feeding, is a major contributor to the development of cachexia (8). About half of all cancer patients show a syndrome of cachexia, characterized by anorexia and loss of adipose tissue and skeletal muscle mass (2). In general, while patients with hematological malignancies and breast cancer seldom have substantial weight loss, most other solid tumors are associated with a higher frequency of cachexia (8). Weight loss and problems with nutrition may also be a significant emotional burden, as nutrition and nutritional status have a central position in the concept of health and wellbeing for many patients and care givers, and weight loss and inadequate nutritional intake can lead to anxiety and hopelessness (1). In contrast to these needs, cachexia often is overlooked or not assessed or treated adequately, as it is considered to be unavoidably linked with disease progression (1). Cachexia represents a significant unmet need (1).

PATHOPHYSIOLOGY

Neuropeptidergic Cascade Downstream of Leptin Signaling

Leptin is an afferent signal from the periphery to the brain that regulates adipose tissue mass (9–11). The level of leptin is positively correlated with body fat mass, and dynamic changes in plasma leptin concentrations in either direction activate the efferent energy regulation pathways (9,12). Leptin reduces appetite and increases energy expenditure and evidently elicits these effects via the central nervous system (9,12). This is achieved by hypothalamic neuropeptides downstream of leptin that regulate food intake and energy expenditure. A loss of body fat (starvation) leads to a decrease in leptin, which in turn leads to a state of positive energy balance, wherein food intake exceeds energy expenditure. This compensatory response is mediated by the increased production, release, and/or action of ghrelin, neuropeptide Y (NPY) and other orexigenic neuropeptides, as well as decreased activity of anorexigenic neuropeptides such as corticotropin-releasing factor (CRF) and melanocortin (Fig. 1A). Thus, if a disease process was to produce factors that induce or mimic the hypothalamic effect of excess negative feedback signaling from leptin, the expected outcome would be sustained anorexia and weight loss that is not accompanied by the usual compensatory response (2).

In tumor-bearing states, cachectic factors such as cytokines elicit effects on energy homeostasis that mimic leptin in some respects and suppress orexigenic ghrelin-NPY signaling. Consequently, the increases and decreases in hypothalamic actions caused by these mediators induce anorexia and unopposed weight loss, respectively (Fig. 1B). This could be accomplished through persistent inhibition of the

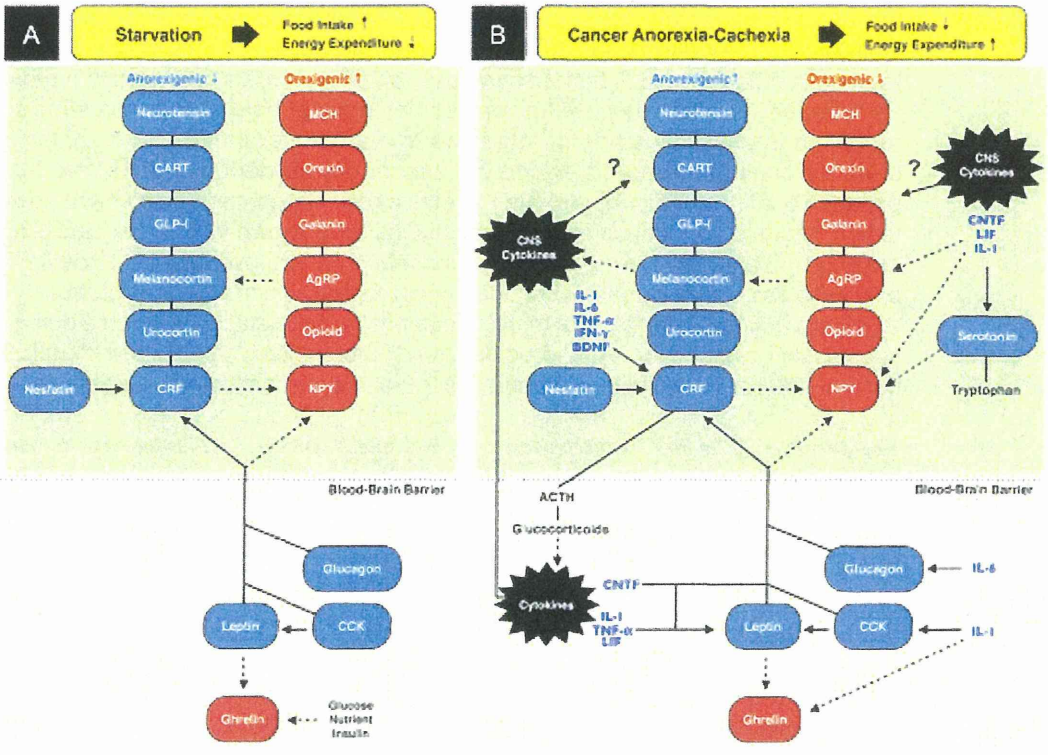

Figure 1. A simplified model of the hypothalamic neuropeptide circuitry in response to starvation (A) and cancer anorexia–cachexia (B) Source: (2) with modification. Full line arrows indicate the activation of the process, and broken line arrows indicate the inhibition of the process. AgRP = agouti-related peptide. MCH = melanin-concentrating hormone. CART = cocaine- and amphetamine-related transcript. GLP-I = glucagon-like peptide-I. CCK = cholecystokinin. IL-1 = interleukin-1. IL-6 = interleukin-6. TNF-α = tumor necrosis factor-alpha. IFN-γ = interferon-gamma. CNTF = ciliary neurotrophic factor. LIF = leukemia inhibitory factor. ACTH = adrenocorticotropic hormone.

