Muscle wasting is the key feature of cachexia (Muscaritoli et al., 2010; Zhou et al., 2010). Prevention of muscle catabolism has been suggested to prolong survival independent of the disease course (Zhou et al., 2010). Although the pathological mechanisms of cachexia and muscle wasting have been under investigation, insights have primarily been gained on the association of muscle wasting and feeding-regulatory peptides such as leptin, ghrelin, and melanocortin (Molfino et al., 2010). Herein, we demonstrate the control of food intake and muscle wasting, focused on the interaction between brain and muscle.

2. Hypothalamic and peripheral regulation of muscle metabolism and food intake

The regulation of food intake is coordinated in the hypothalamus. In particular, the arcuate nucleus of the hypothalamus (ARC) is critical for appetite regulation. Many factors are implicated in the hypothalamic regulation of food intake, melanin-concentrating hormone (MCH), neuropeptide Y (NPY), agouti-related protein (AgRP), proopiomelanocortin (POMC), cocaine-and-amphetamine regulated transcript (CART). Of the peripheral peptides, ghrelin and leptin have the orexigenic and anorexigenic effects respectively, and make the regulatory feedback loop between the periphery and brain. There is another crosstalk between the brain and muscle, where melanocortin and ghrelin have the important role in the mechanism of cachexia (Fig. 1). Among the numerous circulating appetite regulating peptides, these two hormones, ghrelin and leptin are particularly important in cachexia, and we will principally discuss these two hormones here.

2.1. Melanocortins

The melanocortin system is a central component of the regulation of feeding. It is composed of two types of neurons, the neurons; NYP/AgRP and POMC/CART. These neurons are located in the ARC. NPY/AgRP neurons release the orexigenic peptides NPY and AgRP, an antagonist melanocortin, which increase food intake (Williams et al., 2011; Xu et al., 2011). By contrast, POMC neurons synthesize and secrete an anorexigenic peptide, α-melanocyte-stimulating hormone (α-MSH), which activates type4 melanocortin receptor (MC4R) and decreases food intake.

The increase of cytokines stimulates the central melanocortin system (Reyes and Sawchenko, 2002). Cytokines induce the hypothalamic expression of the serotonin, which stimulate POMC anorexigenic pathway. In the result MC4R is activated by serotonin leading to induce anorexia (Tecott, 2007).

A recent study has noted that AgRP, the endogenous inverse agonist at the melanocortin-4 receptor (MC4R), ameliorates cachexia associated with cancer (Joppa et al., 2007), uremia (Cheung et al., 2008), and chronic kidney disease (Cheung and Mak, 2012) by increasing food intake and reducing energy expenditure. Whereas the release of AgRP is diminished by inflammation, AgRP treatment decreases proinflammatory cytokines, and improves energy expenditure, food intake, muscle mass, body weight, fat mass (Joppa et al., 2007; Cheung and Mak, 2012). In contrast to AgRP administration, treatment of tumor-bearing rats with i.c.v. NPY worsens anorexia, suggesting that cachexia does not result from a selective reduction in NPY release (Grossberg et al., 2010a). In addition to AgRP, the administration of MC4-R antagonists increases food intake. The MC4-R blocker decreases cyclic adenosine monophosphate accumulation, indicating inverse agonist activity. Tumor-bearing mice treated with MC4-R blocker maintain lean body mass. Furthermore, orally available selective MC4-R antagonists also stimulate food intake and reduce cancer-induced cachexia in mice (Weyermann et al., 2009).

Together, AgRP and α-MSH will be the clues for the understanding of the underlying mechanism and possible therapeutic target for muscle wasting and anorexia.

2.2. Leptin

Leptin is a 16-kDa protein hormone secreted by adipocytes. Plasma leptin concentration increases in proportion to body fat mass and regulates food intake and energy expenditure to maintain body fat stores. Leptin acts in the hypothalamus, where it inhibits NPY and causes anorexia (Elmquist et al., 1999).

Leptin also plays a key role in cancer anorexia-cachexia syndrome (Engineer and Garcia, 2012). Circulating leptin levels are decreased in cancer cachexia animal models and in cancer cachexia patients (Werynska et al., 2009; Smiechowska et al., 2010). Furthermore, Leptin levels decreases gradually with tumor stage and aggressiveness (Salageanu et al., 2010). In esophageal cancer patients, leptin levels correlate directly with body mass index, tumor necrosis factor-alpha (TNF-α), albumin, and hemoglobin and indirectly with IL-6, IL-8, and high-sensitivity C-reactive protein (Diakowska et al., 2010).

Adipose-derived factors such as leptin, TNF-α, resistin, and adiponectin have been shown to affect muscle metabolism, protein dynamics, or both directly. Leptin mediates the production of inflammatory cytokines independent of its effects on food intake (Burgos-Ramos et al., 2012). Despite low leptin levels, leptin intense the inflammatory response and the levels of inflammatory cytokines. Proinflammatory cytokines, such as TNF-α, interleukin (IL)-1, and IL-6, have been proposed to cause cachexia by increasing the expression of the hypothalamic leptin receptor (Salageanu et al., 2010).

Although it is well known that leptin is an adipokine derived from adiposity, a recent study has suggested that cultured myocytes also release leptin (Wolsk et al., 2012). In skeletal muscle, insulin sensitivity is improved by enhancing intracellular glucose transporter type 4 transport (Sainz et al., 2012).

These studies imply that leptin acts to regulate muscle metabolism and the production of cytokines in addition to the control of appetite and energy expenditure in cachexia.

