* (2001), who addressed the influence of Crohn's disease severity on appetite variables, indicates that baseline appetite sensations are altered. Both desire to eat and hunger ratings are depressed in patients compared with healthy controls, and the greatest suppression of appetite is evident in patients with active disease, as indicated by the Harvey-Bradshaw index (Harvey & Bradshaw, 1980). This finding may suggest that in this population at least it is the initiation of feeding that contributes to the associated anorexia.

In other disorders in which poor nutritional status is evident and wasting occurs (most extensively reported in cancer patients) early satiety is frequently reported along with anorexia. This outcome has been observed in appetizing studies conducted pretransplant in patients with chronic liver disease (McCollum, 2000), for whom levels of hunger and desire to eat were found to be similar to those of healthy controls. However, post-meal satiety ratings were found to be higher and longer lasting in subjects with chronic liver disease, indicating an enhanced satiety response rather than a failure to initiate ingestion. These appetite studies suggest that motivation (meal initiation), satiation (relating to meal length) and satiety (inhibition of eating) may be altered in disease. Since motivation is a behaviour generated centrally and satiety is a peripherally-generated response to the delivery of food to the stomach (distention) and small intestine (incretin-mediated satiety), effective pharmacological intervention to improve ingestive behaviour may need to be targeted both centrally and peripherally. This approach may in turn lead to more effective strategies for weaning patients from enteral tube feeding to resumption of adequate oral

intake and may positively impact on rehabilitation and recovery.

### Pharmacological strategies to improve ingestive behaviour

The use of appetite stimulants such as megestrol acetate for anorexia associated with cancer has long been considered beneficial (Berenstein & Ortiz, 2006), with improvements being reported in well-being as well as increased appetite. However, studies in which a positive correlation between appetite and increased energy intake is evident are sparse. The use of cannabinoid receptor agonists is currently being considered because of their application to clinical states other than cancer (Jonsson *et al.* 2006). More novel intervention strategies with EPA that had initially shown good promise of reversing the weight loss (Barber *et al.* 1998) and appetite loss in cancer cachexia (Congalves *et al.* 2006) associated with pancreatic cancer in particular, now appear questionable (Fearon *et al.* 2006). In addition, evidence to support the concomitant repletion of functional tissue that is critical to recovery is less impressive (Bruera *et al.* 2003).

Targeting key neurotransmitter pathways in the hypothalamic nuclei has been proposed as a possible strategy to ameliorate anorexia. However, drugs that oppose the actions of neurotransmitter pathways involved in central induction of satiety, such as 5-hydroxytryptamine, have failed to improve intake (Edelman *et al.* 1999). On the other hand, they may show some benefit in enhancing enjoyment of food, which in itself is useful, particularly where treatment is palliative in nature. Novel strategies to improve intake through administration of anti-cytokine drugs such as thalidomide (Mantovani *et al.* 2001) may also be of benefit.

As a result of the extensive research into obesity that has uncovered peptide pathways both in the brain (hypothalamic nuclei) and mediating communication via the gut-brain axis, novel pharmaceuticals such as incretin mimetics are beginning to emerge as candidates for improving energy intakes in many clinical states (Adrian, 2005; Mayer *et al.* 2006). In particular, the growth hormone receptor analogue and 'hunger hormone' ghrelin has provided encouraging results in conditions in which anorexia is resistant to other interventions.