ghrelin-NPY orexigenic network and stimulation of anorexigenic neuropeptides, although the hypothalamic pathways participating in this response remain to be determined. Serotonin may also play a role in the development of cancer anorexia. Increased levels of plasma and brain tryptophan, the precursor of serotonin and IL-1 may underlie the increased serotonergic activity seen in the cancer anorexia–cachexia syndrome.

Nesfatin-1, a new anorectic peptide localized to the paraventricular nucleus (PVN), is stimulated by stressors. Intracerebroventricular administration of nesfatin-1 activates 5HT neurons, CRF neurons and the hypothalamic-pituitary-adrenal axis, and nesfatin-1 activates isolated CRF neurons (13). It has recently been shown that plasma nesfatin-1 levels are altered in lung cancer patients with anorexia–cachexia. Hence, nesfatin-1 appears to be involved in cancer anorexia–cachexia. Novel bioactive peptides such as neuropeptide W and neuroendocrine regulatory peptide have also recently been identified; however, the role of these proteins in cancer anorexia–cachexia remains to be determined.

Cytokine Actions within the Regulatory Feedback Loop

Numerous cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-γ), have been postulated to play a role in the etiology of cancer cachexia (3,14–18). It is not certain whether the cytokine production is primarily from tumor or host inflammatory cells. It has been hypothesized that either tumor cell production of pro-inflammatory cytokines or the host inflammatory cell response to tumor cells is the source of the acute phase protein response seen in many malignancies and in cachexia (19).

Cytokines are protein molecules released by lymphocytes and/or monocyte macrophages (2). They may be released into the circulation and transported to the brain through the blood–brain barrier (BBB) and circumventricular organs (leaky areas in the BBB), as is the case for IL-6 (17,18,20–23). Peripheral cytokines may influence the brain via neural pathways or second messengers such as nitric oxide (NO) and prostanoids (2). Cytokines are also produced by neurons and glial cells within the brain, partly in response to peripheral cytokines (17,18,20–23). Although the site of synthesis of cytokines within the brain is dependent on the nature of the stimulus, systemic disease seems to predominantly influence the expression in the hypothalamus, the area with the highest densities of receptors for most cytokines that have been observed (22).

High serum levels of TNF-α, IL-6 and IL-1 have been found in some, but not all, cancer patients, and the levels of these cytokines seem to correlate with the progression of some tumors (24–26). Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and reproducing different features of the cancer anorexia–cachexia syndrome (3,24–27). The role of TNF-α in mediating cancer-associated anorexia is supported by evidence that intraperitoneal injection of a recombinant human soluble TNF receptor antagonist improves anorexia in tumor-bearing animals (28). In humans, IL-1 appears to play a significant role in mediating anorexia–cachexia, as megestrol acetate has been shown to exert its effects via reduced expression of IL-1 by mononuclear cells beyond its influence on hypothalamic neuropeptide Y (NPY) concentrations, which shows an orexigenic effect (29). Interestingly, anorexigenic neurons, such as proopiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons, in the arcuate nucleus (ARC) of the hypothalamus express the type 1 IL-1 receptor, and intracerebroventricular injection of IL-1 increases the frequency of action potentials of POMC/CART neurons and stimulates the release of alpha-melanocyte-stimulating hormone (α-MSH), which shows an anorexigenic effect as well (30).

TNF-α, IL-1, IL-6 and IFN-γ have been implicated in the induction of cancer-related muscle wasting (31). There is growing evidence that the accelerated muscle proteolysis seen during malignant tumor growth is mediated by the activation of the non-lysosomal adenosine triphosphate-dependent (ATP-dependent) ubiquitin proteasome pathway (32,33). In addition, inflammatory cytokines influence the expression of functionally relevant enzymes in cardiac cachexia (31). It has been demonstrated that TNF-α, IFN-γ and IL-1β, which are known to be increased in cachectic patients, are potent activators of inducible NO synthase (iNOS) expression (31), which in turn produces toxic levels of NO high enough to inhibit the key enzymes of oxidative phosphorylation (31). It has also been shown *in vitro* that NO is able to impair the contractile performance of skeletal muscle (34).