2.3. Ghrelin

Ghrelin is a peptide hormone that stimulates growth hormone release and positive energy balance via binding to growth hormone secretagogue receptor (GHSR)-1a. Patients with cancer cachexia exhibited increased circulating concentrations of ghrelin (Wolf et al., 2006). In recent study, it is suggested that ghrelin has the effect to decrease inflammatory cytokines. In fact, the inflammatory cytokines are decreased in ghrelin-treated animals. Ghrelin inhibits the expression of IL-1 receptor in the brainstem and decreases the expression of pro-hormone convertase-2, an enzyme involved in the processing of POMC to α-MSH. Ghrelin also increase the expression of AgRP and NPY in the hypothalamus (Deboer et al., 2008). Furthermore, ghrelin reduces the elevated mRNA expression of TNF-α and IL-6 in muscle and normalized plasma glucocorticoid levels (Balasubramaniam et al., 2009). Injection of ghrelin causes ghrelin resistance despite upregulation of hypothalamic GHS-R expression in MCG 101-bearing mice, which show characteristic anorexia, fat loss, and muscle wasting owing to increased concentration of prostaglandinE2 and proinflammatory cytokines (IL-1β, IL-6, TNF-α) (Wang et al., 2006).

Ghrelin has also have attention for its anticatabolic effects (Balasubramaniam et al., 2009; Sugiyama et al., 2012). Treatment with ghrelin and ghrelin receptor agonists increases food intake and improves lean body mass (Deboer et al., 2007, 2008).

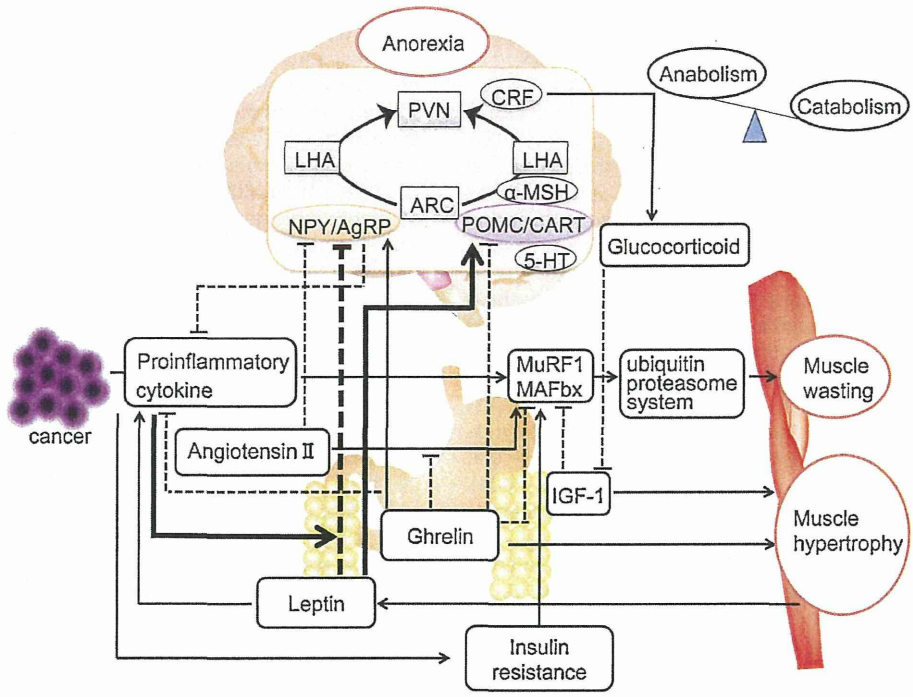

Fig. 1. The crosstalk between brain and muscle. Proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, induce muscle atrophy via upregulation of MuRF1 and MAFbx. Insulin resistance is present in cancer cachexia. In insulin resistant state, PI3K activity is decreased, leading to increase MuRF1 and MAFbx, resulting in muscle atrophy. IGF-1 induces skeletal muscle hypertrophy, in contrast, inhibit muscle wasting by decreasing MuRF1 and MAFbx. Glucocorticoids induce muscle atrophy by inhibiting the action of insulin and IGF-1. Ghrelin has the effect to decrease inflammatory cytokines. Ghrelin inhibit the expression of MuRF-1 and MAFbx, lead to improve muscle catabolism. Ang II induces skeletal muscle atrophy by increasing MuRF-1. Ang II reduce food intake by inhibiting NPY expression in hypothalamus. Leptin mediates the production of inflammatory cytokines. Although leptin is decreased in cachexia, proinflammatory cytokines increase expression of the hypothalamic leptin receptor, leading to cause anorexia by inhibiting NPY/AgRP and increasing POMC/CART. AgRP has the effect to decrease proinflammatory cytokines and to increase body weight, food intake, and muscle mass. Muscle Ring Finger1 (MuRF1), Muscle Atrophy F-box (MAFbx), insulin-like growth factor 1 (IGF-1), Angiotensin II (Ang II), neuropeptide Y (NPY), agouti-related protein (AgRP), proopiomelanocortin (POMC), cocaine-and-amphetamine responsive transcript (CART), corticotrophin releasing factor (CRF), 5-hydroxytryptamine (5-HT), periventricular nucleus (PVN) arcuate nucleus (ARC), lateral hypothalamic area (LHA).

