Molecular and neuroendocrine mechanisms of cancer cachexia

Maria Carolina S Mendes, Gustavo D Pimentel, Felipe O Costa and José B C Carvalheira

Department of Internal Medicine, Faculty of Medical Sciences, State University of Campinas (UNICAMP), MA: 13083-970 Campinas, Sao Paulo, Brazil

Correspondence should be addressed to J B C Carvalheira
Email
carvalheirajbc@uol.com.br

Abstract

Cancer and its morbidities, such as cancer cachexia, constitute a major public health problem. Although cancer cachexia has afflicted humanity for centuries, its underlying multifactorial and complex physiopathology has hindered the understanding of its mechanism. During the last few decades we have witnessed a dramatic increase in the understanding of cancer cachexia pathophysiology. Anorexia and muscle and adipose tissue wasting are the main features of cancer cachexia. These apparently independent symptoms have humoral factors secreted by the tumor as a common cause. Importantly, the hypothalamus has emerged as an organ that senses the peripheral signals emanating from the tumoral environment, and not only elicits anorexia but also contributes to the development of muscle and adipose tissue loss. Herein, we review the roles of factors secreted by the tumor and its effects on the hypothalamus, muscle and adipose tissue, as well as highlighting the key targets that are being exploited for cancer cachexia treatment.

Key Words
- hypothalamus
- cancer
- muscle
- neuropeptides
- neuroendocrinology

Journal of Endocrinology (2015) **226**, R29–R43

Introduction

The earliest report of significant weight loss dates back to Hippocrates' School of Medicine (about 460–377 BC). Since that era, this syndrome has been recognized as a condition associated with poor prognosis, justifying the name cachexia, from the Greek *kakos* (i.e., bad) and *hexis* (i.e., condition or appearance), or 'bad condition'. It is associated with many chronic or end-stage diseases such as cancer, cardiac, respiratory, renal or hepatic failure and infectious diseases, as well as aging (Doehner & Anker 2002). During human history, weight loss has always been recognized as a marker in the perception of control and damage in relation to health and disease. Notably, a fit appearance is associated with willpower and self-discipline, whilst the perception of potential harm and loss of control is related to changing body states, such as the development of obesity and especially cachexia (Chamberlain 2004).

Patients' and their families' perception of muscle wasting makes the disease visible and represents an indication that death is closer (Hopkinson *et al.* 2006). As cachexia goes on, wasting of skeletal muscle tissue diminishes mobility and lethargy impairs concentration, leading patients towards isolation and depression (Watanabe & Bruera 1996, Stewart *et al.* 2006). Importantly, cachexia not only affects the patient, but also their families, caregivers, and healthcare professionals, who often experience emotions of fright and hopelessness as they try to palliate symptoms by feeding the patients (Reid *et al.* 2009). The emotional distress experienced by healthcare professionals and nihilism regarding the effectiveness of cachexia treatment frequently block conversation about weight loss, which makes even the discussion of cachexia a taboo (Booth *et al.* 1996, Parle *et al.* 1997, Churm *et al.* 2009). In this review, we will highlight the mechanistic

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

foundation of cancer cachexia, the knowledge of which has started to change the current nihilistic therapeutic approach to this devastating condition.

Cancer cachexia

Cancer cachexia is defined as a multifactorial syndrome, characterized by anorexia as well as diminished body weight, loss of skeletal muscle, and atrophy of adipose tissue (Fearon *et al*. 2011). Specifically, weight loss of more than 5% in previously healthy individuals or more than 2% in subjects with depletion of current body weight (BMI less than 20 kg/m^2) or in individuals with reduced appendicular muscle index (males less than 7.26 kg/m^2 and females less than 5.45 kg/m^2) constitute the diagnosis of cancer cachexia (Fearon *et al*. 2011). Recently, it has been recognized that weight loss alone is insufficient to express the complexity of cachexia, and two other clinical characteristics have been incorporated into its definition: It cannot be fully reversed by conventional nutritional support and it leads to functional impairment (Muscaritoli *et al*. 2010, Fearon *et al*. 2011). Its incidence varies according to tumor type, from 31% in patients with good-risk non-Hodgkin's lymphoma to 87% in those with gastric cancer in some series (Dewys *et al*. 1980, Teunissen *et al*. 2007). Importantly, since cachexia is accompanied by the incapacity for improvement of nutritional status through supplements, it leads to frailty and ultimately accounts for approximately 20% of cancer deaths (Dewys *et al*. 1980, Ross *et al*. 2004, Bachmann *et al*. 2008, Fearon *et al*. 2011, 2013). The cachexia-mediated increased mortality is probably due to lower response to chemotherapy and worse toxicity in anti-cancer treatment, besides higher susceptibility to infections and other clinical complications (Costa & Donaldson 1979, Andreyev *et al*. 1998, Nitenberg & Raynard 2000, Arrieta *et al*. 2010).

It is well known that anorexia alone is not able to cause cachexia. This is one of the main characteristics that distinguishes cachexia from starvation. In the former, both adipose tissue and skeletal muscle mass are depleted, while muscle mass is preserved during starvation (Fearon 2011). It is noteworthy that starvation in cancer patients, may be associated with upper digestive obstruction or fistula, particularly in head and neck, esophageal, gastric and pancreatic cancer patients, or peritoneal carcinomatosis-induced multi-level abdominal obstruction (Dechaphunkul *et al*. 2013). However, the great majority of advanced-cancer patients, mainly those with lung, hepatic or bone metastasis and lung, cervical or head and neck primary cancers, present a hypermetabolic state that is characteristic of cachexia.

The physiopathology of cancer cachexia remains unclear. Several cancer-related metabolic pathways induce weight loss, muscle and adipose tissue wasting, anorexia, anemia, and asthenia. The apparent causes of these symptoms are energy imbalance (increased energy expenditure rate), negative protein balance (increased proteolysis and decreased protein synthesis), and increased lipolysis. Mechanistically, several factors such as increased levels of hormones, cytokines and factors secreted by the tumor as well as deregulation of control by the hypothalamus of energy expenditure and hunger/satiety promote cancer cachexia (Fig. 1).

In fact, cancer cachexia is characterized by maladaptive maintenance of inflammation. In contrast, acute activation of the immune system in response to tissue stress or infection serves as an adaptive response that is essential to host survival (Ramos *et al*. 2004). These responses include fever, headache, changes in the sleep–wake cycle, anorexia, fatigue, and nausea referred to as 'sickness behavior' (Hart 1988, Elmquist *et al*. 1997). The organismal advantages of these actions are demonstrated by their wide expression among vertebrates and also partial expression in some invertebrates (Kluger 1991). For instance, force-feeding acutely infected animals is associated with higher mortality, signifying short-term anorexia as a host defense mechanism in infection and tissue injury (Murray & Murray 1979). Additionally, somnolence and fatigue diminish energy expenditure during periods of caloric intake restriction (Hart 1988, Saper & Breder 1992, 1994).

Molecular mechanisms of skeletal muscle wasting

Cachexia-induced muscle atrophy occurs as a result of both reduced protein synthesis at initiation and elongation steps and increased protein degradation. Muscle wasting is the main cause of poor prognosis and low quality of life. Skeletal muscle protein degradation is promoted by ubiquitin–proteasome and autophagy–lysosomal pathways, as well as the calcium-dependent enzymes (calpains), which can be activated by the proteolysis-inducing factor (PIF), myostatin, activin A (ActA), and cytokines (Matzuk *et al*. 1994, Tisdale 2009, Zhou *et al*. 2010, Johns *et al*. 2013).

PIF, a glycoprotein first isolated from the MAC16 tumor, has been detected in the urine of cancer patients with cachexia (Todorov *et al*. 1996, Cariuk *et al*. 1997).

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

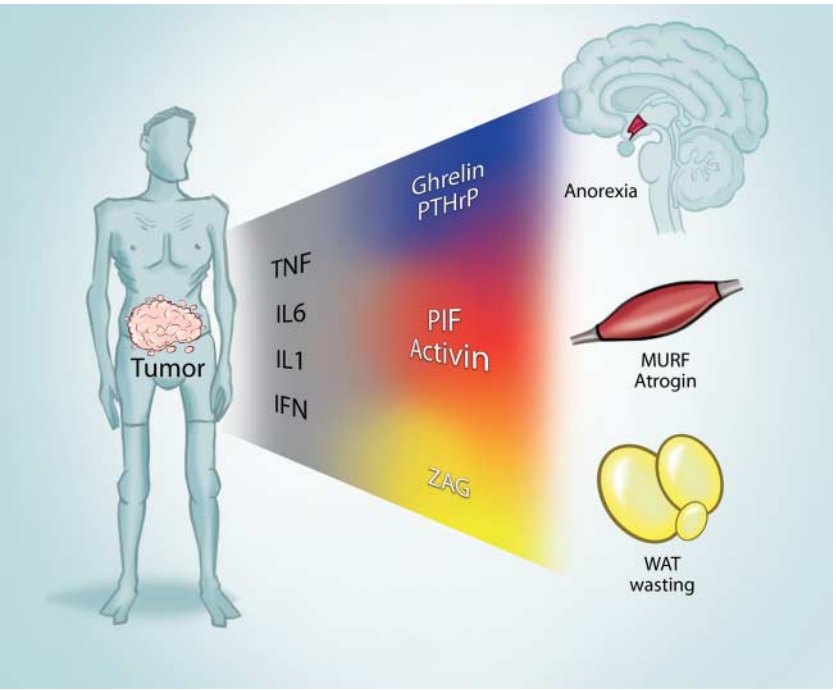

Figure 1
Tumor-secreted factors promote central- and peripheral-mediated cancer cachexia. Tumor growth results in the secretion of pro-inflammatory factors that promote cachexia by signaling anorexia, muscle wasting, and white adipose tissue (WAT) atrophy. In particular, treatment with ghrelin and parathyroid hormone-related protein (PTHrP) alleviates anorexia in the hypothalamus. Tumors also secrete both the proteolysis-inducing factor (PIF) and activin, which leads to skeletal muscle degradation and sarcopenia. Tumor-secreted zinc-alpha2-glycoprotein (ZAG) induces lipid oxidation and WAT loss. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Journal of Endocrinology

Specifically, patients bearing a vast range of cancers, such as pancreatic, breast, ovary, lung, and colon and rectum, present increased circulating levels of PIF (Cariuk *et al.* 1997). Importantly, the isolation of this protein and subsequent injection into mice induced severe and prompt body-weight loss (Tisdale 2003). In striking contrast, it has been reported that PIF is not related to either survival or muscle wasting in patients with advanced cancers (Wieland *et al.* 2007). Mechanistically, PIF not only promotes protein degradation by increasing mRNA levels of ubiquitin-carrier protein and proteasome subunits (Tisdale 2003), but also inhibits protein synthesis through activation of the RNA-dependent protein kinase (PKR) (Eley & Tisdale 2007). The latter effect is dependent on eukaryotic initiation factor 2 alpha-subunit (eIF2α) phosphorylation, which suppresses protein synthesis by the eIF2 complex (Eley & Tisdale 2007, Eley *et al.* 2010). Interestingly, PKR also induces muscle protein degradation by activating the transcription factor nuclear factor κB (NF-κB). Nuclear accumulation of NF-κB increases the expression of the muscle-specific ubiquitin E3 ligases, and RING-finger protein 1 (MuRF1) as well as some proteasome subunits upregulating the ubiquitin–proteasome proteolytic mechanism and therefore promoting skeletal muscle breakdown (Bodine *et al.* 2001, Argilés *et al.* 2014). PIF also induces transitory formation of reactive oxygen species (ROS) through activation of NADPH oxidase by protein kinase C (Fan *et al.* 1990, Smith *et al.* 2004). Since ROS induce NF-κB nuclear translocation (Schreck *et al.* 1991), this pathway also contributes to increasing the expression of MuRF1 in skeletal muscle (Li *et al.* 2003, Cai *et al.* 2004, Yu *et al.* 2008).