More direct evidence of cytokine involvement comes from experiments in which specific neutralization of cytokines can relieve anorexia and cachexia in experimental animal models (3,25,26,35). Examples of antibodies that have been shown to successfully relieve anorexia and cachexia when administered include the anti-TNF-α, anti-IL-6, anti-IL-1 and anti-IFN-γ antibodies, although no single antibody has been proven to reverse all of the features of wasting seen in cancer cachexia (25). These studies revealed that cachexia can rarely be attributed to any one cytokine but rather is associated with a set of cytokines and other cachectic factors that work in concert (2). Current new trends include the use of an anti-IL-6 humanized monoclonal antibody, which appears to inhibit cancer cachexia in murine models (36). The therapeutic impact of which on cancer-related anorexia and cachexia may be of clinical significance in cancer patients (36).

The problem with ascribing specific tissue responses to individual cytokines is that considerable overlap and redundancy exist in the cytokine network (16,20–23). Administration of either TNF-α or IL-1 will induce the synthesis of a variety of other proinflammatory cytokines, such as IL-6 (2). Thus, studies that use pharmacological administration of recombinant cytokines may not discriminate between biological responses induced directly by the administered cytokine and those induced secondarily by other stimulated cytokines (2). Systemic disease such as cancer and inflammation may elicit a cytokine cascade in which several cytokines are induced simultaneously (16).

Protein Degradation in Cancer Anorexia–Cachexia

In adults, the muscle mass remains fairly constant in the absence of stimuli such as exercise, such that protein synthesis and degradation remain in balance (37). In cachexia, muscle atrophy occurs, which results from a depression in protein synthesis, an increase in protein degradation or a combination of both (37) (Fig. 2). In recent years, it has become evident that specific regulating molecules are upregulated (e.g. members of the ubiquitin–proteasome system, myostatin and apoptosis-inducing factors), whereas other factors (e.g. insulin-like growth factor 1, IGF-1) are downregulated in cachexia muscle wasting (31). A major barrier to the effective management of skeletal muscle wasting is the inadequate understanding of its underlying biological mechanisms (31). The most evident metabolic explanation for muscle decline is an imbalance between protein catabolism and anabolism (31).

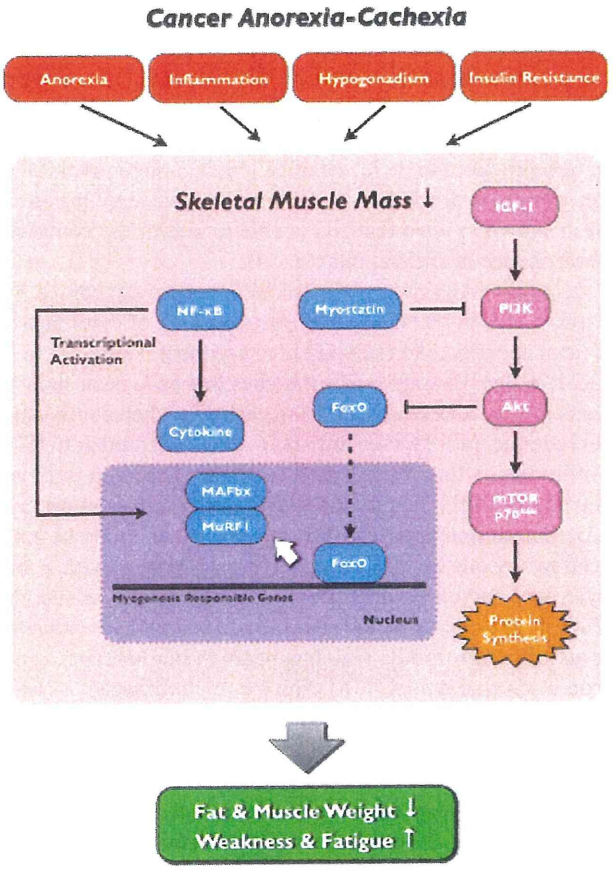

Figure 2. An abbreviated schematic diagram of skeletal muscle in cancer anorexia–cachexia. Source: (31) and (69) with modification. Arrows indicate the activation of the process, -| indicates the inhibition of the process. The balance of skeletal muscle has been shifted towards protein breakdown, finally leading to the weight loss, weakness and fatigue that characterize cancer anorexia–cachexia. Muscle RING-finger protein-1 (MuRF1). Atrogin-1/muscle atrophy F-box (MAFbx). Nuclear factor kappa B (NF-κB). Insulin-like growth factor 1 (IGF-1). forkhead box O (FoxO). phosphatidylinositol-3-kinase (PI3K). mTOR = mammalian target of rapamycin. p70S6K = p70 S6 kinase.

In addition to an increase in catabolism, a reduction in anabolism has been shown to occur in cancer-related cachexia (31). Skeletal muscle wasting in cancer cachexia can be mediated by multiple factors derived from tumor and host cells (38).