Ghrelin and its analogs improve body weight by regulating the expression of muscle ring finger 1 (MuRF-1) and muscle atrophy f-box (MAFbx) (Palus et al., 2011) further inhibiting the expression of myostatin in skeletal muscle (Lenk et al., 2013). Expression of the muscle-specific E3 ubiquitin ligases MuRF1 and MAFbx are normalized by ghrelin (Balasubramaniam et al., 2009). In angiotensin II induced muscle catabolism, ghrelin also improves body weight loss and skeletal muscle catabolism (Sugiyama et al., 2012).

Although only acyl ghrelin can bind GHSR, both ghrelin and des-acyl ghrelin stimulate proliferating C2C12 skeletal myoblasts to differentiate via activation of p38 (Filigheddu et al., 2007). The expression of des-acyl ghrelin impairs skeletal muscle atrophy induced by either fasting or denervation without stimulating muscle hypertrophy and GHSR-1a-mediated activation of the growth hormone/insulin-like growth factor-1 (IGF-1) axis (Porporato et al., 2013). In GHSR-deficient mice, both acyl ghrelin and des-acyl ghrelin induce phosphorylation of Akt in skeletal muscle and impair fasting-induced atrophy, implicating acyl ghrelin and des-acyl ghrelin in the blocking of skeletal muscle atrophy independent of growth hormones (Porporato et al., 2013).

Thus it is suggested that ghrelin and ghrelin receptor agonist has the therapeutic potential, which lead to improve skeletal muscle wasting as well as anorexia owing to its suppressive effect on muscle proteolysis and its anti-inflammatory action.

3. Cytokine actions within the regulatory feedback loop

In anorexia-cachexia syndrome, the balance between proinflammatory and anti-inflammatory cytokines is important for the development of the cachexia (Argiles et al., 2003). Inflammatory cytokines such as IL-1β, IL-6, TNF-α, and interferon-γ (IFN-γ) are potential causes of reduced food intake and increased energy expenditure (Plata-Salaman, 2001). By contrast, anti-inflammatory cytokines, including IL-4, IL-10, IL-12, and IL-15, have anti-cachectic properties. IL-15 increases glucose uptake in skeletal muscle (Busquets et al., 2006), and is reported as an anabolic factor for skeletal muscle. Muscle-derived IL-15 can decrease fat deposition and adipocyte metabolism via a muscle-to-fat endocrine pathway, and overexpression of IL-15 induces skeletal muscle hypertrophy in vitro (Quinn et al., 2002; Quinn, 2008). The administration of IL-12 to mice with colon-26 carcinoma alleviates body weight loss and other abnormalities associated with cachexia.

Proinflammatory cytokines initiate a cascade of events that ultimately leads to a state of wasting, malnourishment, and eventually death (Ramos et al., 2004). Those cytokines are involved in cancer related anorexia by increasing the levels of corticotrophin-releasing hormone, a central nervous anorexigenic neurotransmitter, lead to suppress food intake. They also mediate muscle atrophy. In particular, IL-1β, IL-6, TNF-α and leukemia inhibitory factor (LIF) have been associated with the initiating event in muscle catabolism in clinical and experimental cachexia. Acute and chronic central administration of IL-1β results in muscle atrophy (Braun et al., 2011). This effect is dependent on hypothalamic-pituitary-adrenal axis activation, as central nervous system IL-1β-induced atrophy is abrogated by adrenalectomy. These data suggest that central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis (Braun et al., 2011). IL-6 plays

an important role in regulating fat metabolism in muscle, increasing rates of fatty acid oxidation and attenuating the lipogenic effects of insulin. TNF-α levels are elevated in the circulations of patients with cancer cachexia (Argiles et al., 2003). TNF-α binds to its receptor and induces the activation of the NF-κB family of transcription factors (Von Haehling et al., 2002; Glass, 2005). NF-κB activation was shown to be required for cytokine-induced loss of skeletal muscle proteins (Glass, 2005). IL-6 plays a crucial role in the para-neoplastic syndromes, including anorexia and cachexia (Barton, 2005). LIF expression in the pituitary is necessary to drive increased POMC mRNA expression and adrenocorticotropic hormone release by pituitary corticotrophs in response to inflammation (Ray et al., 1998; Chesnokova and Melmed, 2000). Gp130 is the signal-transducing subunit of the LIF-receptor complex. This process is depend on gp130-mediated activation of Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling, which underlies the induction of POMC mRNA expression by leptin, suggesting that LIF may activate hypothalamic POMC neurons in a similar manner (Stefana et al., 1996; Bates et al., 2003). Indeed, LIF induces anorexia by directly activating POMC neurons (Grossberg et al., 2010a, 2010b).

In an animal model of anorexia-cachexia syndrome with deregulated expression of a number of cytokines including IL-10, pharmacologic intervention to impair protein synthesis restores cytokine production to near normal levels, delays anorexia-cachexia progression, and extends host survival (Robert et al., 2012). These findings suggest a new therapeutic possibility for the treatment of anorexia-cachexia syndrome that targets protein synthesis by blocking the production of procachexic factors. Those cytokines act via the hypothalamic central melanocortin system to regulate skeletal muscle metabolism (Braun and Marks, 2011).