Myostatin and activins are members of the transforming growth factor B family, which promote muscle wasting in certain models of cachexia, including cancer cachexia (Carlson *et al.* 1999, Ma *et al.* 2003, Zhou *et al.* 2010, Chen *et al.* 2014). Transgenic mice that lack myostatin, as well as cattle with mutations that reduce the expression of myostatin, show an increased muscle mass phenotype (McPherron & Lee 1997, McPherron *et al.* 1997), whilst recombinant viral overexpression of activins results in muscle wasting and fibrosis (Chen *et al.* 2014). Myostatin and activins share the same receptor, activin type 2

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

receptor B (ActR2B), whose antagonism potently reverses cancer-induced cachexia (Xia & Schneyer 2009, Zhou *et al.* 2010). Interestingly, circulating serum levels of ActA, which has been demonstrated to be secreted by cancer cells, are elevated in cancer cachectic patients (Zhou *et al.* 2010, Loumaye *et al.* 2015). Mechanistically, myostatin and activins trigger skeletal muscle protein breakdown by upregulating MuRF1 and MAFbx/Atrogin1, as well as decreasing protein synthesis via inhibition of the Akt/mTOR pathway (Chen *et al.* 2014, Gallot *et al.* 2014). Activation of this pathway inhibits the activity of the transcriptional factor Forkhead box O (FoxO), which is a major regulator of MuRF1 and MAFbx/Atrogin1 expression. Accordingly, the use of a RNA oligonucleotide to block FoxO1 or dominant-negative FoxO3 attenuates loss of skeletal muscle mass in a model of cachexia by suppressing MAFbx/Atrogin1 transcription (Sandri *et al.* 2004, 2006).

Increasing evidence indicates that cytokines play a pivotal role in promoting skeletal muscle atrophy. It is well established that tumor necrosis factor (TNF) is a key cytokine that induces skeletal muscle wasting. For instance, CHO cells that overexpress TNF promote muscle wasting in mice (Oliff *et al.* 1987, Acharyya *et al.* 2004). In contrast, inhibition of TNF with a chimeric TNF receptor prevented muscle wasting in mice bearing a TNF-producing tumor (Teng *et al.* 1993). More recently, TNF-induced atrophy was demonstrated to be mediated by the induction of MAFbx/Atrogin1 in muscle by the attenuation of FoxO activation (Wang *et al.* 2014) as well as by increasing MuRF1 (Sishi & Engelbrecht 2011). TNF also suppresses the PI3K/Akt pathway (Sishi & Engelbrecht 2011). Interestingly, inhibitor of nuclear factor kappa B kinase subunit beta (IKKβ) conditional knockout mice present hyperphosphorylation of Akt. Conversely, Akt inhibition leads to muscle atrophy, indicating the existence of crosstalk between the IKKβ/NF-κB and PI3K/Akt pathways, which control muscle degradation (Mourkioti *et al.* 2006). Recently, a new member of the TNF superfamily has been described, TNF-like weak inducer of apoptosis (TWEAK), which promotes cachexia by a mechanism similar to that of TNF, i.e., by activating NF-κB and promoting augmented expression of MuRF1, which targets components of the thick filaments (Dogra *et al.* 2007, Mittal *et al.* 2010, Kumar *et al.* 2012).

Increasing levels of interleukin 6 (IL6) also correlate with development of cachexia. Accordingly, treatment with an IL6 receptor antagonist, or MABs to murine IL6, was able to suppress key cachexia parameters (Strassmann *et al.* 1992, Enomoto *et al.* 2004, Zaki *et al.* 2004). However, IL6 alone is not enough to promote cachexia syndrome (Soda *et al.* 1994, 1995). Interestingly, increased IL6 levels are correlated with poor prognosis in patients with advanced cancer (Suh *et al.* 2013), and are associated with increased weight loss, morbidity, and mortality in patients with lung cancer (Bayliss *et al.* 2011). Despite the absence of solid results in cancer cachectic patients, interferon gamma MAB reversed wasting syndrome in a cachexia animal model, indicating a role for this cytokine in cachexia syndrome (Matthys *et al.* 1991).

Molecular mechanisms of adipose tissue loss

Although the mechanisms behind muscle wasting have been extensively studied, much less is known about factors that promote adipose tissue loss in cancer cachectic patients. The fact that viable cancer cells do not induce weight loss, particularly adipose tissue wasting, indicates that tumor-secreted factors could be the cause of fat atrophy (Costa & Holland 1962). The search for these factors led to the discovery of a lipid-mobilizing factor, which was purified from the urine of cachectic individuals (Masuno *et al.* 1981, 1984, Taylor *et al.* 1992, McDevitt *et al.* 1995).

Over the last decade, zinc-alpha2-glycoprotein (ZAG) has been characterized as an adipokine, which induces lipid mobilization and is upregulated in cancer cachexia (Bing *et al.* 2004, 2010, Bao *et al.* 2005). Mechanistically, the lipolytic effect of ZAG is mediated by activation of B3-adrenoceptors (Russell *et al.* 2002), which, through AMPc pathway activation in a GTP-dependent manner, leads to hormone sensitive lipase (HSL) activation and glycerol release (Hirai *et al.* 1998). Accordingly, both genetically-obese (*ob/ob*) mice and outbred NMRI mice treated with human ZAG display decreased body weight, with pronounced carcass fat loss, without change in body water or nonfat mass, and neither changes in food nor water intake (Hirai *et al.* 1998, Russell *et al.* 2004). Moreover, mice bearing xenografts of a tumor cell line that overexpress ZAG display dramatic weight loss (Hale 2002). ZAG also induces lipid utilization, increasing fat oxidation (Russell & Tisdale 2002, 2010), due to upregulation of mitochondrial uncoupling protein 1 (UCP1) mRNA in brown adipose tissue (BAT) (Bing *et al.* 2002, Russell *et al.* 2004), mediated by ZAG binding and activation of B3-adrenoreceptor in adipocytes (Russell *et al.* 2002).

In addition to tumor-derived ZAG effects, inflammatory mediators, such as TNF, modulate white adipose tissue (WAT) homeostasis. Importantly, TNF inhibits

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

lipoprotein lipase activity (Price *et al*. 1986), and increases HSL mRNA expression (Tisdale 2004, Agustsson *et al*. 2007). Additionally, TNF has been shown to inhibit glucose transport, by reducing glucose transporter 4 protein and mRNA levels, decreasing substrates for lipogenesis (Hauner *et al*. 1995). TNF-induced lipolysis is mediated by activation of MAPK kinase, ERK and elevation of intracellular AMPc by decreasing the expression of cyclic-nucleotide phosphodiesterase 3B (Zhang *et al*. 2002). MAPK and JNK activation lead to peroxisome proliferator-activated receptor gamma (PPARY) phosphorylation, inhibiting pre-adipocyte differentiation (Hu *et al*. 1996). It has also been observed that TNF decreases the protein levels of perilipins A and B at the surface of lipid droplets in 3T3L1 adipocytes, inducing lipolysis. Furthermore, overexpression of perilipins by adenovirus infection blocks this effect (Souza *et al*. 1998). In cancer cachexia, TNF increases monocyte chemoattractant protein 1 expression in adipocytes, attracting monocytes to the adipose tissue, resulting in inflammation (Machado *et al*. 2004). The infiltrating macrophages are responsible for increasing TNF production, and also IL6 and IL1 beta, generating a vicious cycle of macrophage recruitment and cytokine production.

Neuroendocrine regulation of food intake and anorexia

The hypothalamus is the master key for the control of energy homeostasis. Importantly, it is in this CNS area that hundreds of signals converge, including hormones, nutrients, and cytokines, to integrate the complex energy expenditure/food intake balance physiology (Schwartz *et al*. 2000, Laviano *et al*. 2008, 2012, Blanco Martínez de Morentin *et al*. 2011, Pimentel *et al*. 2014). The hypothalamus is subdivided into functional areas that fine tune the energy balance by sending signals that coordinately increase food intake and suppress energy expenditure or *vice versa*. Historically, it was loss-of-function experiments, performed in the 1930's, that provided the proof of concept that the CNS is crucial to the regulation of energy balance. The results of these initial studies revealed that different cerebral regions could control energy balance, in particular it was verified that CNS lesions performed in macaques and cats lead to deregulation of food intake and loss of thermogenesis control (Ranson *et al*. 1938). However, it was only in the 1950's that the hypothalamus was established as a crucial organ for this control. Specifically, lesions in the ventromedial region of the hypothalamus of rats induce hyperphagia, while lateral hypothalamus lesions promote anorexia (Anand & Brobeck 1951, Miller 1957, Hervey 1959).

The hypothalamus is constituted by neurons that coordinately secrete anorexigenic (cocaine- and amphetamine-regulated transcript (CART) and pro-opiomelanocortin (POMC)) or orexigenic (agouti-related protein (AgRP) and neuropeptide Y (NPY)) NPs to control food intake. These NPs are produced mainly in the arcuate (ARC) nucleus and paraventricular nucleus (PVN), but also in the ventromedial hypothalamus (VMH) (Schwartz *et al*. 2000, Lage *et al*. 2008, Pimentel *et al*. 2013). The VMH contains neurons that promote increased energy expenditure (Schwartz *et al*. 2000, Blanco Martínez de Morentin *et al*. 2011, Pimentel *et al*. 2013, Martínez *et al*. 2014). Consistent with a VMH tonic pro-anorexigenic effect, VMH-specific injection of colchicine (a neuronal blocker) into anorectic rats increased food intake (Varma *et al*. 2000, Laviano *et al*. 2002). Moreover, certain areas of the brain, such as the nucleus of the solitary tract (NST) have also been implicated in the control of appetite. Accordingly, there is an increase in NST neuron c-Fos activity after i.c.v. IL1B injection (DeBoer *et al*. 2009).

Several lines of evidence indicate that the melanocortin system has a key role in hypothalamus dysfunction in cancer cachexia. This system is mainly composed of POMC neurons that secrete aMSH and exert their anorexigenic effects on neurons that contain the melanocortin 4 receptor (MC4R; Balthasar *et al*. 2005, Cone 2005, Silva *et al*. 2014). It is noteworthy that mouse neuronal cells express both POMC and CART in the same neurons, while CART is not found in perikarya and axons of human POMC neurons (Menyhért *et al*. 2007). Interestingly, MC4R-, but not MC3R-knockout mice, are resistant to cachexia (Marks *et al*. 2001, 2003). Accordingly, the administration of MC4R antagonists directly to the hypothalamus ameliorates cancer-associated and chronic-kidney-disease-associated cachexia and attenuates the anorexigenic actions of the sphingosine 1 phosphate (Wisse *et al*. 2001, Markison *et al*. 2005, Cheung *et al*. 2007, DeBoer *et al*. 2008, Silva *et al*. 2014).