At least four major proteolytic pathways (lysosomal, Ca^{2+}-dependent, caspase-dependent and ubiquitin–proteasome-dependent) operate in skeletal muscle and may be altered during muscle cachexia (31). Aside from these four distinct pathways, the autophagic/lysosomal pathway must also be considered (31). In this pathway, portions of the cytoplasm and cell organelles are sequestered into autophagosomes, which subsequently fuse with lysosomes, where the proteins are digested (39). When dissecting the molecular regulation of the ubiquitin–proteasome-dependent system (UPS) and autophagy, it became evident that forkhead box O (FoxO) transcription factors play a central role (31). FoxO transcription factors, which are normally phosphorylated and inactivated by phosphatidylinositol 3-kinase (PI3K)-Akt/PKB, translocate into the cell nucleus and induce the transcription of the skeletal muscle-specific E3 ubiquitin ligases, muscle RING-finger protein-1 (MuRF1) and atrogin-1/muscle atrophy F-box (MAFbx) (40), as well as autophagy-related genes such as LC3 and Bnip3 (41). Upstream of PI3K-Akt, several factors including reactive oxygen species (ROS), TNF-α, tumor-released proteolysis-inducing factor (PIF), peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) and IGF-1 have been shown to influence this regulatory system (40,42–44). In contrast, protein anabolic factors such as IGF-1 counteract muscle atrophy (31). Aside from inhibiting autophagy and the UPS, IGF-1 activates protein synthesis via the Akt-mammalian target of rapamycin (mTOR)–p70 S6 kinase (p70S6K) signaling pathway (45,46).

The UPS is a major intracellular system that regulates skeletal muscle wasting in response to tumor factors and inflammatory cytokines (38). In cancer cachexia, the decrease in skeletal muscle protein synthesis is partly related to the increased serum levels of PIF (31). Intravenous administration of PIF to normal mice produced a rapid decrease in body weight that was accompanied by increased mRNA levels of ubiquitin in the gastrocnemius muscle (43). There were also increased protein levels of the 20 S proteasome core and the 19 S regulatory subunit, suggesting activation of the ATP–ubiquitin-dependent proteolytic pathway (31). Recent evidence suggests that PIF decreases protein synthesis by inhibiting protein translation initiation through phosphorylation of the eukaryotic initiation factor 2 (eIF2-alpha) (47).

Myostatin is an extracellular cytokine that is mostly expressed in skeletal muscles and is known to play a crucial role in the negative regulation of muscle mass (48). Upon binding to the activin type IIB receptor, myostatin can initiate several different signaling cascades, resulting in decreased muscle growth and differentiation (48). Muscle size is regulated via a complex interplay of myostatin signaling with the IGF-1/PI3K/Akt pathway, which is responsible for increased protein synthesis in muscle (48). Therefore, the regulation of muscle weight is a process in which myostatin plays a central

role, but the mechanism of its action and the role of the signaling cascades involved are not fully understood (48). Myostatin upregulation was observed in the pathogenesis of muscle wasting during cancer cachexia (48).

One of the main positive regulators of muscle growth is IGF-1 (48). Under normal conditions, IGF-1 signaling seems to be dominant and blocks the myostatin pathway (49). However, an inhibition of IGF-1 was observed when myostatin was overexpressed (50,51). IGF-1 can prevent TGF-α family-mediated apoptosis (52), and it was shown that in the absence of IGF-1, the level of apoptosis in C2C12 cells treated with myostatin increased (48). The mechanism by which IGF-1 regulates myostatin signaling includes the inhibition of transcription factors responsible for the induction of atrogenes via phosphorylation through the PI3K/Akt pathway (48). Akt plays a significant role in different metabolic processes in the cell, particularly in the hypertrophic response to insulin and IGF-1 (53,54). Akt is the crossing point between the IGF-1/myostatin pathways (48). It is likely that under conditions of muscle wasting, myostatin can reverse the Akt/mTOR pathway, which is normally responsible for protein synthesis, to inhibit protein synthesis via FoxO, GSK-3β or other unknown patterns, leading to the loss of muscle mass (48). Another factor that may contribute to decreased anabolism is angiotensin II (31). In an animal model of continuously administered angiotensin II, markedly reduced plasma IGF I levels occurred (55). Compared with a sham treatment, angiotensin II-infused hypertensive rats lost 18–26% of their body weight within 1 week, an effect that was completely reversible by losartan, an AT1 receptor antagonist (55).

There is a wealth of evidence in the current literature that oxidative stress is associated with chronic diseases, and it is assumed that an increase in ROS directs muscle cells into a catabolic state that leads to muscle wasting (31,56,57). In cachexia, ROS are regarded as crucial players for muscle protein catabolism via their stimulation of the UPS (31). Reaction products are measured as indirect markers of oxidative stress (31). In cachexia, malondialdehyde is regarded as one such indirect marker (31). In addition, experimental cancer cachexia appears to be mediated by increased nitrosative stress secondary to increased NO formation. Indeed, protein tyrosine nitration is markedly increased in the muscles of tumor-bearing rats with advanced cachexia (58). In cachexia, the increase in protein tyrosine nitration in ROS is due to significantly lower activities of the antioxidant enzymes superoxide dismutase and glutathione peroxidase (59).

