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

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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

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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).

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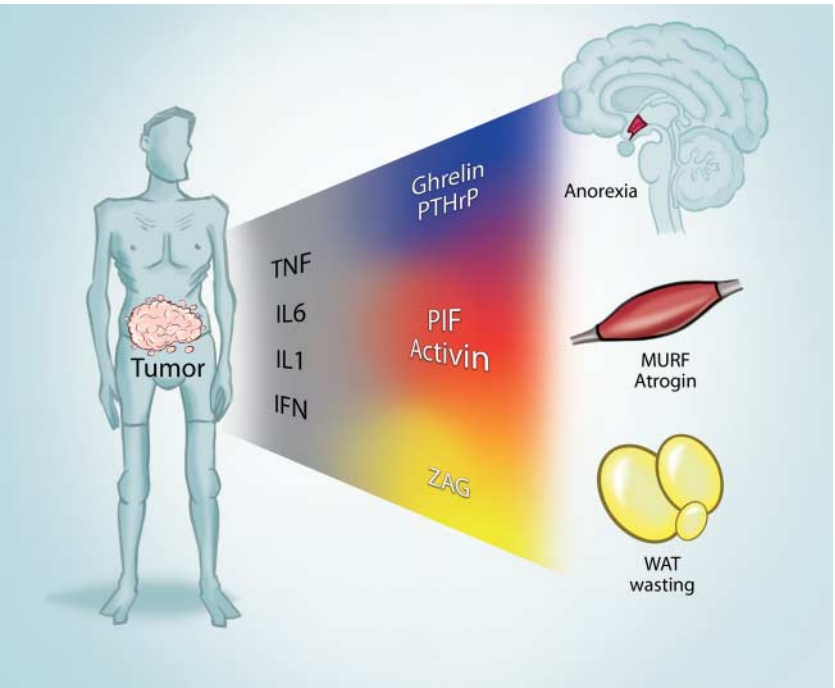

Figure 1

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.

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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

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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

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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

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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

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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

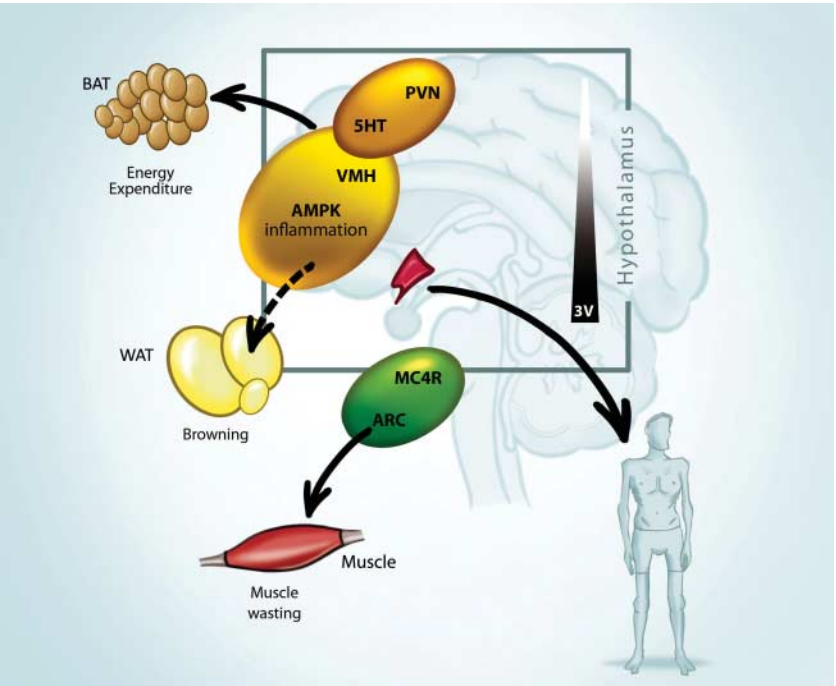

Figure 2
The hypothalamus is at the crossroads of cancer cachexia's main features. Pro-anorexigenic factors are integrated in discrete nuclei of the hypothalamus. The ventromedial nucleus (VMH) promotes heat production in brown adipose tissue (BAT) and may mediate white adipose browning via the B3 adrenergic 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.

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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

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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.

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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.

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