MC4R is also expressed in orexigenic neurons and these neurons are inhibited by a MSH decreasing NPY/AgRP release (Laviano *et al*. 2008). Injection of a melanocortin receptor antagonist attenuates radiation-mediated anorexia and cachexia, when compared with non-irradiated mice, in an AgRP-dependent manner (Joppa *et al*. 2007). Interestingly, treatment with megestrol acetate (MA), a drug approved by the FDA for cancer cachexia, alleviates anorexia due to increased

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

hypothalamic NPY expression (McCarthy *et al.* 1994), which is decreased in anorectic cancer patients (Jatoi *et al.* 2001). Taken together, these findings indicate that decreased activity of NPY/AgRP neurons occurs synergistically to the hyperstimulation of POMC neuronal cells and that the melanocortin system is critical for neuroendocrine-axis-mediated cancer cachexia.

In addition to the melanocortin system, other neuronal circuits have been found to be dysfunctional in cancer cachexia. Among these, hypothalamic serotoninergic and dopaminergic systems are the most studied. Consistent with an anorexigenic effect of the serotoninergic system, 5HT1B-receptor is upregulated in PVN and supraoptic nuclei of tumor-bearing rats (Makarenko *et al.* 2005) and VMH-specific serotoninergic system blockade ameliorates appetite in anorexic rats (Laviano *et al.* 1996). On the other hand, consistent with a dual effect of the dopaminergic system in cancer cachexia, VMH-specific dopamine 1 receptor antagonist leads to decreased appetite and, in contrast, dopamine 2 receptor antagonist administration increases food intake in tumor-bearing rodents (Sato *et al.* 2001). Much less is known about the glutamatergic neural circuit in the genesis of cancer cachexia, but the increased activity of this system is associated with anorexia. Consistent with this, a reduction of vagal/glutamatergic neurotransmission with metabotropic glutamate receptor antagonist (I(+)-AP3) alleviates inflammation-LPS-driven anorexia, cachexia and febrile states (Weiland *et al.* 2006).

Cancer cachexia molecular signals that modulate the hypothalamus

It is beyond the scope of this review to report on the innumerous signals that control energy homeostasis, but these associated with cancer cachexia will be covered. It is well established that pro-inflammatory cytokines released from tumors promote cancer progression and anorexia (Laviano *et al.* 2003, Seruga *et al.* 2008). The results of initial studies have revealed that VMH-specific injection of IL1 receptor antagonist attenuates anorexia in tumor-bearing rats (Laviano *et al.* 1995, 2000). Moreover, s.c. injection of the TNF inhibitor improved food intake, with increased meal number and size in anorectic rats (Torelli *et al.* 1999). Accordingly, tumor-bearing rodents and cancer patients display higher IL1B and TNF levels in cerebrospinal fluid (CSF; Opara *et al.* 1995*a*,*b*, Protas *et al.* 2011).

Mechanistically, cytokines induce anorexia by activating neuronal cells expressing POMC in the ARC nucleus of the hypothalamus, which increases the central melanocortin system timbre (Lawrence & Rothwell 2001, Reyes & Sawchenko 2002, Scarlett *et al.* 2007). Consistent with this model, the use of a selective antagonist of MC4R was enough to attenuate the anorexigenic effects of IL1B (Joppa *et al.* 2005). These data indicate that cytokines are CSF soluble factors critical to hypothalamus-mediated anorexia.

In addition to pro-inflammatory cytokines, other molecules have been implicated in cancer cachexia, such as ghrelin and parathyroid hormone-related protein (PTHrP).

Although cachectic patients present high levels of circulating ghrelin (Shimizu *et al.* 2003, Garcia *et al.* 2005), treatment with ghrelin (s.c.) improves food consumption in both rodents (DeBoer *et al.* 2007, Lage *et al.* 2008, Fujitsuka *et al.* 2011) and cancer patients (Neary *et al.* 2004). These findings indicate that hyperghrelinemia is a compensatory mechanism that fails to overcome the cancer-cachexia-induced decreased ghrelin signaling in the hypothalamus (Fujitsuka *et al.* 2011). The orexigenic ghrelin effects are mediated by the hypothalamus, where this hormone suppresses the expression of IL1R and POMC, and increases AgRP and NPY expression (DeBoer *et al.* 2007). Ghrelin-mediated attenuation of cachexia is reproduced in different models, interestingly in fasting, denervation and chronic-kidney-disease-mediated cachexia, ghrelin treatment attenuated muscle protein degradation due, at least in part, to the inhibition of actinomyosin cleavage (DeBoer *et al.* 2008, Porporato *et al.* 2013).

The results of recent studies have indicated that tumors release PTHrP, which not only decreases food intake but also promotes muscle wasting (Asakawa *et al.* 2010, Kir *et al.* 2014). The results of these studies indicate that blocking PTHrP may be an effective strategy for treating cancer cachexia. Mechanistically, PTHrP activates hypothalamic urocortins 2/3 via vagal afferent pathways and inhibition of gastric emptying (Asakawa *et al.* 2010). Importantly, PTPHrP neutralization is enough to suppress B-adrenergic timbre, which attenuates energy expenditure and muscle mass loss in anorectic mice (Kir *et al.* 2014).

Although the intracellular mechanisms that promote hypothalamic-hormone-mediated anorexia are still unclear, the activation of hypothalamic AMP-activated protein kinase (AMPK) is a crucial event. AMPK is a key mediator of energy balance that modulates food intake and energy expenditure (Blanco Martínez de Morentin *et al.* 2011, Hardie 2015). The results of recent studies indicate that AMPK senses a multitude of nutritional and hormonal signals such as berberine, omega 3 fatty acids, glucose, alpha lipoic acid and leucine, insulin, leptin, thyroid hormones, and inflammatory mediators (Kahn

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

et al. 2005, Ropelle *et al*. 2007, 2008*a*,*b*, Lage *et al*. 2008, Steinberg *et al*. 2009, López *et al*. 2010, Pimentel *et al*. 2013, Santos *et al*. 2013, Zhang *et al*. 2014). Likewise, activation of AMPK not only blunts cancer-induced reduction of food intake, but also attenuates inflammation and prolongs the survival of tumor-bearing rats (Ropelle *et al*. 2007).

Neuroendocrine regulation of cachexia-induced thermogenesis and skeletal muscle sarcopenia

The hypothalamus not only promotes anorexia but also contributes to the development of other cancer cachexia symptoms, such as increased thermogenesis and skeletal muscle sarcopenia (Fig. 2). Interestingly, cancer-associated cachexia increases energy expenditure, an effect mainly mediated by the BAT and coordinated by the hypothalamus (Brooks *et al*. 1981, Bianchi *et al*. 1989, Tsoli *et al*. 2012, Kir *et al*. 2014). This organ senses the increased levels of TNF, the tyrotropin-releasing hormone, and the corticotropin-releasing hormone to promote heat production via a B3-adrenergic neuronal circuit (Arruda *et al*. 2011).

Recently, cachexia has been found to be associated with the conversion of white adipose cells into beige cells, a process described as 'browning' (Kir *et al*. 2014, Nedergaard & Cannon 2014, Petruzzelli *et al*. 2014). Beige cells display abundant levels of UCP1, which reduces the mitochondrial electrochemical gradient to promote thermogenesis. Mechanistically, it has been suggested that cancer cachexia-induced browning is also mediated by an increase in B-adrenergic tonus (Cao *et al*. 2011, Kir *et al*. 2014, Petruzzelli *et al*. 2014). Unfortunately, it is not known whether the CNS is implicated in WAT browning regulation during cancer cachexia. Since several obesity studies have identified the hypothalamus as an important regulator of browning (Cao *et al*. 2011, Baboota *et al*. 2014, Beiroa *et al*. 2014, Owen *et al*. 2014, Ruan *et al*. 2014, Dodd *et al*. 2015), future studies to explore the role of the hypothalamus in cachexia-induced browning are encouraged.

Although the influence of the hypothalamus on the modutation of lean body mass is clear, the mechanisms are only partially elucidated (Marks *et al*. 2001, 2003, Wisse *et al*. 2001, Cheung *et al*. 2008, Braun *et al*. 2011). The hypothalamic–pituitary–adrenal axis is an important

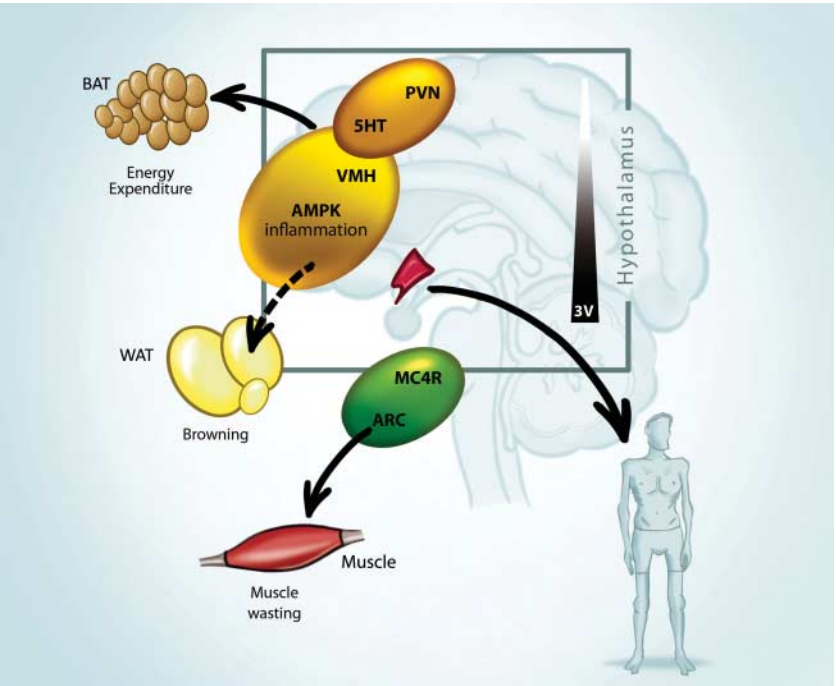

Figure 2
The hypothalamus is at the crossroads of cancer cachexia's main features. Pro-anorexigenic factors are integrated in discrete nuclei of the hypothalamus. The ventromedial nucleus (VMH) promotes heat production in brown adipose tissue (BAT) and may mediate white adipose browning via the B3 adrenergic system. The paraventricular nucleus (PVN) and arcuate (ARC) nucleus are the major integrating centers of food intake, modulating the timbre of serotonin (5HT) expression and melanocortin 4 receptor (MC4R) respectively. Interestingly, pro-opiomelanocortin leads to skeletal muscle breakdown and sarcopenia. 3V, third ventricle.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

axis that links the CNS to the muscle catabolic program. Interestingly, brain–IL1B injection leads to muscle wasting and increases in markers of muscle protein breakdown, such as MURF and Atrogin1. In accordance with the existance of an adrenal-mediated effect, adrenalectomy suppressed IL1B-induced muscle atrophy, whilst glucocorticoid treatment was enough to promote muscle atrophy (Braun *et al*. 2011). Interestingly, in spite of muscle wasting induced by cancer, uremia, or LPS, as well as IL1B-induced anorexia is suppressed by MC4R blockade (Marks *et al*. 2001, 2003, Wisse *et al*. 2001, Cheung *et al*. 2008, Whitaker & Reyes 2008), MC4R-knockout animals are not saved from body lean mass loss after central infusion of IL1B (Braun *et al*. 2011), these findings indicate that different neuronal circuits are involved in the CNS modulation of muscle catabolic programs and that the hypothalamus is crucial for induction and maintenance of the main symptoms of cancer cachexia.

Treatment of cancer cachexia

Initial efforts

Although a number of nutritional supplements and drugs, such as *Cannabis* (Strasser *et al*. 2006), eicosapentaenoic acid (Beck *et al*. 1991, Barber *et al*. 1999, Mantovani *et al*. 2008) and branched-chain amino acids (Eley *et al*. 2007) have shown promising results in pre-clinical studies, the results of phase III clinical trials have failed to demonstrate a substantial effect of these drugs and nutritional supplements as treatments for cancer cachexia.