Experimental data suggest that local IGF-1 may act as a regenerative agent, promoting the recruitment of stem cells to sites of muscle injury (60). Because IGF-1 is reduced in experimental models of cachexia (61), it is reasonable to assume that under conditions of cachexia, the function of satellite cells is impaired (31). Other factors controlling the differentiation of satellite cells into functional fibers include nuclear factor kappa B (NF-κB) and myostatin (31). Data are available that demonstrate a beneficial effect of myostatin inhibition in cancer cachexia (62), but negative study results have also been reported (63). With respect to apoptosis, several reports demonstrated an increase in apoptosis or apoptosis-related proteins in skeletal muscle after the induction of cachexia (31). The skeletal muscle of cachectic tumor-bearing animals reveals the activation of DNA fragmentation, a hallmark of apoptosis (64). In addition to DNA fragmentation, a significant up-regulation of caspase-1, −3, −6, −8, and −9 activity was also documented in the gastrocnemius muscles of tumor-bearing mice (65).

There is a relative deficiency or resistance to anabolic hormones in cachectic states. Up to 50% of men with metastatic cancer can present with low concentrations of testosterone prior to chemotherapy (66). A reduction in testosterone might lead to reduced bone mass, muscle strength and sexual function in both men and women (67,68). Low concentrations of testosterone and other anabolic hormones are major contributors to cachexia-related wasting of skeletal muscle (69). However, with respect to a correlation between body composition (including muscle mass) and the concentration of anabolic hormones, conflicting results have been reported in the current literature (31). Some studies found a correlation (66,70), whereas others reported no association (71).

TRANSLATIONAL ASPECTS OF HERBAL MEDICINE PARTICULARLY FOR CANCER ANOREXIA–CACHEXIA

Many effective chemotherapeutic agents for cancer are burdened by toxicities that can reduce patient's quality of life or hinder their effective use. 5HT3 receptor antagonists, dexamethasone and aprepitant significantly improved chemotherapy-induced nausea and vomiting. Empirical antibiotics significantly improved neutropenic fever. A multinational survey found that 35.9% of cancer patients were either past or present users of CAM. Herbal medicines were by far the most commonly used group of treatments, escalating in use from 5.3% before the diagnosis of cancer to 13.9% after the diagnosis of cancer (72). Herbal medicines are believed by the general public to be safe, cause less side-effects and less likely to cause dependency (73).

Herbal medicine in palliative treatment of cancer is a fast-emerging area. Palliative care in cancer treatment aims not only for disease control but for addressing the patient's physical and psychosocial symptoms, and improving the QOL. The mechanism involves an enhancement of signaling by ghrelin which was discovered in 1999 as an appetite-stimulating peptide from the stomach (74–77). Currently, ghrelin agonists and antagonists are being developed and tested for the treatment of anorexia/cachexia and obesity, respectively.

Rikkunshito as an Activator of Ghrelin Signaling

It is known that plasma ghrelin levels are elevated under cachectic conditions caused by a variety of underlying disorders

(78–82). Although this phenomenon has been called 'ghrelin resistance', these elevations may be a compensatory response that reflects the negative energy balance state (83). Several randomized, double-blind placebo-controlled trials have demonstrated the efficacy and safety of ghrelin or growth hormone (GH) secretagogue (GHS) in patients with cancer-associated cachexia (84–86). Therefore, evaluation of the role of ghrelin in the pathogenesis and treatment of such cachectic conditions is warranted (74).

In our study, it was demonstrated that plasma acyl ghrelin concentrations in tumor-bearing rats were higher than those in free-fed normal rats, but lower than those in pair-fed normal rats, and had an inverse relationship with plasma leptin concentrations (87). These results indicate that changes in ghrelin and leptin secretion in pair-fed animals represent a compensatory mechanism in a persistent catabolic state and that these responses are attenuated in tumor-bearing rats (87). Peripheral ghrelin administration stimulates food intake in melanoma cell-bearing mice and cancer patients (85) in the short term as well as in lean, healthy men and women (88). There were similar therapeutic effects of ghrelin on anorexia and gastrointestinal (GI) dysmotility in cachectic animal models, suggesting that high plasma concentrations of ghrelin may overcome resistance to the appetite-stimulating effects of the endogenous peptide in the short term (87). Oral administration of *rikkunshito* increases plasma acyl ghrelin levels in humans, mice, rats (89,90) and dogs (87). *Rikkunshito* stimulates ghrelin secretion through 5-hydroxytryptamine (5-HT) 2b/2c receptor antagonism, and its active flavonoid ingredients such as hesperidin that antagonize 5-HT2b/2c receptor binding have been identified (89).