4. Pathological mechanism of muscle wasting

Progressive impairment of skeletal muscle is associated with debility, morbidity, and mortality. In catabolic balance, proteolysis and lipolysis are induced leading to the depletion of protein mass and adipose tissue. Muscle wasting appears primarily to be mediated by the activation of the ubiquitin proteasome system (Attaix et al., 1999; Baracos, 2002). Three enzymatic components are required for the muscle metabolism regulating process, an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligating enzyme. Skeletal muscle atrophy occurs via the induction of the E3 ubiquitin ligases. In the model of skeletal muscle atrophy, two ubiquitin ligases have been identified: MuRF1 (Bodine et al., 2001) and MAFbx, also called atrogin-1 (Gomes et al., 2001). These ubiquitin ligases are significantly upregulated under atrophy conditions. The expression of MuRF1 and MAFbx is negatively regulated by insulin/IGF-I signaling (Sacheck et al., 2004).

Another cause of muscle wasting is the TNF-induced weak inducer of apoptosis (TWEAK) and tumor necrosis factor receptor-associated factor 6 (TRAF6), which has been identified as a novel inducer of skeletal muscle wasting. Adult skeletal muscles express minimal levels of Fn14, the bona fide TWEAK receptor. Specific conditions of atrophy such as denervation, immobilization, and unloading rapidly induce the expression of Fn14, leading to TWEAK-induced activation of various proteolytic pathways in skeletal muscle (Kumar et al., 2012).

Angiotensin II (Ang II) induces body weight loss and skeletal muscle catabolism through the ubiquitin-proteasome pathway. Ang II is elevated in cachexia and induces skeletal muscle atrophy by increasing the expression of E3 ligases atrogin-1/MuRF-1. Ang II reduces phosphorylation of AMP-activated protein kinase, an enzyme that regulates NPY expression (Yoshida et al., 2012). Intra-cerebro-ventricular Ang II infusion reduced food intake, and Ang II dose-dependently reduces NPY and orexin expression in hypothalamus (Yoshida et al., 2012). In recent important study, pharmacological blockade of ActRIIB pathway prevents muscle wasting and furthermore dramatically prolongs survival, in the animals in which tumor growth is not inhibited and fat loss and production of proinflammatory cytokines are not reduced (Zhou et al., 2010). ActRIIB pathway blockade abolished the activation of the ubiquitin-proteasome system and the induction of atrophy-specific ubiquitin ligases in muscles and also markedly stimulated muscle stem cell growth (Zhou et al., 2010). This study suggested an important link between activation of the ActRIIB pathway and the development of cancer cachexia.

Branched-chain amino acids such as leucine and valine significantly suppress the loss of body weight through an increase in protein synthesis and a decrease in degradation. Branched-chain amino acids exert anticatabolic effects by promoting protein synthesis and inhibiting intracellular proteolytic pathways (Berk et al., 2008). A recent study has shown that dietary leucine supplementation inhibits muscle protein breakdown in rats. In cultured muscle cells, insulin and leucine have been found to act additively in down regulating E2 ubiquitin-conjugating enzyme expression (Sadiq et al., 2007), whereas branched-chain amino acids reduces atrogin-1 and MuRF1 expression (Herningtyas et al., 2008; Op Den Kamp et al., 2009).

The eicosanoids affect the inflammatory process and are implicated in the process of cancer cachexia. They are unsaturated C20 fatty acids which can be separated into two main groups: lipoxygenase products including leukotrienes and lipoxins, and prostanoids including prostaglandins, prostacyclin and thromboxane. Eicosanoids play a role in generating inflammatory response, which induces peripheral tissue loss. Additionally, eicosanoids play a role in signaling the inflammatory mediators or catabolic factors, for example proteolysis-inducing factor (Ross and Fearon, 2002).

5. Glucocorticoid and insulin signaling

Endogenous glucocorticoids and impaired insulin signaling are also important for muscle catabolism (Dardevet et al., 1998; Schakman et al., 2005; Hu et al., 2009). The stimulation of muscle proteolysis requires 2 events; increased glucocorticoid levels and impaired insulin signaling. Glucocorticoids inhibit protein synthesis and increase the rate of protein breakdown. Glucocorticoids induce muscle atrophy by inhibiting the action of insulin and IGF-1. Growth hormones and IGF-1 stimulate skeletal muscle protein synthesis, whereas the expression of cytokines in skeletal muscle may negatively regulate the autocrine synthesis of IGF-I (Broussard et al., 2003; Frost and Lang, 2004). IGF-I increases muscle mass, whereas myostatin inhibits its development. Although IGF-I is a potent determinant of protein degradation in vitro and is antagonized by glucocorticoids, the glucocorticoid antagonist is insufficient to block muscle wasting (Pickering et al., 2003). In the presence of insulin/IGF-I, Akt-mediated phosphorylation inhibits FoxO nuclear translocation, suppressing FoxO-dependent transcription of atrogin-1 and MuRF1, which in turn inhibits skeletal muscle atrophy (Op Den Kamp et al., 2009).

FoxO activation is associated with the progression of muscle atrophy in cachexia (Reed et al., 2012). The FoxO pathway is activated in skeletal muscle during cachexia. Inhibition of FoxO transcriptional activity prevents muscle fiber atrophy during cachexia and induces hypertrophy (Reed et al., 2012).

Muscle hyperexpressing IGF-1 in both young and aged animals display definitively increased fiber cross-sectional area. By contrast, loss of muscle mass or reduction of fiber size in tumor-bearing mice is not modified by IGF-1 expression (Penna et al., 2010). These

Table 1
Clinical studies on the treatment of cachexia and sarcopenia.

