

Journal Club feature

Anorexia: a taste of things to come?

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Introduction

Anorexia, the loss of the desire to eat, is common in patients with cancer. Studies report a prevalence of up to 66% and clinical practice suggests that it is an almost universal experience as the cancer progresses.¹ It generally leads to a reduction in food intake that contributes to the development of malnutrition and cachexia, impairing quality of life and increasing morbidity and mortality.² Successful curative or palliative treatment of the underlying cancer is an effective approach. When this is not possible, there are limited treatment options, which generally have not been shown to be practicable, tolerable, effective or safe in the long-term management of the cachexia–anorexia syndrome. Recent increases in the understanding of the physiology of energy intake and of the pathophysiology of anorexia are helping to guide the development of rational approaches. This journal club provides an outline of the pathophysiology of anorexia and highlights a paper that may provide an exciting glimpse of the future.³

Pathophysiology of anorexia

The hypothalamus is the site of complex interactions between neuropeptides, monoamines and other messengers that are central to the regulation of food (i.e., energy) intake.^{4,5} Fasting, leading to an energy deficit, is accompanied by changes in digestive processes, metabolism and fat stores generating hormonal and other signals, e.g., insulin, ghrelin, malonyl-CoA, which act upon the arcuate nucleus in the hypothalamus. These signals *stimulate* orexigenic neurones, containing agouti-related protein (AgRP) and neuropeptide Y (NPY) and *inhibit* anorexigenic neurones, containing pro-opiomelanocortin

(POMC), a precursor for α -melanocyte stimulating hormone (α -MSH), leading to an increase in food intake (Figure 1a). Melanocortin receptors, particularly melanocortin-4 (MC4-R), appear important in tonically inhibiting food intake and energy storage, e.g., mice and humans lacking this receptor have an obese phenotype.⁵ Thus the orexigenic AgRP and NPY act as functional antagonists at MC4-R and the anorexigenic α -MSH is an agonist.^{2,6}

In cancer, and many other chronic diseases, there is an increased expression of cytokines, e.g., interleukin-1 and tumour necrosis factor- α , that *inhibit* the normal hypothalamic response to energy deficit signals and the orexigenic neurones (NPY receptors are downregulated) and *stimulate* the anorexigenic neurones, probably via serotonin (5-HT_{1B} receptors are upregulated), resulting in anorexia, increased energy expenditure and weight loss (Figure 1b).^{7–9} Hence a range of anti-inflammatory, anticytokine, antiserotonergic and hormonal agents have been or are being investigated.^{2,6,8} Blockade of MC4-R appears to be a particularly promising therapeutic approach. Cancer-related (and uraemic) anorexia does not occur in mice lacking MC4-R and can be reversed by the use of physiological (e.g., AgRP) or synthetic melanocortin receptor antagonists.^{3,10,11} However, these peptide antagonists have to be administered by intracerebroventricular injection, limiting their clinical potential. The paper discussed below is the first comprehensive report of the effect of a MC4-R antagonist that can be given peripherally.

Markinson and colleagues examined the characteristics and actions of a MC4-R antagonist (NBI-12i) using a series of *in vitro* and *in vivo* experiments involving normal mice, receptor knock-out mice and a mouse cancer model.³ This involved animals being inoculated with a fixed number of lung cancer cells subcutaneously into the upper flank to produce a local tumour. Study treatment was administered from the 11th until the 15th day after tumour inoculation, when the animals were killed, before metastatic disease developed. Body composition was assessed by dual-energy X-ray absorptiometry (DEXA) scan. The *in vivo* experiments were controlled,