The central 5-HT system has been implicated in the processes of meal satiation and satiety (87). 5-HT reuptake inhibitors such as fenfluramine and 5-HT2cR agonists attenuate food intake and weight gain in rodents and humans (91–93), with the involvement of potentiated MC signaling and decreased ghrelin secretion (87). 5-HT also inhibits NPY/AgRP neurons by activating the 5-HT1bR, leading to decreased orexigenic signaling and inhibitory drive onto POMC cells (87). However, the previous study has demonstrated that the 5-HT2cR has a major role in the regulation of physiological fasted and fed motor activities in addition to feeding through changes in endogenous ghrelin (90). In this study, the decreases in food intake and GI motor activities in tumor-bearing rats were recovered after administration of either a 5-HT2cR antagonist or ghrelin (87). The 5-HT concentration in the hypothalamus is increased in humans and animals with cancer (94,95); in addition, NPY and dopamine concentrations decrease simultaneously, while 5-HT concentration increases in the PVN at the onset of anorexia in tumor-bearing rats (96). These findings suggest that 5-HT2cR activation in tumor-bearing rats induces anorexia in part via decreased ghrelin secretion (87).

The hypothermia in tumor-bearing rats may be due to a state of negative energy balance or a decrease in the threshold for the activation of thermogenesis, which is involved in starvation-induced hypothermia (97). IL-1β and leptin (98) decrease the expression of ghrelin mRNA in the stomach, whereas IL-6 produced in various cells, including adipocytes, regulates leptin production (99). These findings suggest that cytokines have an important role in energy balance through the persistent activation of the leptin system and the inhibition of the ghrelin-NPY/agouti-related peptide orexigenic network in tumor-bearing rats (87). In addition to NPY and agouti-related peptide, the level of POMC mRNA was also decreased in the hypothalamus of the tumor-bearing rats (87). Synaptic input organization and mRNA expression of POMC neurons have been shown to be increased in adrenalectomized animals and restored by corticosterone replacement (100). Thus, activity of hypothalamic POMC neurons may be affected by changes in circulating levels of corticosterone and a state of negative energy balance (87).

Hypothalamic 5-HT and CRF activities are stimulated by proinflammatory cytokines in the circulation and the hypothalamus (101,102). A CRF receptor antagonist attenuated cancer anorexia–cachexia, and administration of the 5-HT2cR antagonist or *rikkunshito* reduced hypothalamic CRF levels and anxiety-related behaviors in tumor-bearing rats (87). The improvement in anxiety by *rikkunshito* may lead to a higher quality of life in cancer patients (87). Some studies suggest that ghrelin induce anxiety, whereas others suggest that the elevated ghrelin helps animals cope with stress by producing anxiolytic-like response (103). Future studies are needed to sort out the effect of ghrelin on anxiety-like behavior as in the case of NPY (76). Importantly, a hypothalamic 5-HT-CRF receptor pathway that regulates ghrelin secretion has a major role in cancer anorexia–cachexia (87).

It has been previously shown that a central 5-HT2cR pathway regulates ghrelin secretion without downstream activation of melanocortin 3/4 receptors (90). The 5-HT2cR is expressed in many brain regions and its expression is restricted to the central nervous system (87). Dual-neurohistochemical labeling has revealed that approximately one-half of PVN CRF-containing neurons co-express 5-HT2cR mRNA (104). In this study, 5-HT activated single CRF neurons isolated from the PVN, and the activities of the CRF neurons were blocked by simultaneous administration of *rikkunshito* (87). Moreover, intracerebroventricular administration of CRF decreased plasma acyl ghrelin in fasted rats (87). These findings suggest that CRF neurons are involved in 5-HT-regulated ghrelin secretion (87).

The GH secretagogue receptor (GHS-R) is reportedly expressed in vagal afferent neurons, and the gastric vagus nerve system is involved in the effect of ghrelin on food intake and GI motor activities (105,106). It was demonstrated that ghrelin decreased the afferent activity of the gastric vagus nerve (87). Gastric ghrelin signaling via vagal afferents stimulated the efferent activities of both the gastric and the celiac branches of the vagus nerve and suppressed the activity of the sympathetic nerve (87). Peripheral administration of a higher dose of ghrelin increased the discharge rate of the vagal efferent nerve, probably in part through the GHS-R in the ARC of the hypothalamus (87). It has also been shown that *rikkunshito*