Currently, the only FDA-approved drug for the treatment of cancer cachexia is medroxyprogesterone. Medroxyprogesterone acetate and MA are both synthetic progestins currently used to improve appetite and promote weight gain in cancer cachexia (Tchekmedyian *et al*. 1992). In accordance, the results of recent meta-analysis indicated that MA is associated with a small effect on weight gain and increase in appetite (Ruiz *et al*. 2013). Although the mechanism of action is unknown, these drugs reduce pro-inflammatory cytokines and increase NPY levels in the hypothalamus (Mantovani *et al*. 2001). Corticosteroids are alternative orexigenic agents for the treatment of cancer cachexia (Popiela *et al*. 1989, Shih & Jackson 2007). Importantly, dexamethasone treatment resulted in similar-magnitude effects on weight gain and increased appetite when compared with MA; however, this approach was associated with an increased drug discontinuation rate because of increased collateral effects (Loprinzi *et al*. 1999).

New perspectives for the treatment of cancer cachexia

Triggered by better knowledge of the molecular mechanisms of cachexia, we are observing an increasing number of cancer cachexia clinical trials. One of the most promising approaches for cancer cachexia is ghrelin treatment. A proof of concept study of ghrelin infusion revealed that this resulted in an increase of energy intake and in pleasantness of the meal in patients with advanced incurable cancer in a dose-dependent manner (Neary *et al*. 2004, Strasser *et al*. 2008, Hiura *et al*. 2012). More recently, an oral mimetic of ghrelin (anamorelin) has been tested and promising results were achieved with 16 cachectic patients with different types of tumors (Garcia *et al*. 2013). Numerous clinical trials to evaluate beneficial effects of ghrelin and anamorelin in the treatment of cancer cachexia are active (NCT0933361, NCT00681486, NCT00225745, and NCT01505764). Although the use of ghrelin in these patients appears to be safe, more studies are necessary to confirm its efficacy and safety.

Despite the proven importance of TNF in the pathogenesis of cancer cachexia, treatment with infliximab (a MAB to TNF) did not result in improvement in cachexia cases (Jatoi *et al*. 2001, 2010, Wiedenmann *et al*. 2008). In contrast, cancer cachexia treatment with thalidomide, a drug with potent anti-inflammatory effects (Moreira *et al*. 1993, Fujita *et al*. 2001, Keifer *et al*. 2001, Richardson *et al*. 2002) presented encouraging preliminary results (Davis *et al*. 2012), but we still do not have sufficient data to recommend this drug in clinical practice (Reid *et al*. 2012).

Cancer cachexia promotes insulin resistance, which not only blunts muscle glucose uptake and liver glucose production, but also inhibits protein anabolism, contributing to muscle atrophy (Yoshikawa *et al*. 2001, Winter *et al*. 2012). Metformin, the most widely used agent for the treatment of type 2 diabetes, increases food intake and prolongs survival in cachectic rats bearing Walker256 tumors (Ropelle *et al*. 2007). Interestingly, the results of a clinical trial in individuals with prostate cancer without cancer cachexia indicated that the association of metformin, exercise, and low-glycemic-index diet improved body weight (Nobes *et al*. 2012). Another insulin sensitizer, rosiglitazone, a PPAR agonist that improves insulin sensitivity, prevented weight loss, and helped avoid muscle protein degradation in an experimental colon cancer model of cachexia. These effects were paralleled by a decrease in Atrogin1 and MuRF1 expression (Asp *et al*. 2010). Interestingly, emerging evidence has indicated that insulin resistance-mediated blunted protein

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

anabolism is not refractory to post-prandial physiological amino-acid infusion, indicating conventional nutritional support to be a promising approach for overcoming anabolic resistance (Winter *et al*. 2012). As such, insulin sensitizers are good candidates for the therapeutic treatment of cancer cachexia, but clinical studies to confirm experimental data are necessary.

The use of an ActR2B decoy receptor (sActR2B) prevents muscle wasting and inhibits muscle loss in different animal models of cachexia (Zhou *et al*. 2010). Since the levels of activins are increased in cancer cachectic patients (Loumaye *et al*. 2015), a promising approach for cancer cachexia treatment may be the blockade of ActR2B.

Conclusion

Although cancer cachexia has been a major burden on our society for centuries, it is only in recent decades that there has been unprecedented progress in the understanding of its molecular basis. A broad concept that has emerged is that the hypothalamus is a key center for the control of anorexia and fat loss in cancer cachexia. Additionally, the results of animal studies have revealed numerous factors produced by the tumor that act in muscle, promoting its wasting. Although the potential therapeutic implications have not yet been fully exploited in humans, this collective work has already demonstrated that targeting the hypothalamus and tumor-secreted factors are attractive therapeutic approaches for alleviating cancer cachexia.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding
J B C C was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; 306821/2010-9) and the Fundação de Amparo à Pesquisa de São Paulo (2013/07607-8). G D P was supported by grants from the Fundação de Amparo à Pesquisa de São Paulo (2014/22347-5).

Author contribution statement
M C S M, G D P, and F O C wrote the initial drafts of the manuscript and J B C C revised the manuscript.

Acknowledgements
We thank Nicola Conran for reviewing the English.

References

Acharyya S, Ladner KJ, Nelsen LL, Damrauer J, Reiser PJ, Swoap S & Guttridge DC 2004 Cancer cachexia is regulated by selective targeting of skeletal muscle gene products. *Journal of Clinical Investigation* **114** 370–378. (doi:10.1172/JCI200420174)

Agustsson T, Rydén M, Hoffstedt J, van Harmelen V, Dicker A, Laurencikiene J, Isaksson B, Permert J & Arner P 2007 Mechanism of increased lipolysis in cancer cachexia. *Cancer Research* **67** 5531–5537. (doi:10.1158/0008-5472.CAN-06-4585)

Anand BK & Brobeck JR 1951 Hypothalamic control of food intake in rats and cats. *Yale Journal of Biology and Medicine* **24** 123–140.

Andreyev HJ, Norman AR, Oates J & Cunningham D 1998 Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *European Journal of Cancer* **34** 503–509. (doi:10.1016/S0959-8049(97)10090-9)

Argilés JM, Busquets S, Stemmler B & López-Soriano FJ 2014 Cancer cachexia: understanding the molecular basis. *Nature Reviews. Cancer* **14** 754–762. (doi:10.1038/nrc3829)

Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G, Serna-Thomé MG, Flores-Estrada D, Diaz-Romero C, Rodríguez CM, Martínez L & Sánchez-Lara K 2010 Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel–cisplatin chemotherapy: a prospective study. *BMC Cancer* **10** 50. (doi:10.1186/1471-2407-10-50)

Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, Carvalho DP, Carvalheira JB & Velloso LA 2011 Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. *Endocrinology* **152** 1314–1326. (doi:10.1210/en.2010-0659)

Asakawa A, Fujimiya M, Niijima A, Fujino K, Kodama N, Sato Y, Kato I, Nanba H, Laviano A, Meguid MM *et al*. 2010 Parathyroid hormone-related protein has an anorexigenic activity via activation of hypothalamic urocortins 2 and 3. *Psychoneuroendocrinology* **35** 1178–1186. (doi:10.1016/j.psyneuen.2010.02.003)

Asp ML, Tian M, Wendel AA & Belury MA 2010 Evidence for the contribution of insulin resistance to the development of cachexia in tumor-bearing mice. *International Journal of Cancer* **126** 756–763. (doi:10.1002/ijc.24784)

Baboota RK, Murtaza N, Jagtap S, Singh DP, Karmase A, Kaur J, Bhutani KK, Boparai RK, Premkumar LS, Kondepudi KK *et al*. 2014 Capsaicin-induced transcriptional changes in hypothalamus and alterations in gut microbial count in high fat diet fed mice. *Journal of Nutritional Biochemistry* **25** 893–902. (doi:10.1016/j.jnutbio.2014.04.004)

Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Büchler MW, Friess H & Martignoni ME 2008 Cachexia worsens prognosis in patients with resectable pancreatic cancer. *Journal of Gastrointestinal Surgery* **12** 1193–1201. (doi:10.1007/s11605-008-0505-z)

Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD *et al*. 2005 Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell* **123** 493–505. (doi:10.1016/j.cell.2005.08.035)

Bao Y, Bing C, Hunter L, Jenkins JR, Wabitsch M & Trayhurn P 2005 Zinc-α_2-glycoprotein, a lipid mobilizing factor, is expressed and secreted by human (SGBS) adipocytes. *FEBS Letters* **579** 41–47. (doi:10.1016/j.febslet.2004.11.042)

Barber MD, Ross JA, Voss AC, Tisdale MJ & Fearon KC 1999 The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *British Journal of Cancer* **81** 80–86. (doi:10.1038/sj.bjc.6690654)

Bayliss TJ, Smith JT, Schuster M, Dragnev KH & Rigas JR 2011 A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. *Expert Opinion on Biological Therapy* **11** 1663–1668. (doi:10.1517/14712598.2011.627850)

Published by Bioscientifica Ltd.

Beck SA, Smith KL & Tisdale MJ 1991 Anticachectic and antitumor effect of eicosapentaenoic acid and its effect on protein turnover. *Cancer Research* **51** 6089–6093.

Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, Villarroya F, Serrano M, Fernø J, Salvador J, Escalada J *et al.* 2014 GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. *Diabetes* **63** 3346–3358. (doi:10.2337/db14-0302)

Bianchi A, Bruce J, Cooper AL, Childs C, Kohli M, Morris ID, Morris-Jones P & Rothwell NJ 1989 Increased brown adipose tissue activity in children with malignant disease. *Hormone and Metabolic Research* **21** 640–641. (doi:10.1055/s-2007-1009308)

Bing C, Russell ST, Beckett EE, Collins P, Taylor S, Barraclough R, Tisdale MJ & Williams G 2002 Expression of uncoupling proteins-1, -2 and -3 mRNA is induced by an adenocarcinoma-derived lipid-mobilizing factor. *British Journal of Cancer* **86** 612–618. (doi:10.1038/sj.bjc.6600101)

Bing C, Bao Y, Jenkins J, Sanders P, Manieri M, Cinti S, Tisdale MJ & Trayhurn P 2004 Zinc-α2-glycoprotein, a lipid mobilizing factor, is expressed in adipocytes and is up-regulated in mice with cancer cachexia. *PNAS* **101** 2500–2505. (doi:10.1073/pnas.0308647100)

Bing C, Mracek T, Gao D & Trayhurn P 2010 Zinc-α2-glycoprotein: an adipokine modulator of body fat mass? *International Journal of Obesity* **34** 1559–1565. (doi:10.1038/ijo.2010.105)

Blanco Martínez de Morentin P, González CR, Saha AK, Martins L, Diéguez C, Vidal-Puig A, Tena-Sempere M & López M 2011 Hypothalamic AMP-activated protein kinase as a mediator of whole body energy balance. *Reviews in Endocrine & Metabolic Disorders* **12** 127–140. (doi:10.1007/s11154-011-9165-5)

Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, Poueymirou WT, Panaro FJ, Na E, Dharmarajan K *et al.* 2001 Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* **294** 1704–1708. (doi:10.1126/science.1065874)

Booth K, Maguire PM, Butterworth T & Hillier VF 1996 Perceived professional support and the use of blocking behaviours by hospice nurses. *Journal of Advanced Nursing* **24** 522–527. (doi:10.1046/j.1365-2648.1996.22012.x)

Braun TP, Zhu X, Szumowski M, Scott GD, Grossberg AJ, Levasseur PR, Graham K, Khan S, Damaraju S, Colmers WF *et al.* 2011 Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic–pituitary–adrenal axis. *Journal of Experimental Medicine* **208** 2449–2463. (doi:10.1084/jem.20111020)

Brooks SL, Neville AM, Rothwell NJ, Stock MJ & Wilson S 1981 Sympathetic activation of brown-adipose-tissue thermogenesis in cachexia. *Bioscience Reports* **1** 509–517. (doi:10.1007/BF01121584)

Cai D, Frantz JD, Tawa NE, Melendez PA, Oh BC, Lidov HG, Hasselgren PO, Frontera WR, Lee J, Glass DJ *et al.* 2004 IKKβ/NF-κB activation causes severe muscle wasting in mice. *Cell* **119** 285–298. (doi:10.1016/j.cell.2004.09.027)

Cao L, Choi EY, Liu X, Martin A, Wang C, Xu X & During MJ 2011 White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic–adipocyte axis. *Cell Metabolism* **14** 324–338. (doi:10.1016/j.cmet.2011.06.020)

Cariuk P, Lorite MJ, Todorov PT, Field WN, Wigmore SJ & Tisdale MJ 1997 Induction of cachexia in mice by a product isolated from the urine of cachectic cancer patients. *British Journal of Cancer* **76** 606–613. (doi:10.1038/bjc.1997.433)

Carlson CJ, Booth FW & Gordon SE 1999 Skeletal muscle myostatin mRNA expression is fiber-type specific and increases during hindlimb unloading. *American Journal of Physiology* **277** R601–R606.