Drug	Company	Type	Pathological condition	Phase of trials	References
Megace ES	Par Pharmaceutical	Carnitine + celecoxib +/− megestrol acetate	Cancer	Phase III	Madeddu et al. (2012)
Anamorelin	Helsinn Therapeutics	Ghrelin receptor agonist	Cancer	Phase III	Garcia et al. (2013)
EPA	Nestle, Danone, Abbott, Fresenius	SOD agonist and UPP activator	Cancer	Phase II/III	Barber (2001), Hardman (2004) and Fearon et al. (2006)
H-4864-GMP	Bachem	Human ghrelin	Cancer	Phase II	Neary et al. (2004)
GT_X-024 (enobosarm)	GT_X	Selective androgen receptor modular (SARM)	Cancer	Phase II	Dalton et al. (2011) and Dobs et al. (2013)
U-1250	Bachem	Synthetic human ghrelin	Cancer	Phase II	Strasser et al. (2008)
P-0861	Polypeptide Laboratories	Synthetic human ghrelin	Cancer	Phase II	Lundholm et al. (2010)
SUN11031	Asubio Pharmaceuticals	Synthetic human ghrelin	COPD	Phase II	Levinson and Gertner (2012)
INCB018424	Incyte	Jak1/2 inhibitor	Leukemia	Phase II	Eghtedar et al. (2012)
OHR118	OHR Pharmaceutical	Peptide nucleic acid immunomodulator	AIDS	Phase II	Chasen et al. (2011)
Celecoxib (Celebrex)	Pfizer	COX-2 inhibitor	Cancer	Phase II	Mantovani et al. (2010)
MT-102	PsiOxus Therapeutics	β-blocker	Cancer	Phase II	Stewart Coats et al. (2011)
ALD518 (BMS-945429)	Alder Biopharmaceuticals	Humanized IL-6 monoclonal antibody	Cancer	Phase II	Bayliss et al. (2011)
CK-2017357	Cytokinetics	Skeletal muscle troponin activator	ALS	Phase II	Shefner et al. (2012)

5-HT2b/2c = 5-hydroxytryptamine 2b/2c; EPA = eicosapentaenoic acid; SOD = superoxide dismutase; UPP = ubiquitin proteasome pathway; COPD = chronic obstructive pulmonary disease; AIDS = acquired immune deficiency syndrome; COX-2 = cyclooxygenase-2; ALS = amyotrophic lateral sclerosis; MC4 = melanocortin-4; CRF2R = corticotropin-releasing factor 2 receptor.

results demonstrate that muscle wasting is not associated with the downregulation of molecules involved in anabolic response and appears inconsistent with reduced activity of the IGF-1 signaling pathway (Penna et al., 2010).

On the other hand, IL-6 and TNF-α cause insulin resistance, IGF-1 resistance, and reduce the levels of testosterone and luteinizing hormone. IL-6 family ligands activate the JAK/STAT3 pathway. Skeletal muscle STAT3 phosphorylation, nuclear localization, and target gene expression are activated in cancer cachexia. STAT3 activation is a common feature of muscle wasting, activated in muscle by IL-6 in vivo and in vitro and by different types of cancer (Bonetto et al., 2012). STAT3 is a primary mediator of muscle wasting in cancer cachexia and other conditions of IL-6 family signaling (Bonetto et al., 2012).

6. Possible treatments for cancer-cachexia and muscle wasting

Weight loss, fatigue, and markers of systemic inflammation are most strongly and consistently associated with adverse quality of life, reduced functional capabilities, increased symptoms and shorter survival (Wallengren et al., 2013). Recently, several different therapeutic entities has emerged and under investigation in pre-clinical and in clinical models. The therapeutic target for cachexia is including ghrelin and ghrelin analogs, selective androgen receptor modulators (SARMs), testosterone, insulin-like growth factor, myostatin antibodies, and also melanocortin-4 receptor antagonist. Recently, several interventional trials have been performed in humans, and some promising treatments are in phase III (Table 1).

Ghrelin is a leading candidate for muscle wasting treatment because ghrelin levels are elevated in cancer cachexia and ghrelin controls mediators involved in the cachectic process (Argiles and Stemmler, 2013). In the clinical study, ghrelin treatment markedly increased energy intake and increased appetite (Neary et al., 2004). In other study, daily and long-term provision of ghrelin to weight-losing cancer patients with solid tumors improved appetite, and attenuated catabolism in a randomized, double-blind, phase 2 study (Lundholm et al., 2010).

Anamorelin, an orally activated ghrelin receptor agonist, has been shown to increase body weight and anabolic hormone levels in healthy volunteers and is being investigated for the treatment of cancer cachexia. Anamorelin increases appetite and body weight in cancer patients (Garcia et al., 2013). A phase III, randomized, placebo-controlled clinical trial assessing anamorelin hydrochloride in patients with cachexia is recruiting patients (Fearon et al., 2013).

The traditional Japanese medicine rikkunshito helps stimulate endogenous ghrelin secretion by blocking the serotonin 2b/2c receptor pathway and enhancing GHSR activity. Rikkunshito has been shown to increase food intake in rats that have cancer or have been administered chemotherapeutics (Fujitsuka et al., 2011). Although ghrelin attenuates anorexia-cachexia in the short term, it does not prolong survival (Fujitsuka et al., 2011), whereas rikkunshito improves anorexia, gastrointestinal dysmotility, muscle wasting, and anxiety-related behavior and prolongeds survival in animals and patients with cancer (Fujitsuka et al., 2011). The appetite-stimulating effect of rikkunshito is blocked by (D-Lys3)-GHRP-6. The active components of rikkunshito, hesperidin and atractylodin, potentiate ghrelin secretion and receptor signaling, respectively, and atractylodin prolonged survival in tumor-bearing rats (Fujitsuka et al., 2011). A potentiator of ghrelin signaling such as rikkunshito may represent a novel approach for the treatment of cancer cachexia (Hattori, 2010; Fujitsuka et al., 2012). Larger clinical trials are required to develop ghrelin into an available and reimbursable pharmaceutical intervention (Strasser, 2012).