### The case for ghrelin

Of the numerous peptides implicated in feeding behaviour that have been identified recently, one of the most promising that may actually make the leap to clinical usage is ghrelin. The peptide was first discovered as a growth hormone-releasing peptide from the stomach (Kojima *et al.* 1999). Subsequently, it has shown properties that may be of major benefit to nutritional support in the critically ill, including a dose-dependent increase in gastric motility and promotion of energy storage through adipogenesis (Akamizu & Kengawa, 2007). The putative anabolic effects of this peptide and the evidence that these effects may involve the inhibition of cytokine release and the

action of leptin has generated the suggestion that the presence and extent of inflammation may be associated with plasma ghrelin levels. Very recently, an association between ghrelin levels and inflammatory markers has been confirmed (Akamizu & Kengawa, 2007). Boyes *et al.* (2006) have demonstrated that elective surgery depresses circulating levels of ghrelin. In addition, in the early post-operative phase (up to 5 d following the surgical insult) ghrelin levels (assessed by area under the curve) are negatively correlated with C-reactive protein. This finding has warranted early trials of the effects of ghrelin administration in patients to address whether nutritional, metabolic and functional outcomes can be improved.

Results of early intervention studies include those of a randomised placebo-controlled trial in malnourished patients (Wynne *et al.* 2005) receiving peritoneal dialysis. Ghrelin was administered before a test meal to patients with mild- to moderate malnutrition, as defined by their global subjective assessment score. A significant increase in energy intake at the meal was reported, with a mean increase of 1047 kJ ( $P < 0.01$ ) compared with the control day. However, no significant differences in daily energy intakes in the 3 d following administration were found, although on each of the days the mean intakes were higher for the treated group. This finding suggests that at best there is a short-term increase in dietary intake following ghrelin administration.

In an attempt to address whether ghrelin could be used to improve functional status in the cachexia associated with chronic obstructive pulmonary disease, Nagaya *et al.* (2005) administered ghrelin intravenously over 3 weeks and assessed nutritional and functional status of patients. Significant improvements in functional status determined by hand grip ( $P < 0.05$ ), inspiratory and expiratory pressure ( $P < 0.05$ ) and 6 min timed walk were found. Small but significant increases ( $P < 0.05$ ) in body weight and lean body mass were noted, as well as improved dietary intake assessed by a semi-quantitative method.

Previously, improvements in appetite and energy intake were reported in cancer patients given ghrelin by intravenous infusion (Neary *et al.* 2004). In this study energy intake from a buffet lunch was found to increase by 31% in the treatment group compared with placebo group. In addition, patients reported an increased pleasantness of food on ingestion. Adverse effects of food ingestion in patients with cancer often include dialogue on how unpleasant food tastes or 'that it just doesn't taste the same' and are a problem in motivating cancer patients to eat. This effect of ghrelin alone should be investigated further to address a key issue in the anorexia of patients with cancer.

### Other potential strategies

The extent of metabolic abnormality that accompanies disease determines the utilisation of nutrients, even when adequate energy is provided. This abnormality most commonly includes insulin insensitivity, and in critical illness glycaemic control dramatically influences mortality and morbidity (van den Berghe *et al.* 2003). Derangements are

common in other disorders in which inflammation is apparent (usually defined as a raised C-reactive protein). This situation promotes a state of catabolism and enhances loss of lean body mass as the preferential fuel supply to the muscle becomes limited. Insulin insensitivity, under-nutrition and the presence of inflammation can predict survival in certain conditions such as chronic kidney disease (Stenvinkel, 2006). Attempts to break this catabolic cycle to promote accretion of lean body mass and redress the metabolic picture to one of anabolism have proved successful when exercise intervention strategies have been employed (Milani *et al.* 2004), and such strategies show concomitant reductions in inflammatory markers (Febbraio & Pedersen, 2002). Consequent nutritional benefits will undoubtedly accompany this outcome by promotion of an anti-inflammatory state, and in the undernourished patient are likely to include improvement of appetite and ingestive behaviour. Definitive protocols in relation to exercise that are disease specific have been proposed (Pedersen & Saltin, 2006) but have not been universally adopted, and both resistance training and low-intensity exercise appear to be beneficial (Smith *et al.* 2006). In particular, in a population such as the critically ill, for whom suggested protocols may be impractical and unachievable, current physical therapy interventions should be aligned with nutritional support strategies to provide integrated care, so that there is the potential to improve not only ingestive behaviour and functional status but also to impact on disease pathogenesis and progression.

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