Chamberlain K 2004 Food and health: expanding the agenda for health psychology. *Journal of Health Psychology* **9** 467–481. (doi:10.1177/1359105304044030)

Chen JL, Walton KL, Winbanks CE, Murphy KT, Thomson RE, Makanji Y, Qian H, Lynch GS, Harrison CA & Gregorevic P 2014 Elevated expression of activins promotes muscle wasting and cachexia. *FASEB Journal* **28** 1711–1723. (doi:10.1096/fj.13-245894)

Cheung WW, Kuo HJ, Markison S, Chen C, Foster AC, Marks DL & Mak RH 2007 Peripheral administration of the melanocortin-4 receptor antagonist NBI-12i ameliorates uremia-associated cachexia in mice. *Journal of the American Society of Nephrology* **18** 2517–2524. (doi:10.1681/ASN.2006091024)

Cheung WW, Rosengren S, Boyle DL & Mak RH 2008 Modulation of melanocortin signaling ameliorates uremic cachexia. *Kidney International* **74** 180–186. (doi:10.1038/ki.2008.150)

Churm D, Andrew IM, Holden K, Hildreth AJ & Hawkins C 2009 A questionnaire study of the approach to the anorexia–cachexia syndrome in patients with cancer by staff in a district general hospital. *Supportive Care in Cancer* **17** 503–507. (doi:10.1007/s00520-008-0486-1)

Cone RD 2005 Anatomy and regulation of the central melanocortin system. *Nature Neuroscience* **8** 571–578. (doi:10.1038/nn1455)

Costa G & Donaldson SS 1979 Current concepts in cancer: effects of cancer and cancer treatment on the nutrition of the host. *New England Journal of Medicine* **300** 1471–1474. (doi:10.1056/NEJM197906283002606)

Costa G & Holland JF 1962 Effects of Krebs-2 carcinoma on the lipide metabolism of male Swiss mice. *Cancer Research* **22** 1081–1083.

Davis M, Lasheen W, Walsh D, Mahmoud F, Bicanovsky L & Lagman R 2012 A phase II dose titration study of thalidomide for cancer-associated anorexia. *Journal of Pain and Symptom Management* **43** 78–86. (doi:10.1016/j.jpainsymman.2011.03.007)

DeBoer MD, Zhu XX, Levasseur P, Meguid MM, Suzuki S, Inui A, Taylor JE, Halem HA, Dong JZ, Datta R *et al.* 2007 Ghrelin treatment causes increased food intake and retention of lean body mass in a rat model of cancer cachexia. *Endocrinology* **148** 3004–3012. (doi:10.1210/en.2007-0016)

DeBoer MD, Zhu X, Levasseur PR, Inui A, Hu Z, Han G, Mitch WE, Taylor JE, Halem HA, Dong JZ *et al.* 2008 Ghrelin treatment of chronic kidney disease: improvements in lean body mass and cytokine profile. *Endocrinology* **149** 827–835. (doi:10.1210/en.2007-1046)

DeBoer MD, Scarlett JM, Levasseur PR, Grant WF & Marks DL 2009 Administration of IL-1β to the 4th ventricle causes anorexia that is blocked by agouti-related peptide and that coincides with activation of tyrosine-hydroxylase neurons in the nucleus of the solitary tract. *Peptides* **30** 210–218. (doi:10.1016/j.peptides.2008.10.019)

Dechaphunkul T, Martin L, Alberda C, Olson K, Baracos V & Gramlich L 2013 Malnutrition assessment in patients with cancers of the head and neck: a call to action and consensus. *Critical Reviews in Oncology/Hematology* **88** 459–476. (doi:10.1016/j.critrevonc.2013.06.003)

Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, Cohen MH, Douglass HO, Engstrom PF, Ezdinli EZ *et al.* 1980 Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *American Journal of Medicine* **69** 491–497. (doi:10.1016/S0149-2918(05)80001-3)

Dodd GT, Decherf S, Loh K, Simonds SE, Wiede F, Balland E, Merry TL, Münzberg H, Zhang ZY, Kahn BB *et al.* 2015 Leptin and insulin act on POMC neurons to promote the browning of white fat. *Cell* **160** 88–104. (doi:10.1016/j.cell.2014.12.022)

Doehner W & Anker SD 2002 Cardiac cachexia in early literature: a review of research prior to Medline. *International Journal of Cardiology* **85** 7–14. (doi:10.1016/S0167-5273(02)00230-9)

Dogra C, Changotra H, Wedhas N, Qin X, Wergedal JE & Kumar A 2007 TNF-related weak inducer of apoptosis (TWEAK) is a potent skeletal muscle-wasting cytokine. *FASEB Journal* **21** 1857–1869. (doi:10.1096/fj.06-7537com)

Eley HL & Tisdale MJ 2007 Skeletal muscle atrophy, a link between depression of protein synthesis and increase in degradation. *Journal of Biological Chemistry* **282** 7087–7097. (doi:10.1074/jbc.M610378200)

Eley HL, Russell ST & Tisdale MJ 2007 Effect of branched-chain amino acids on muscle atrophy in cancer cachexia. *Biochemical Journal* **407** 113–120. (doi:10.1042/BJ20070651)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

Eley HL, Russell ST & Tisdale MJ 2010 Mechanism of activation of dsRNA-dependent protein kinase (PKR) in muscle atrophy. *Cellular Signalling* **22** 783–790. (doi:10.1016/j.cellsig.2010.01.002)

Elmquist JK, Scammell TE & Saper CB 1997 Mechanisms of CNS response to systemic immune challenge: the febrile response. *Trends in Neurosciences* **20** 565–570. (doi:10.1016/S0166-2236(97)01138-7)

Enomoto A, Rho MC, Fukami A, Hiraku O, Komiyama K & Hayashi M 2004 Suppression of cancer cachexia by 20S,21-epoxy-resibufogenin-3-acetate–a novel nonpeptide IL-6 receptor antagonist. *Biochemical and Biophysical Research Communications* **323** 1096–1102. (doi:10.1016/j.bbrc.2004.08.196)

Fan XT, Huang XP, Da Silva C & Castagna M 1990 Arachidonic acid and related methyl ester mediate protein kinase C activation in intact platelets through the arachidonate metabolism pathways. *Biochemical and Biophysical Research Communications* **169** 933–940. (doi:10.1016/0006-291X(90)91983-Y)

Fearon KC 2011 Cancer cachexia and fat–muscle physiology. *New England Journal of Medicine* **365** 565–567. (doi:10.1056/NEJMcibr1106880)

Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G *et al.* 2011 Definition and classification of cancer cachexia: an international consensus. *Lancet. Oncology* **12** 489–495. (doi:10.1016/S1470-2045(10)70218-7)

Fearon K, Arends J & Baracos V 2013 Understanding the mechanisms and treatment options in cancer cachexia. *Nature Reviews. Clinical Oncology* **10** 90–99. (doi:10.1038/nrclinonc.2012.209)

Fujita J, Mestre JR, Zeldis JB, Subbaramaiah K & Dannenberg AJ 2001 Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2. *Clinical Cancer Research* **7** 3349–3355.

Fujitsuka N, Asakawa A, Uezono Y, Minami K, Yamaguchi T, Niijima A, Yada T, Maejima Y, Sedbazar U, Sakai T *et al.* 2011 Potentiation of ghrelin signaling attenuates cancer anorexia–cachexia and prolongs survival. *Translational Psychiatry* **1** e23. (doi:10.1038/tp.2011.25)

Gallot YS, Durieux AC, Castells J, Desgeorges MM, Vernus B, Plantureux L, Rémond D, Jahnke VE, Lefai E, Dardevet D *et al.* 2014 Myostatin gene inactivation prevents skeletal muscle wasting in cancer. *Cancer Research* **74** 7344–7356. (doi:10.1158/0008-5472.CAN-14-0057)

Garcia JM, Garcia-Touza M, Hijazi RA, Taffet G, Epner D, Mann D, Smith RG, Cunningham GR & Marcelli M 2005 Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. *Journal of Clinical Endocrinology and Metabolism* **90** 2920–2926. (doi:10.1210/jc.2004-1788)

Garcia JM, Friend J & Allen S 2013 Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. *Supportive Care in Cancer* **21** 129–137. (doi:10.1007/s00520-012-1500-1)

Hale LP 2002 Zinc α-2-glycoprotein regulates melanin production by normal and malignant melanocytes. *Journal of Investigative Dermatology* **119** 464–470. (doi:10.1046/j.1523-1747.2002.01813.x)

Hardie DG 2015 AMPK: positive and negative regulation, and its role in whole-body energy homeostasis. *Current Opinion in Cell Biology* **33** 1–7. (doi:10.1016/j.ceb.2014.09.004)

Hart BL 1988 Biological basis of the behavior of sick animals. *Neuroscience and Biobehavioral Reviews* **12** 123–137. (doi:10.1016/S0149-7634(88)80004-6)

Hauner H, Petruschke T, Russ M, Röhrig K & Eckel J 1995 Effects of tumour necrosis factor alpha (TNFα) on glucose transport and lipid metabolism of newly-differentiated human fat cells in cell culture. *Diabetologia* **38** 764–771. (doi:10.1007/s001250050350)

Hervey GR 1959 The effects of lesions in the hypothalamus in parabiotic rats. *Journal of Physiology* **145** 336–352. (doi:10.1113/jphysiol.1959.sp006145)

Hirai K, Hussey HJ, Barber MD, Price SA & Tisdale MJ 1998 Biological evaluation of a lipid-mobilizing factor isolated from the urine of cancer patients. *Cancer Research* **58** 2359–2365.