Enobosarm, nonsteroidal SARMs has tissue-selective anabolic effects in muscle and bone. Selective androgen receptor modulators have been developed for the treatment of muscle wasting. In a double-blind, placebo-controlled phase II trial, enobosarm improved lean body mass and physical function in healthy elderly men (Dalton et al., 2011).

A weight-loss study conducted on cancer patients using a randomized controlled trial of weekly nandrolone decanoate for 4 weeks in combination with standard chemotherapy (Bossola et al., 2007) demonstrated significantly longer survival time in the group receiving androgen therapy with a trend for less severe weight loss with nandrolone decanoate. Testosterone is capable of reducing systemic inflammatory cytokines such as TNF-α, IL1-β, and IL-6 and stimulating the anti-inflammatory cytokine IL-10 (Malkin et al., 2004).

Recent studies also propose the combination therapies like megestrol acetate plus L-carnitine, celecoxib (Madeddu et al., 2012). We hope the progress of clinical trials and the establishment of new therapeutic guidelines in the future.

7. Conclusion

Anorexia-cachexia and muscle wasting affect morbidity, mortality, and quality of life. A considerable amount of recent progress has been made in the understanding of the brain-muscle crosstalk, which mediate the food intake and muscle atrophy. Although the pathological mechanism of anorexia-cachexia and muscle wasting has been revealed, available and satisfactory treatment has not yet emerged. These findings help to give hope for the future novel drug target. Further clinical randomized studies are needed to enhance beneficial nutritional and improve clinical outcomes of patients with cachexia.

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Cachexiaの診断，病態と治療（総論）

Diagnosis, pathology and treatment of cachexia

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SUMMARY

Cachexiaは食欲不振，持続的な体重減少，骨格筋の減少を主徴とした病態であり，癌をはじめ多くの基礎疾患に合併して認められる。その病態の背景にはサイトカインによる全身性の炎症があり，たんぱく質とエネルギーのバランスが負に傾くことが特徴である。Cachexiaの治療は薬物療法のみならず，心理・栄養など，多方面からの包括的なアプローチが重要である。

KEY WORDS

- cachexia
- 包括的治療
- QOL
- 診断基準
- 食欲・体重調節

I
はじめに

悪液質（cachexia）は食欲不振，体脂肪量ならびに骨格筋減少（サルコペニア）を主徴とした病態で，癌をはじめ，後天性免疫不全症候群，リウマチ，慢性肺疾患，心不全，炎症性腸疾患など，多くの基礎疾患に合併して認められる。古くは紀元前4世紀，古代ギリシアのヒポクラテスのころより認識されていたとされるが，近年の医学の進歩により，患者自身のQOLや生命予後との関連が明らかになってきたことで，治療の必要な病態として強く認識されるようになった[1]。

癌に伴う癌悪液質（cancer cachexia）は消化器系癌を中心に，進行性癌患者全体の60～80％に認められ，癌死因の20～25％を占めるといわれる[2)-4)]。一般にcancer cachexiaは，癌の進行に伴い不可逆性の栄養障害に進展していくとされるが（図1），癌腫によって発生率や進行速度はさまざまである[5]。

Cancer cachexiaは高齢者や小児にも多くみられ，高齢者では全身状態の悪化，小児では成長障害を引き起こすため，その治療介入は重要である[2]。また，発熱，痛み，腸閉塞，抑うつなどや癌の浸潤・転移に伴う合併症，外科手術・化学療法・放射線療法など，2次的要因に基づくcachexiaも存在し，その後の治療耐性に大きく影響する[6) 7)]。

本稿では主にcancer cachexiaを中心に，診断，病態ならびに治療について概説する。

II
Cachexiaの診断

2008年，国際悪液質学会により発表されたcachexiaの診断基準（図2）によると，cachexiaは「悪液質の原因疾患の存在下で，12ヵ月以内に5％以上体重が減少し，かつ筋力低下，疲労，食欲不振，除脂肪量低下，血液検査異常の5項目のうち3項目を満たす場合」とされる。この基準にてcachexiaと診断された場合は「治療が必要なcachexia」であり，薬物療法のみならず栄養療法や心理カウンセリングなどを含めた包括的な治療が早急に必要となる。