activated the efferent vagus nerve, which may be mediated by both the vagal afferent nerve and the direct central action (87). In addition, ghrelin-induced cellular signaling in GHS-R-expressing cells was enhanced by pretreatment with *rikkunshito* and its active components, such as atractylodin, which stimulate ghrelin/GHS-R binding activity (87). Similar potentiating effects of *rikkunshito* were observed in rat ARC NPY neurons (87). These findings suggest that the physiological functions of endogenous ghrelin are enhanced by the dual actions of *rikkunshito*, which involve the stimulation of ghrelin secretion and the activation of GHS-R activity, possibly due to allosteric changes in the receptor (87). This potentiation of the ghrelin effect by *rikkunshito* on NPY neurons could be orexigenic because the activity of ghrelin-responsive NPY neurons is coupled to feeding (107,108). As mentioned in the past section, ghrelin strongly stimulates GH secretion in humans (109–112), which regulates IGF-1 levels, and increases muscle strength (113,114). Moreover, ghrelin induces the anti-inflammatory cytokine (115,116), while suppresses the production of proinflammatory cytokines (115,117–119), and inhibits the activation of NF-κB which may regulate skeletal muscle proteasome expression and protein degradation (83,116,118). Consequently, potentiation of ghrelin receptor signaling with *rikkunshito* can be valuable in the treatment of anorexia and muscle wasting which characterize cancer anorexia–cachexia syndrome (87).

The adverse effect of (D-Lys3)-GHRP-6 on survival in tumor-bearing rats has been indicated in this study, suggesting that the potentiation of ghrelin signaling is critical to the attenuation of anorexia–cachexia and the prolongation of survival in subjects with cancer (87). *Rikkunshito* and its active component, atractylodin, prolonged survival in these animals, and this effect was enhanced by the concomitant administration of cisplatin (87). Cancer patients receiving chemotherapy or radiation therapy may experience nausea, vomiting, taste changes, stomatitis and diarrhea, which could contribute to weight loss and decreased survival (87). Therefore, cancer anorexia–cachexia syndrome is a major obstacle in cancer chemotherapy (8). The use of *rikkunshito* in tumor-bearing rats was effective not only against anorexia–cachexia, but also for promoting survival, particularly in combination with chemotherapy (87). However, daily administration of a 5-HT2c receptor antagonist failed to prolong survival, suggesting that a sensitizing effect on the GHS-R may be essential for ameliorating ghrelin resistance in anorexia–cachexia in the long term (87). Pancreatic cancer patients generally respond poorly to chemotherapy, resulting in a higher frequency of anorexia–cachexia (87). These results suggest that *rikkunshito* may be useful in clinical practice for cachectic

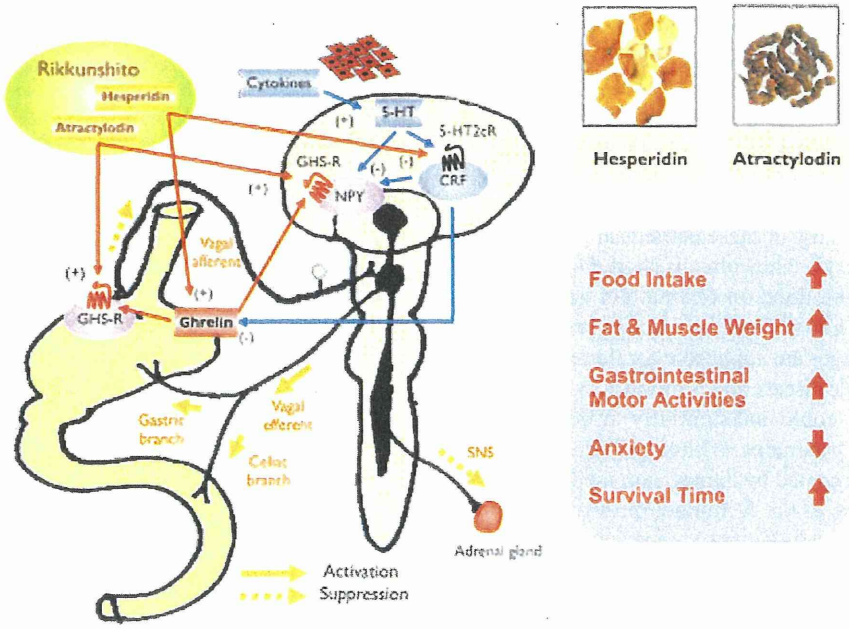

Figure 3. The dual actions of rikkunshito on ghrelin signaling and their therapeutic benefits on cancer anorexia–cachexia. Source: (87) with modification. Hypothalamic CRF neurons are activated by cytokines through serotonin (5-HT) and the 5-HT 2c receptor (5-HT2cR), which show a functional divergence. The existence of a novel 5-HT-CRF neuronal pathway inhibits ghrelin secretion and has a pathogenetic role in cancer anorexia–cachexia. *Rikkunshito* and its active component, hesperidin, a principal component of *Aurantii Nobilis Pericarpium,* stimulate ghrelin secretion from the stomach by interrupting this 5-HT-CRF pathway via 5-HT2cR antagonism. Another active component, atractylodin, a principal component of *Atractylodis Lanceae Rhizoma,* potentiates the action of ghrelin, presumably by allosterically sensitizing the GHS-R on the vagal afferent terminals of the stomach or the NPY neurons of the hypothalamic arcuate nucleus (ARC). Thus, both the release of ghrelin and the potentiation of ghrelin/GHS-R signaling are important for mitigating ghrelin insufficiency and resistance, which are characteristics of cancer anorexia–cachexia. Consequently, potentiation of ghrelin receptor signaling with *rikkunshito* may be an attractive treatment for anorexia and muscle wasting and may prolong survival in patients with cancer anorexia–cachexia.

cancer patients via its dual action on ghrelin secretion and receptor sensitization (Fig. 3) (87). Prospective randomized trials are warranted.