Hiura Y, Takiguchi S, Yamamoto K, Takahashi T, Kurokawa Y, Yamasaki M, Nakajima K, Miyata H, Fujiwara Y, Mori M *et al.* 2012 Effects of ghrelin administration during chemotherapy with advanced esophageal cancer patients: a prospective, randomized, placebo-controlled phase 2 study. *Cancer* **118** 4785–4794. (doi:10.1002/cncr.27430)

Hopkinson JB, Wright DN, McDonald JW & Corner JL 2006 The prevalence of concern about weight loss and change in eating habits in people with advanced cancer. *Journal of Pain and Symptom Management* **32** 322–331. (doi:10.1016/j.jpainsymman.2006.05.012)

Hu E, Kim JB, Sarraf P & Spiegelman BM 1996 Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARγ. *Science* **274** 2100–2103. (doi:10.1126/science.274.5295.2100)

Jatoi A, Loprinzi CL, Sloan JA, Klee GG & Windschitl HE 2001 Neuropeptide Y, leptin, and cholecystokinin 8 in patients with advanced cancer and anorexia: a North Central Cancer Treatment Group exploratory investigation. *Cancer* **92** 629–633. (doi:10.1002/1097-0142(20010801)92:3<629::AID-CNCR1363>3.0.CO;2-M)

Jatoi A, Ritter HL, Dueck A, Nguyen PL, Nikcevich DA, Luyun RF, Mattar BI & Loprinzi CL 2010 A placebo-controlled, double-blind trial of infliximab for cancer-associated weight loss in elderly and/or poor performance non-small cell lung cancer patients (N01C9). *Lung Cancer* **68** 234–239. (doi:10.1016/j.lungcan.2009.06.020)

Johns N, Stephens NA & Fearon KC 2013 Muscle wasting in cancer. *International Journal of Biochemistry & Cell Biology* **45** 2215–2229. (doi:10.1016/j.biocel.2013.05.032)

Joppa MA, Ling N, Chen C, Gogas KR, Foster AC & Markison S 2005 Central administration of peptide and small molecule MC4 receptor antagonists induce hyperphagia in mice and attenuate cytokine-induced anorexia. *Peptides* **26** 2294–2301. (doi:10.1016/j.peptides.2005.03.002)

Joppa MA, Gogas KR, Foster AC & Markison S 2007 Central infusion of the melanocortin receptor antagonist agouti-related peptide (AgRP(83–132)) prevents cachexia-related symptoms induced by radiation and colon-26 tumors in mice. *Peptides* **28** 636–642. (doi:10.1016/j.peptides.2006.11.021)

Kahn BB, Alquier T, Carling D & Hardie DG 2005 AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metabolism* **1** 15–25. (doi:10.1016/j.cmet.2004.12.003)

Keifer JA, Guttridge DC, Ashburner BP & Baldwin AS 2001 Inhibition of NF-κB activity by thalidomide through suppression of IκB kinase activity. *Journal of Biological Chemistry* **276** 22382–22387. (doi:10.1074/jbc.M100938200)

Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE & Spiegelman BM 2014 Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. *Nature* **513** 100–104. (doi:10.1038/nature13528)

Kluger MJ 1991 Fever: role of pyrogens and cryogens. *Physiological Reviews* **71** 93–127.

Kumar A, Bhatnagar S & Paul PK 2012 TWEAK and TRAF6 regulate skeletal muscle atrophy. *Current Opinion in Clinical Nutrition and Metabolic Care* **15** 233–239. (doi:10.1097/MCO.0b013e328351c3fc)

Lage R, Diéguez C, Vidal-Puig A & López M 2008 AMPK: a metabolic gauge regulating whole-body energy homeostasis. *Trends in Molecular Medicine* **14** 539–549. (doi:10.1016/j.molmed.2008.09.007)

Laviano A, Renvyle T, Meguid MM, Yang ZJ, Cangiano C & Rossi Fanelli F 1995 Relationship between interleukin-1 and cancer anorexia. *Nutrition* **11** 680–683.

Laviano A, Cangiano C, Preziosa I, Meguid MM, Muscaritoli M, Conversano L, Cascino A, Torelli GF, Cherubini S & Rossi Fanelli F 1996 Serotoninergic block in the ventromedial nucleus of hypothalamus improves food intake in anorectic tumor bearing rats. *Advances in Experimental Medicine and Biology* **398** 551–553. (doi:10.1007/978-1-4613-0381-7_88)

Laviano A, Gleason JR, Meguid MM, Yang ZJ, Cangiano C & Rossi Fanelli F 2000 Effects of intra-VMN mianserin and IL-1ra on meal number in anorectic tumor-bearing rats. *Journal of Investigative Medicine* **48** 40–48.

Laviano A, Meguid MM, Gleason JR & Rossi-Fanelli F 2002 VMN/LHA functional inhibition in tumor-bearing rats suggests hypothalamic involvement in cancer anorexia. *Nutritional Neuroscience* **5** 443–456. (doi:10.1080/1028415021000039202)

Published by Bioscientifica Ltd.

Laviano A, Meguid MM & Rossi-Fanelli F 2003 Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. *Lancet. Oncology* **4** 686–694. (doi:10.1016/S1470-2045(03)01247-6)

Laviano A, Inui A, Marks DL, Meguid MM, Pichard C, Rossi Fanelli F & Seelaender M 2008 Neural control of the anorexia–cachexia syndrome. *American Journal of Physiology. Endocrinology and Metabolism* **295** E1000–E1008. (doi:10.1152/ajpendo.90252.2008)

Laviano A, Seelaender M, Rianda S, Silverio R & Rossi Fanelli F 2012 Neuroinflammation: a contributing factor to the pathogenesis of cancer cachexia. *Critical Reviews in Oncogenesis* **17** 247–251. (doi:10.1615/CritRevOncog.v17.i3.20)

Lawrence CB & Rothwell NJ 2001 Anorexic but not pyrogenic actions of interleukin-1 are modulated by central melanocortin-3/4 receptors in the rat. *Journal of Neuroendocrinology* **13** 490–495. (doi:10.1046/j.1365-2826.2001.00660.x)

Li YP, Chen Y, Li AS & Reid MB 2003 Hydrogen peroxide stimulates ubiquitin-conjugating activity and expression of genes for specific E2 and E3 proteins in skeletal muscle myotubes. *American Journal of Physiology. Cell Physiology* **285** C806–C812. (doi:10.1152/ajpcell.00129.2003)

López M, Varela L, Vázquez MJ, Rodríguez-Cuenca S, González CR, Velagapudi VR, Morgan DA, Schoenmakers E, Agassandian K, Lage R *et al.* 2010 Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. *Nature Medicine* **16** 1001–1008. (doi:10.1038/nm.2207)

Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, Rowland KM, Camoriano JK, Novotny PJ & Christensen BJ 1999 Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *Journal of Clinical Oncology* **17** 3299–3306.

Loumaye A, de Barsy M, Nachit M, Lause P, Frateur L, van Maanen A, Trefois P, Gruson D & Thissen JP 2015 Role of activin A and myostatin in human cancer cachexia. *Journal of Clinical Endocrinology and Metabolism* **100** 2030–2038. (doi:10.1210/jc.2014-4318)

Ma K, Mallidis C, Bhasin S, Mahabadi V, Artaza J, Gonzalez-Cadavid N, Arias J & Salehian B 2003 Glucocorticoid-induced skeletal muscle atrophy is associated with upregulation of myostatin gene expression. *American Journal of Physiology. Endocrinology and Metabolism* **285** E363–E371. (doi:10.1152/ajpendo.00487.2002)

Machado AP, Costa Rosa LF & Seelaender MC 2004 Adipose tissue in Walker 256 tumour-induced cachexia: possible association between decreased leptin concentration and mononuclear cell infiltration. *Cell and Tissue Research* **318** 503–514. (doi:10.1007/s00441-004-0987-2)

Makarenko IG, Meguid MM, Gatto L, Goncalves CG, Ramos EJ, Chen C & Ugrumov MV 2005 Hypothalamic 5-HT_{1B}-receptor changes in anorectic tumor bearing rats. *Neuroscience Letters* **376** 71–75. (doi:10.1016/j.neulet.2004.11.026)

Mantovani G, Macciò A, Massa E & Madeddu C 2001 Managing cancer-related anorexia/cachexia. *Drugs* **61** 499–514. (doi:10.2165/00003495-200161040-00004)

Mantovani G, Macciò A, Madeddu C, Gramignano G, Serpe R, Massa E, Dessì M, Tanca FM, Sanna E, Deiana L *et al.* 2008 Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. *Nutrition* **24** 305–313. (doi:10.1016/j.nut.2007.12.010)

Markison S, Foster AC, Chen C, Brookhart GB, Hesse A, Hoare SR, Fleck BA, Brown BT & Marks DL 2005 The regulation of feeding and metabolic rate and the prevention of murine cancer cachexia with a small-molecule melanocortin-4 receptor antagonist. *Endocrinology* **146** 2766–2773. (doi:10.1210/en.2005-0142)

Marks DL, Ling N & Cone RD 2001 Role of the central melanocortin system in cachexia. *Cancer Research* **61** 1432–1438.

Marks DL, Butler AA, Turner R, Brookhart G & Cone RD 2003 Differential role of melanocortin receptor subtypes in cachexia. *Endocrinology* **144** 1513–1523. (doi:10.1210/en.2002-221099)

Martínez D, Pentinat T, Ribó S, Daviaud C, Bloks VW, Cebrià J, Villalmanzo N, Kalko SG, Ramón-Krauel M, Díaz R *et al.* 2014 *In utero* undernutrition in male mice programs liver lipid metabolism in the second-generation offspring involving altered *Lxra* DNA methylation. *Cell Metabolism* **19** 941–951. (doi:10.1016/j.cmet.2014.03.026)

Masuno H, Yamasaki N & Okuda H 1981 Purification and characterization of a lipolytic factor (toxohormone-L) from cell-free fluid of ascites sarcoma 180. *Cancer Research* **41** 284–288.

Masuno H, Yoshimura H, Ogawa N & Okuda H 1984 Isolation of a lipolytic factor (toxohormone-L) from ascites fluid of patients with hepatoma and its effect on feeding behavior. *European Journal of Cancer & Clinical Oncology* **20** 1177–1185. (doi:10.1016/0277-5379(84)90127-5)

Matthys P, Heremans H, Opdenakker G & Billiau A 1991 Anti-interferon-γ antibody treatment, growth of Lewis lung tumours in mice and tumour-associated cachexia. *European Journal of Cancer* **27** 182–187. (doi:10.1016/0277-5379(91)90483-T)

Matzuk MM, Finegold MJ, Mather JP, Krummen L, Lu H & Bradley A 1994 Development of cancer cachexia-like syndrome and adrenal tumors in inhibin-deficient mice. *PNAS* **91** 8817–8821. (doi:10.1073/pnas.91.19.8817)

McCarthy HD, Crowder RE, Dryden S & Williams G 1994 Megestrol acetate stimulates food and water intake in the rat: effects on regional hypothalamic neuropeptide Y concentrations. *European Journal of Pharmacology* **265** 99–102. (doi:10.1016/0014-2999(94)90229-1)

McDevitt TM, Todorov PT, Beck SA, Khan SH & Tisdale MJ 1995 Purification and characterization of a lipid-mobilizing factor associated with cachexia-inducing tumors in mice and humans. *Cancer Research* **55** 1458–1463.