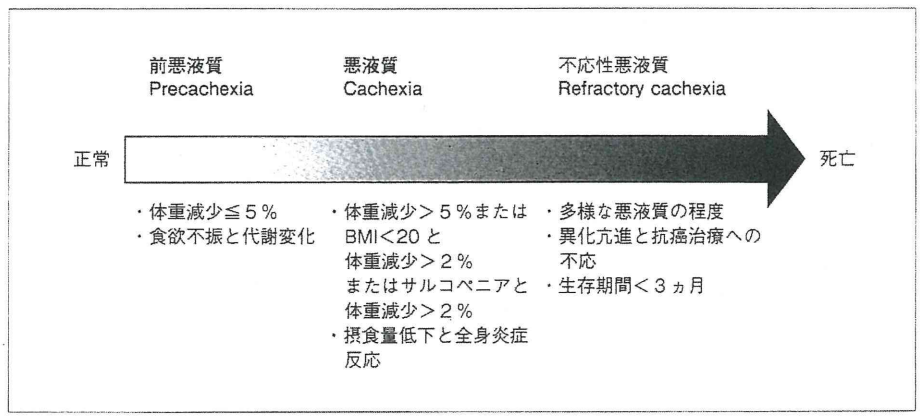

図1．Cachexiaのステージ

（文献18）より改変・引用）

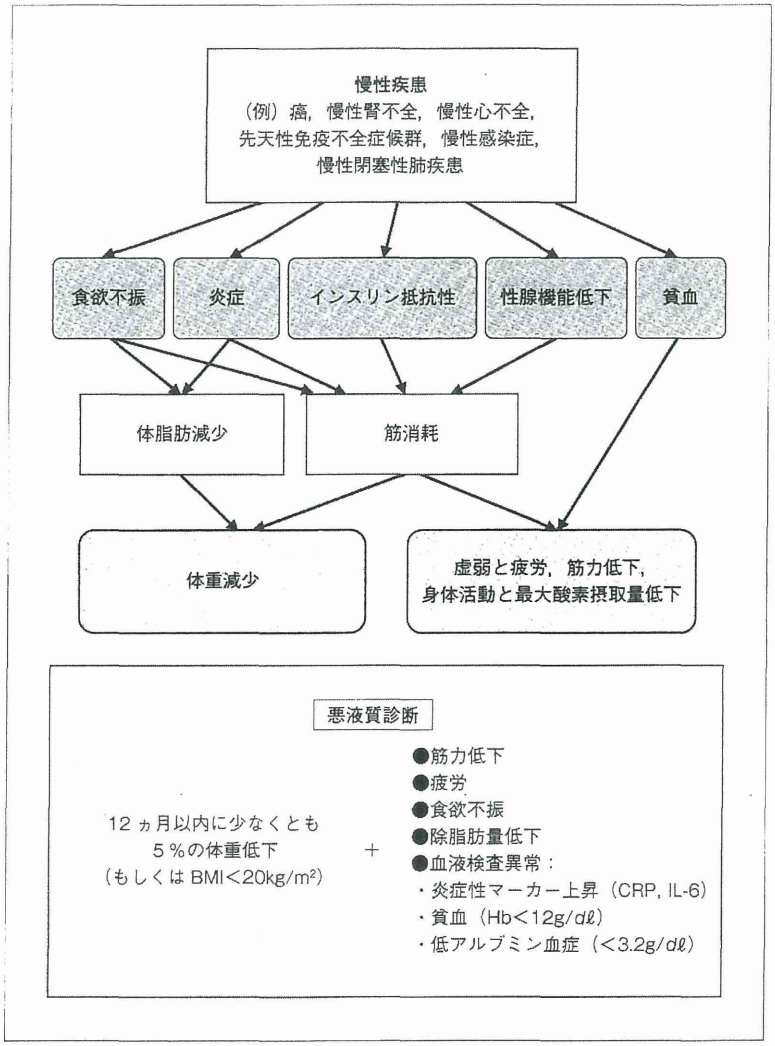

図2．Cachexiaの診断

（文献19）より改変・引用）

Ⅲ Cachexiaの病態

食欲不振やサルコペニアをはじめとするcachexiaの複雑な病態を理解する際，サイトカインが重要なファクターとなる。腫瘍壊死因子（tumor necrosis factor-α；TNF-α），インターロイキン-1（interleukin-1；IL-1），IL-6，インターフェロン-γ（interferon-gamma；IFN-γ）などのサイトカインは癌細胞や宿主の免疫担当細胞から過剰に産生・放出され，全身性の炎症を引き起こす。その結果，たんぱく質とエネルギーのバランスが負に傾くのではないかという考え方が，cachexiaの病態・成因におけるコンセンサスを得ている[2) 3) 8) -12)]。

Cachexiaの代表的な病態の1つとして，食欲不振・体重減少がある。一般に，末梢のエネルギー状態を中枢に伝え制御する食欲・体重調節機構は，主に視床下部において統合的に調節されており，これはヒトの進化の長い歴史のなかで，飢餓への応答として備わったメカニズムである。末梢のエネルギー状態を伝える代表的な因子としてレプチンならびにグレリンがあり，レプチンは体脂肪量に応じて血中に分泌される満腹ホルモンで[13)]，体脂肪量が増加すると血中レプチンが増加して視床下部の食欲促進系が抑制され，体脂肪量が減少すると血中レプチンも低下し食欲促進系が活性化される。一方，1999年に成長ホルモン分泌促進因子受容体の内因性リガンドとして胃から分離・同定されたグレリンは，食欲促進や体重増加作用を発現する末梢で唯一の空腹ホルモンで，中枢に液性・神経性に作用して，強力な食欲促進系の神経ペプチドY（neuropeptide Y；NPY）/アグーチ関連ペプチド（agouti-related peptide；AgRP）を活性化させる[14)]。こうしたレプチンやグレリンなどによる食欲・体重調節機構が，サイトカインによって破綻する病態がcachexiaではないかと考えられる。すなわち，サイトカインがレプチン様のシグナル（体脂肪量が十分に存在するという「誤った」シグナル）を視床下部に伝え，結果的に飢餓に対する応答であるNPY/AgRP系を中心とした食欲促進系が抑制されるために，食欲不振，基礎代謝量の増加，持続的な体重減少といったcachexiaの病態が形成されることが強く示唆されている[8)]。