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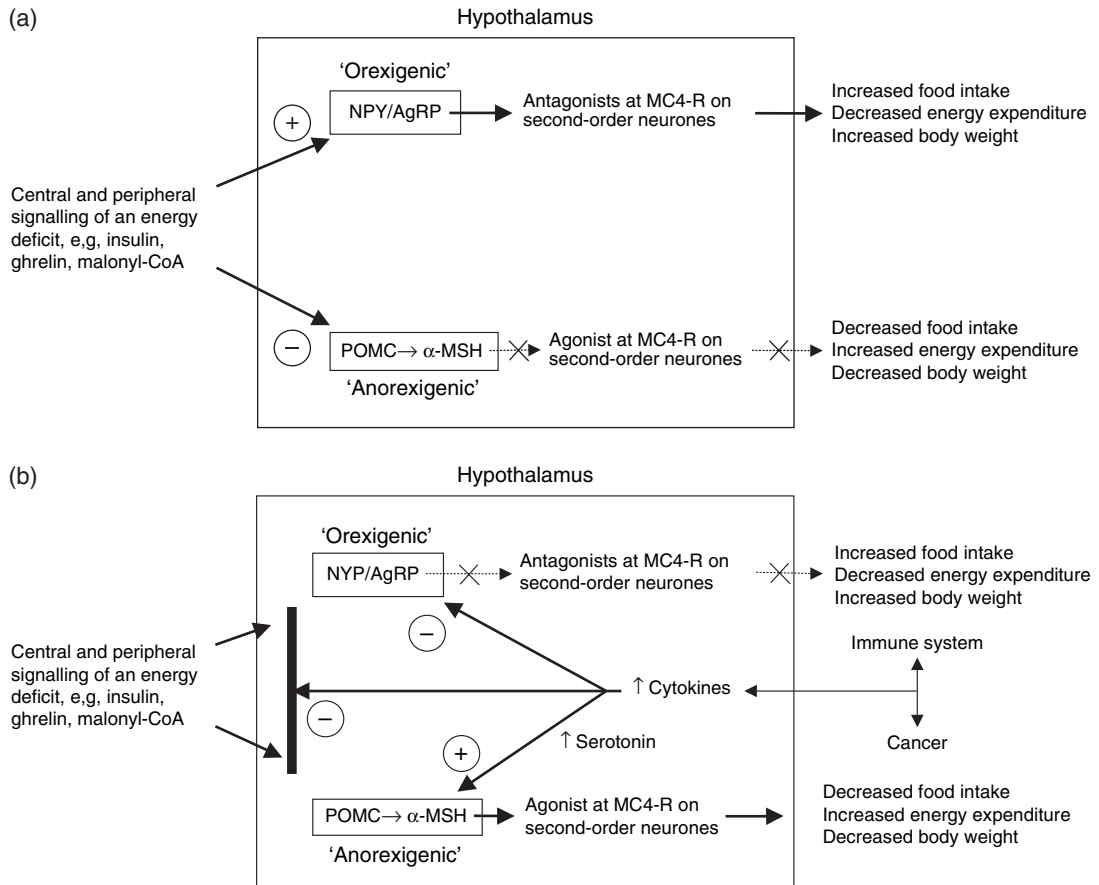


Figure 1 The role of the hypothalamus in regulating food intake. (a) Physiological response to an energy-deficient state and (b) pathological response in cancer (for explanation, see text).

with the mice receiving NBI-12i or saline by intraperitoneal injection. The results indicate that NBI-12i is a selective and competitive inhibitor of MC4-R, able to reduce the stimulatory effect of α -MSH. Its administration reduces oxygen uptake and energy expenditure in normal mice and significantly increases food intake in normal and MC3-R knock-out mice, but not MC4-R knock-out mice. In the mouse cancer model, NBI-12i significantly increases food intake and body weight (12% versus 3% for saline), via an increase in both fat and lean body mass.

Commentary

There is a world of difference between mice and man, and the relevance of these findings to humans is not yet known. However, if the small-molecule MC4-R antagonists such as NBI-12i are able to improve the anorexia and the disordered (increased) metabolism seen in cancer as a way of increasing body weight, particularly muscle mass, then they potentially offer a unique and ideal approach to the management of cachexia–anorexia. An essential part of their development will be to demonstrate

sustained benefit in the setting of advanced cancer when the cytokine/inflammatory burden is progressively increasing; the direct effect of cytokines on muscle breakdown could still result in the loss of muscle mass despite a normal/improved appetite and metabolism.

Conclusions

This and other studies suggest that small-molecule MC4-R antagonists are well worth pursuing as a potential therapeutic approach for the future and they are expected to enter clinical trials very soon.^{3,12,13} MC4-R antagonists appear to block a key step, as they prevent cachexia–anorexia from a variety of causes, e.g., animal models of inflammation, infection and renal failure, and as such they may be of benefit in a wide range of clinical settings.

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