McPherron AC & Lee SJ 1997 Double muscling in cattle due to mutations in the myostatin gene. *PNAS* **94** 12457–12461. (doi:10.1073/pnas.94.23.12457)

McPherron AC, Lawler AM & Lee SJ 1997 Regulation of skeletal muscle mass in mice by a new TGF-β superfamily member. *Nature* **387** 83–90. (doi:10.1038/387083a0)

Menyhért J, Wittmann G, Lechan RM, Keller E, Liposits Z & Fekete C 2007 Cocaine- and amphetamine-regulated transcript (CART) is colocalized with the orexigenic neuropeptide Y and agouti-related protein and absent from the anorexigenic α-melanocyte-stimulating hormone neurons in the infundibular nucleus of the human hypothalamus. *Endocrinology* **148** 4276–4281. (doi:10.1210/en.2007-0390)

Miller NE 1957 Experiments on motivation. Studies combining psychological, physiological, and pharmacological techniques. *Science* **126** 1271–1278. (doi:10.1126/science.126.3286.1271)

Mittal A, Bhatnagar S, Kumar A, Lach-Trifilieff E, Wauters S, Li H, Makonchuk DY & Glass DJ 2010 The TWEAK–Fn14 system is a critical regulator of denervation-induced skeletal muscle atrophy in mice. *Journal of Cell Biology* **188** 833–849. (doi:10.1083/jcb.200909117)

Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA & Kaplan G 1993 Thalidomide exerts its inhibitory action on tumor necrosis factor α by enhancing mRNA degradation. *Journal of Experimental Medicine* **177** 1675–1680. (doi:10.1084/jem.177.6.1675)

Mourkioti F, Kratsios P, Luedde T, Song YH, Delafontaine P, Adami R, Parente V, Bottinelli R, Pasparakis M & Rosenthal N 2006 Targeted ablation of IKK2 improves skeletal muscle strength, maintains mass, and promotes regeneration. *Journal of Clinical Investigation* **116** 2945–2954. (doi:10.1172/JCI28721)

Murray MJ & Murray AB 1979 Anorexia of infection as a mechanism of host defense. *American Journal of Clinical Nutrition* **32** 593–596.

Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P *et al.* 2010 Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia–anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clinical Nutrition* **29** 154–159. (doi:10.1016/j.clnu.2009.12.004)

Neary NM, Small CJ, Wren AM, Lee JL, Druce MR, Palmieri C, Frost GS, Ghatei MA, Coombes RC & Bloom SR 2004 Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized,

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism* **89** 2832–2836. (doi:10.1210/jc.2003-031768)

Nedergaard J & Cannon B 2014 The browning of white adipose tissue: some burning issues. *Cell Metabolism* **20** 396–407. (doi:10.1016/j.cmet.2014.07.005)

Nitenberg G & Raynard B 2000 Nutritional support of the cancer patient: issues and dilemmas. *Critical Reviews in Oncology/Hematology* **34** 137–168. (doi:10.1016/S1040-8428(00)00048-2)

Nobes JP, Langley SE, Klopper T, Russell-Jones D & Laing RW 2012 A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. *BJU International* **109** 1495–1502. (doi:10.1111/j.1464-410X.2011.10555.x)

Oliff A, Defeo-Jones D, Boyer M, Martinez D, Kiefer D, Vuocolo G, Wolfe A & Socher SH 1987 Tumors secreting human TNF/cachectin induce cachexia in mice. *Cell* **50** 555–563. (doi:10.1016/0092-8674(87)90028-6)

Opara EI, Laviano A & Meguid MM 1995*a* Correlation between food intake and cerebrospinal fluid interleukin 1α in anorectic tumor-bearing rats. *Nutrition* **11** 678–679.

Opara EI, Laviano A, Meguid MM & Yang ZJ 1995*b* Correlation between food intake and CSF IL-1α in anorectic tumor bearing rats. *Neuroreport* **6** 750–752. (doi:10.1097/00001756-199503270-00011)

Owen BM, Ding X, Morgan DA, Coate KC, Bookout AL, Rahmouni K, Kliewer SA & Mangelsdorf DJ 2014 FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metabolism* **20** 670–677. (doi:10.1016/j.cmet.2014.07.012)

Parle M, Maguire P & Heaven C 1997 The development of a training model to improve health professionals' skills, self-efficacy and outcome expectancies when communicating with cancer patients. *Social Science & Medicine* **44** 231–240. (doi:10.1016/S0277-9536(96)00148-7)

Petruzzelli M, Schweiger M, Schreiber R, Campos-Olivas R, Tsoli M, Allen J, Swarbrick M, Rose-John S, Rincon M, Robertson G *et al.* 2014 A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metabolism* **20** 433–447. (doi:10.1016/j.cmet.2014.06.011)

Pimentel GD, Ropelle ER, Rocha GZ & Carvalheira JB 2013 The role of neuronal AMPK as a mediator of nutritional regulation of food intake and energy homeostasis. *Metabolism* **62** 171–178. (doi:10.1016/j.metabol.2012.07.001)

Pimentel GD, Ganeshan K & Carvalheira JB 2014 Hypothalamic inflammation and the central nervous system control of energy homeostasis. *Molecular and Cellular Endocrinology* **397** 15–22. (doi:10.1016/j.mce.2014.06.005)

Popiela T, Lucchi R & Giongo F 1989 Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. *European Journal of Cancer & Clinical Oncology* **25** 1823–1829. (doi:10.1016/0277-5379(89)90354-4)

Porporato PE, Filigheddu N, Reano S, Ferrara M, Angelino E, Gnocchi VF, Prodam F, Ronchi G, Fagoonee S, Fornaro M *et al.* 2013 Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice. *Journal of Clinical Investigation* **123** 611–622. (doi:10.1172/JCI39920)

Price SR, Olivecrona T & Pekala PH 1986 Regulation of lipoprotein lipase synthesis by recombinant tumor necrosis factor – the primary regulatory role of the hormone in 3T3-L1 adipocytes. *Archives of Biochemistry and Biophysics* **251** 738–746. (doi:10.1016/0003-9861(86)90384-X)

Protas PT, Holownia A, Muszynska-Roslan K, Wielgat P, Krawczuk-Rybak M & Braszko JJ 2011 Cerebrospinal fluid IL-6, TNF-α and MCP-1 in children with acute lymphoblastic leukaemia during chemotherapy. *Neuropediatrics* **42** 254–256. (doi:10.1055/s-0031-1295477)

Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A & Meguid MM 2004 Cancer anorexia–cachexia syndrome: cytokines and neuropeptides. *Current Opinion in Clinical Nutrition and Metabolic Care* **7** 427–434. (doi:10.1097/01.mco.0000134363.53782.cb)

Ranson SW, Fisher C & Ingram WR 1938 Adiposity and diabetes mellitus in a monkey with hypothalamic lesions. *Endocrinology* **23** 7. (doi:10.1210/endo-23-2-175)

Reid J, McKenna H, Fitzsimons D & McCance T 2009 Fighting over food: patient and family understanding of cancer cachexia. *Oncology Nursing Forum* **36** 439–445. (doi:10.1188/09.ONF.439-445)

Reid J, Mills M, Cantwell M, Cardwell CR, Murray LJ & Donnelly M 2012 Thalidomide for managing cancer cachexia. In *Cochrane Database of Systematic Reviews* CD008664. (doi:10.1002/14651858.CD008664.pub2)

Reyes TM & Sawchenko PE 2002 Involvement of the arcuate nucleus of the hypothalamus in interleukin-1-induced anorexia. *Journal of Neuroscience* **22** 5091–5099.

Richardson P, Hideshima T & Anderson K 2002 Thalidomide: emerging role in cancer medicine. *Annual Review of Medicine* **53** 629–657. (doi:10.1146/annurev.med.53.082901.104043)

Ropelle ER, Pauli JR, Zecchin KG, Ueno M, de Souza CT, Morari J, Faria MC, Velloso LA, Saad MJ & Carvalheira JB 2007 A central role for neuronal adenosine 5′-monophosphate-activated protein kinase in cancer-induced anorexia. *Endocrinology* **148** 5220–5229. (doi:10.1210/en.2007-0381)

Ropelle ER, Fernandes MF, Flores MB, Ueno M, Rocco S, Marin R, Cintra DE, Velloso LA, Franchini KG, Saad MJ *et al.* 2008*a* Central exercise action increases the AMPK and mTOR response to leptin. *PLoS ONE* **3** e3856. (doi:10.1371/journal.pone.0003856)

Ropelle ER, Pauli JR, Fernandes MF, Rocco SA, Marin RM, Morari J, Souza KK, Dias MM, Gomes-Marcondes MC, Gontijo JA *et al.* 2008*b* A central role for neuronal AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) in high-protein diet-induced weight loss. *Diabetes* **57** 594–605. (doi:10.2337/db07-0573)

Ross PJ, Ashley S, Norton A, Priest K, Waters JS, Eisen T, Smith IE & O'Brien ME 2004 Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *British Journal of Cancer* **90** 1905–1911. (doi:10.1038/sj.bjc.6601781)

Ruan HB, Dietrich MO, Liu ZW, Zimmer MR, Li MD, Singh JP, Zhang K, Yin R, Wu J, Horvath TL *et al.* 2014 *O*-GlcNA transferase enables AgRP neurons to suppress browning of white fat. *Cell* **159** 306–317. (doi:10.1016/j.cell.2014.09.010)

Ruiz GV, López-Briz E, Carbonell SR, Gonzalvez PJL & Bort-Marti S 2013 Megestrol acetate for treatment of anorexia–cachexia syndrome. *Cochrane Database of Systematic Reviews* CD004310. (doi:10.1002/14651858.CD004310.pub3)

Russell ST & Tisdale MJ 2002 Effect of a tumour-derived lipid-mobilising factor on glucose and lipid metabolism *in vivo*. *British Journal of Cancer* **87** 580–584. (doi:10.1038/sj.bjc.6600493)

Russell ST & Tisdale MJ 2010 Antidiabetic properties of zinc-α_2-glycoprotein in *ob/ob* mice. *Endocrinology* **151** 948–957. (doi:10.1210/en.2009-0827)

Russell ST, Hirai K & Tisdale MJ 2002 Role of β3-adrenergic receptors in the action of a tumour lipid mobilizing factor. *British Journal of Cancer* **86** 424–428. (doi:10.1038/sj.bjc.6600086)

Russell ST, Zimmerman TP, Domin BA & Tisdale MJ 2004 Induction of lipolysis *in vitro* and loss of body fat *in vivo* by zinc-α_2-glycoprotein. *Biochimica et Biophysica Acta* **1636** 59–68. (doi:10.1016/j.bbalip.2003.12.004)

Sandri M, Sandri C, Gilbert A, Skurk C, Calabria E, Picard A, Walsh K, Schiaffino S, Lecker SH & Goldberg AL 2004 Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell* **117** 399–412. (doi:10.1016/S0092-8674(04)00400-3)

Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, Goldberg AL & Spiegelman BM 2006 PGC-1α protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. *PNAS* **103** 16260–16265. (doi:10.1073/pnas.0607795103)

Santos GA, Moura RF, Vitorino DC, Roman EA, Torsoni AS, Velloso LA & Torsoni MA 2013 Hypothalamic AMPK activation blocks

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

lipopolysaccharide inhibition of glucose production in mice liver. *Molecular and Cellular Endocrinology* **381** 88–96. (doi:10.1016/j.mce.2013.07.018)

Saper CB & Breder CD 1992 Endogenous pyrogens in the CNS: role in the febrile response. *Progress in Brain Research* **93** 419–428 (discussion 428–429). (doi:10.1016/S0079-6123(08)64587-2)

Saper CB & Breder CD 1994 The neurologic basis of fever. *New England Journal of Medicine* **330** 1880–1886. (doi:10.1056/NEJM199406303302609)

Sato T, Meguid MM, Fetissov SO, Chen C & Zhang L 2001 Hypothalamic dopaminergic receptor expressions in anorexia of tumor-bearing rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **281** R1907–R1916.