サルコペニアもcachexiaの代表的な病態の1つであるが，これにもサイトカインの関与が多数報告されている。たとえばTNF-αなどのサイトカインはたんぱく質分解系であるユビキチン-プロテアソーム系を活性化するが，一方で，インスリン様成長因子（insulin like growth

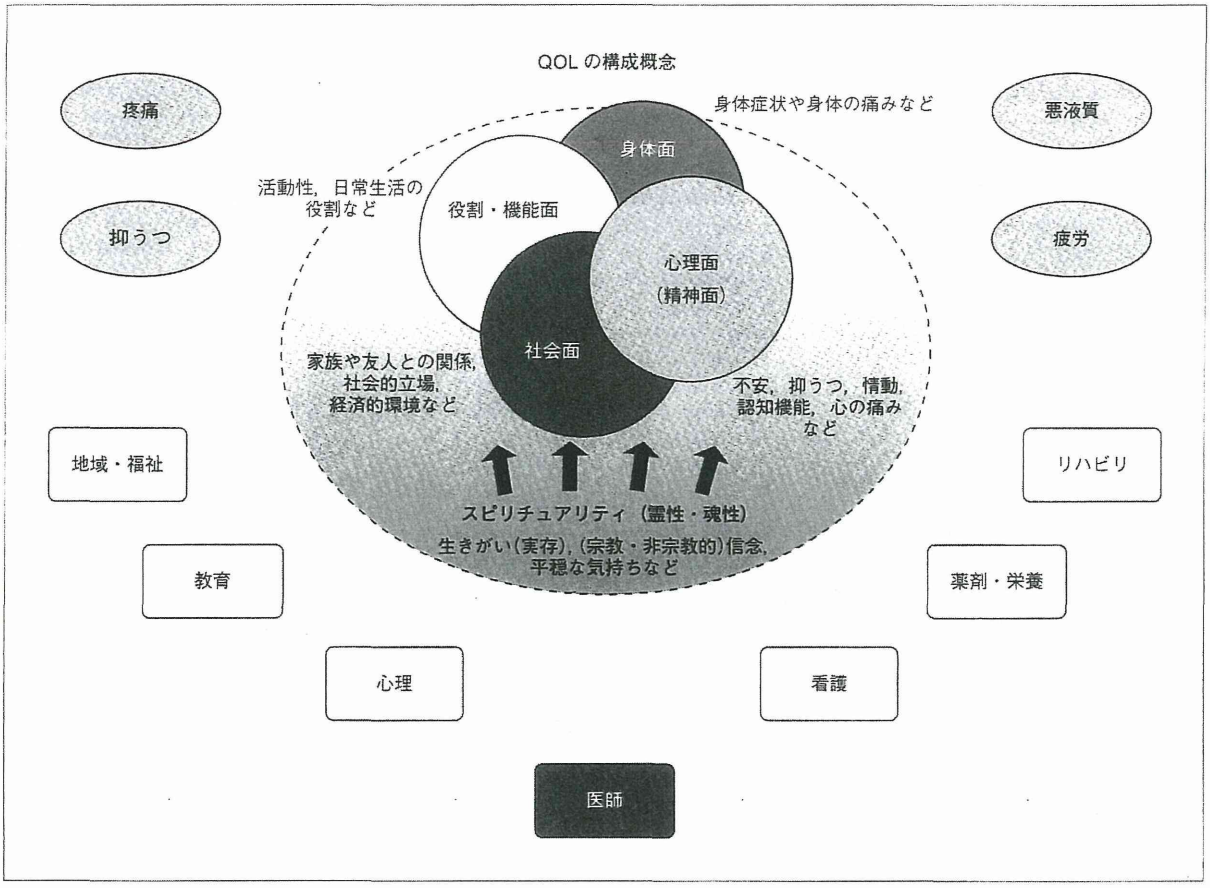

図3．Cachexiaに対する包括的医療

（文献20）より一部改変・引用）

actor；IGF）などのたんぱく質合成・筋線維再生における因子の発現を抑制する[15]。その結果，飢餓とは異なるcachexiaの特徴である骨格筋の崩壊・萎縮が引き起こされる[10) 15)]。ほかにも，lipid mobilizing factor（LMF），proteolysis inducing factor（PIF）などの癌組織から産生される局所因子が，脂肪や筋肉組織に直接作用し組織の崩壊を導くことが報告されている[10)16)]。さらに，炎症性サイトカインは疲労，痛み，不安，抑うつなどのsickness behaviorを引き起こす[17]。

IV
Cachexiaの治療

Cachexia治療の目標は，患者の病態を心身両面から検討し，包括的な医療を行うことにある[2]。現在のところ，薬物療法単独でのcachexia治療は不可能であり，薬物療法・栄養療法・心理療法・リハビリテーションを基本とした多方面からのアプローチが症状緩和に重要となる。実際には，cachexiaの成因論に基づいた薬物療法を選択し，併発する痛み，疲労，抑うつなどの周辺症状に対し，心身両面から治療していくこととなる。この実現のためには，医師や看護師，薬剤師，栄養士，臨床心理士，ソーシャルワーカーなど，業種を超えた連携が不可欠である（図3）。

V
おわりに

Cachexiaの診断，病態ならびに治療について概説した。肥満や糖尿病，メタボリックシンドロームなどの過栄養病態と対極をなすcachexiaは，その複雑な病態，多彩な臨床症状からいまだ多くの研究や議論の余地を残しており，さらなる解明が待たれる。

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