Scarlett JM, Jobst EE, Enriori PJ, Bowe DD, Batra AK, Grant WF, Cowley MA & Marks DL 2007 Regulation of central melanocortin signaling by interleukin-1β. *Endocrinology* **148** 4217–4225. (doi:10.1210/en.2007-0017)

Schreck R, Rieber P & Baeuerle PA 1991 Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-κB transcription factor and HIV-1. *EMBO Journal* **10** 2247–2258.

Schwartz MW, Woods SC, Porte D, Seeley RJ & Baskin DG 2000 Central nervous system control of food intake. *Nature* **404** 661–671. (doi:10.1038/35007534)

Seruga B, Zhang H, Bernstein LJ & Tannock IF 2008 Cytokines and their relationship to the symptoms and outcome of cancer. *Nature Reviews. Cancer* **8** 887–899. (doi:10.1038/nrc2507)

Shih A & Jackson KC 2007 Role of corticosteroids in palliative care. *Journal of Pain & Palliative Care Pharmacotherapy* **21** 69–76. (doi:10.1080/J354v21n04_14)

Shimizu Y, Nagaya N, Isobe T, Imazu M, Okumura H, Hosoda H, Kojima M, Kangawa K & Kohno N 2003 Increased plasma ghrelin level in lung cancer cachexia. *Clinical Cancer Research* **9** 774–778.

Silva VR, Micheletti TO, Pimentel GD, Katashima CK, Lenhare L, Morari J, Mendes MC, Razolli DS, Rocha GZ, de Souza CT *et al.* 2014 Hypothalamic S1P/S1PR1 axis controls energy homeostasis. *Nature Communications* **5** 4859. (doi:10.1038/ncomms5859)

Sishi BJ & Engelbrecht AM 2011 Tumor necrosis factor alpha (TNF-α) inactivates the PI3-kinase/PKB pathway and induces atrophy and apoptosis in L6 myotubes. *Cytokine* **54** 173–184. (doi:10.1016/j.cyto.2011.01.009)

Smith HJ, Wyke SM & Tisdale MJ 2004 Role of protein kinase C and NF-κB in proteolysis-inducing factor-induced proteasome expression in C_2C_{12} myotubes. *British Journal of Cancer* **90** 1850–1857. (doi:10.1038/sj.bjc.6601767)

Soda K, Kawakami M, Kashii A & Miyata M 1994 Characterization of mice bearing subclones of colon 26 adenocarcinoma disqualifies interleukin-6 as the sole inducer of cachexia. *Japanese Journal of Cancer Research* **85** 1124–1130. (doi:10.1111/j.1349-7006.1994.tb02917.x)

Soda K, Kawakami M, Kashii A & Miyata M 1995 Manifestations of cancer cachexia induced by colon 26 adenocarcinoma are not fully ascribable to interleukin-6. *International Journal of Cancer* **62** 332–336. (doi:10.1002/ijc.2910620317)

Souza SC, de Vargas LM, Yamamoto MT, Lien P, Franciosa MD, Moss LG & Greenberg AS 1998 Overexpression of perilipin A and B blocks the ability of tumor necrosis factor α to increase lipolysis in 3T3-L1 adipocytes. *Journal of Biological Chemistry* **273** 24665–24669. (doi:10.1074/jbc.273.38.24665)

Steinberg GR, Watt MJ & Febbraio MA 2009 Cytokine regulation of AMPK signalling. *Frontiers in Bioscience* **14** 1902–1916. (doi:10.2741/3350)

Stewart GD, Skipworth RJ & Fearon KC 2006 Cancer cachexia and fatigue. *Clinical Medicine* **6** 140–143. (doi:10.7861/clinmedicine.6-2-140)

Strasser F, Luftner D, Possinger K, Ernst G, Ruhstaller T, Meissner W, Ko YD, Schnelle M, Reif M, Cerny T *et al.* 2006 Comparison of orally administered *Cannabis* extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia–cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the *Cannabis*-In-Cachexia-Study-Group. *Journal of Clinical Oncology* **24** 3394–3400. (doi:10.1200/JCO.2005.05.1847)

Strasser F, Lutz TA, Maeder MT, Thuerlimann B, Bueche D, Tschöp M, Kaufmann K, Holst B, Brändle M, von Moos R *et al.* 2008 Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia: a randomised, placebo-controlled, double-blind, double-crossover study. *British Journal of Cancer* **98** 300–308. (doi:10.1038/sj.bjc.6604148)

Strassmann G, Fong M, Kenney JS & Jacob CO 1992 Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *Journal of Clinical Investigation* **89** 1681–1684. (doi:10.1172/JCI115767)

Suh SY, Choi YS, Yeom CH, Kwak SM, Yoon HM, Kim DG, Koh SJ, Park J, Lee MA, Lee YJ *et al.* 2013 Interleukin-6 but not tumour necrosis factor-alpha predicts survival in patients with advanced cancer. *Supportive Care in Cancer* **21** 3071–3077. (doi:10.1007/s00520-013-1878-4)

Taylor DD, Gercel-Taylor C, Jenis LG & Devereux DF 1992 Identification of a human tumor-derived lipolysis-promoting factor. *Cancer Research* **52** 829–834.

Tchekmedyian NS, Hickman M, Siau J, Greco FA, Keller J, Browder H & Aisner J 1992 Megestrol acetate in cancer anorexia and weight loss. *Cancer* **69** 1268–1274. (doi:10.1002/cncr.2820690532)

Teng MN, Turksen K, Jacobs CA, Fuchs E & Schreiber H 1993 Prevention of runting and cachexia by a chimeric TNF receptor-Fc protein. *Clinical Immunology and Immunopathology* **69** 215–222. (doi:10.1006/clin.1993.1172)

Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE & de Graeff A 2007 Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of Pain and Symptom Management* **34** 94–104. (doi:10.1016/j.jpainsymman.2006.10.015)

Tisdale MJ 2003 The 'cancer cachectic factor'. *Supportive Care in Cancer* **11** 73–78. (doi:10.1007/s00520-002-0408-6)

Tisdale MJ 2004 Cancer cachexia. *Langenbeck's Archives of Surgery* **389** 299–305. (doi:10.1007/s00423-004-0486-7)

Tisdale MJ 2009 Mechanisms of cancer cachexia. *Physiological Reviews* **89** 381–410. (doi:10.1152/physrev.00016.2008)

Todorov P, Cariuk P, McDevitt T, Coles B, Fearon K & Tisdale M 1996 Characterization of a cancer cachectic factor. *Nature* **379** 739–742. (doi:10.1038/379739a0)

Torelli GF, Meguid MM, Moldawer LL, Edwards CK, Kim HJ, Carter JL, Laviano A & Rossi Fanelli F 1999 Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *American Journal of Physiology* **277** R850–R855.

Tsoli M, Moore M, Burg D, Painter A, Taylor R, Lockie SH, Turner N, Warren A, Cooney G, Oldfield B *et al.* 2012 Activation of thermogenesis in brown adipose tissue and dysregulated lipid metabolism associated with cancer cachexia in mice. *Cancer Research* **72** 4372–4382. (doi:10.1158/0008-5472.CAN-11-3536)

Varma M, Laviano A, Meguid MM, Gleason JR, Yang ZJ & Oler A 2000 Comparison of early feeding pattern dynamics in female and male rats after reversible ventromedial nucleus of hypothalamus block. *Journal of Investigative Medicine* **48** 417–426.

Wang DT, Yin Y, Yang YJ, Lv PJ, Shi Y, Lu L & Wei LB 2014 Resveratrol prevents TNF-α-induced muscle atrophy via regulation of Akt/mTOR/FoxO1 signaling in C2C12 myotubes. *International Immunopharmacology* **19** 206–213. (doi:10.1016/j.intimp.2014.02.002)

Watanabe S & Bruera E 1996 Anorexia and cachexia, asthenia, and lethargy. *Hematology/Oncology Clinics of North America* **10** 189–206. (doi:10.1016/S0889-8588(05)70334-8)

Weiland TJ, Anthony-Harvey-Beavis D, Voudouris NJ & Kent S 2006 Metabotropic glutamate receptors mediate lipopolysaccharide-induced fever and sickness behavior. *Brain, Behavior, and Immunity* **20** 233–245. (doi:10.1016/j.bbi.2005.08.007)

Whitaker KW & Reyes TM 2008 Central blockade of melanocortin receptors attenuates the metabolic and locomotor responses to peripheral interleukin-1β administration. *Neuropharmacology* **54** 509–520. (doi:10.1016/j.neuropharm.2007.10.014)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.

Wiedenmann B, Malfertheiner P, Friess H, Ritch P, Arseneau J, Mantovani G, Caprioni F, Van Cutsem E, Richel D, DeWitte M *et al.* 2008 A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. *Journal of Supportive Oncology* **6** 18–25.

Wieland BM, Stewart GD, Skipworth RJ, Sangster K, Fearon KC, Ross JA, Reiman TJ, Easaw J, Mourtzakis M, Kumar V *et al.* 2007 Is there a human homologue to the murine proteolysis-inducing factor? *Clinical Cancer Research* **13** 4984–4992. (doi:10.1158/1078-0432.CCR-07-0946)

Winter A, MacAdams J & Chevalier S 2012 Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. *Clinical Nutrition* **31** 765–773. (doi:10.1016/j.clnu.2012.05.003)

Wisse BE, Frayo RS, Schwartz MW & Cummings DE 2001 Reversal of cancer anorexia by blockade of central melanocortin receptors in rats. *Endocrinology* **142** 3292–3301. (doi:10.1210/endo.142.8.8324)

Xia Y & Schneyer AL 2009 The biology of activin: recent advances in structure, regulation and function. *Journal of Endocrinology* **202** 1–12. (doi:10.1677/JOE-08-0549)

Yoshikawa T, Noguchi Y, Doi C, Makino T & Nomura K 2001 Insulin resistance in patients with cancer: relationships with tumor site, tumor stage, body-weight loss, acute-phase response, and energy expenditure. *Nutrition* **17** 590–593. (doi:10.1016/S0899-9007(01)00561-5)

Yu Z, Li P, Zhang M, Hannink M, Stamler JS & Yan Z 2008 Fiber type-specific nitric oxide protects oxidative myofibers against cachectic stimuli. *PLoS ONE* **3** e2086. (doi:10.1371/journal.pone.0002086)

Zaki MH, Nemeth JA & Trikha M 2004 CNTO 328, a monoclonal antibody to IL-6, inhibits human tumor-induced cachexia in nude mice. *International Journal of Cancer* **111** 592–595. (doi:10.1002/ijc.20270)

Zhang HH, Halbleib M, Ahmad F, Manganiello VC & Greenberg AS 2002 Tumor necrosis factor-α stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP. *Diabetes* **51** 2929–2935. (doi:10.2337/diabetes.51.10.2929)

Zhang Z, Zhang H, Li B, Meng X, Wang J, Zhang Y, Yao S, Ma Q, Jin L, Yang J *et al.* 2014 Berberine activates thermogenesis in white and brown adipose tissue. *Nature Communications* **5** 5493. (doi:10.1038/ncomms6493)

Zhou X, Wang JL, Lu J, Song Y, Kwak KS, Jiao Q, Rosenfeld R, Chen Q, Boone T, Simonet WS *et al.* 2010 Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell* **142** 531–543. (doi:10.1016/j.cell.2010.07.011)

Received in final form 12 June 2015
Accepted 22 June 2015
Accepted Preprint published online 25 June 2015

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0170

Published by Bioscientifica Ltd.