A recent study regarding the underlying mechanisms of *rikkunshito* has shown that *rikkunshito* and its component 10-gingerol may inhibit the degradation of acyl-ghrelin by inhibiting the circulating ghrelin degrading enzyme (120). Another study has shown that administration of *rikkunshito* reversed the decrease in hypothalamic ghrelin secretion and food intake 24 h after cisplatin treatment (121). Cisplatin-induced anorexia is mediated through reduced hypothalamic ghrelin secretion (121). Cerebral serotonin 2C receptor activation partially induces decrease in hypothalamic ghrelin secretion, and *rikkunshito* suppresses cisplatin-induced anorexia by enhancing this secretion (121).

Altogether, the synergism of activity of the herbs demonstrated in these studies highlights the importance of adopting traditional approaches in the utilization of traditional medicines.

CONCLUSIONS

The best way of treating cancer cachexia is to cure cancer, but unfortunately this remains an infrequent achievement among adults with advanced solid tumors (8,122). Appetite, body weight and survival are endpoints for cancer anorexia–cachexia management. Therefore, the treatment goal for cachexia should be the reversal of the loss of body weight and muscle mass with a variety of pharmacological agents (Fig. 4) (8). The European Palliative Care Research Collaboration has developed evidence-based recommendations on classification and treatment of cachexia in advanced cancer patients as part of its clinical guideline work (1). These treatment guidelines focus on patients with advanced cancer likely to suffer from refractory cachexia. Many of these patients are receiving palliative care, and life expectancy often is short. Only little cachexia research has been done on this patient group, and the treatment guidelines had to consider whether research results from other disease stages are applicable for these patients with advanced and incurable disease and for refractory cachexia (1).

Herbal medicine could substantially influence cancer therapy as adjuvant treatment. Although herbal medicines have not been fully accepted by mainstream medicine because of the complex nature of the formulae, the stringent quality control of Japanese herbal (Kampo) medicine and reproducibility of preclinical findings, together with few adverse events, have made herbal medicines more and more attractive for the management of intractable diseases such as cancer. In recent years, studies on the evaluation of the therapeutic and toxic activities of herbal medicinal products became available and popular (123). The advances in modern biotechnology have led to the discovery of many new active constituents (123). Although the working mechanisms of some of the herbs are unclear and remain to be elucidated, they are worth further studying as newly potential therapy agents for cancer

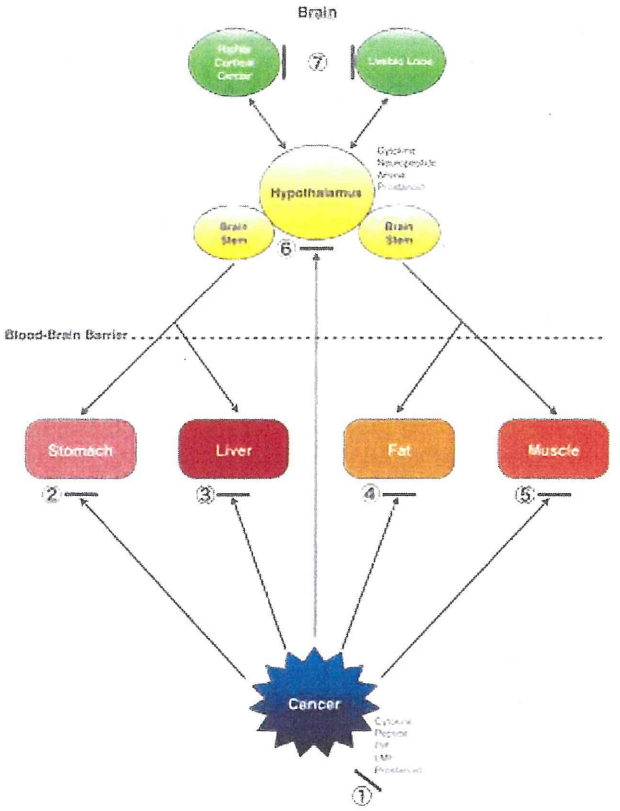

Figure 4. The potential modalities of pharmacological intervention of cancer anorexia–cachexia syndrome. Source: (8) with modification. Agents were classified as those established (first-line) or those unproven/investigational (second-line), depending on their site or mechanism of actions. ①, inhibitors of production/release of cytokines and other factors; ②, gastroprokinetic agents with or without antinausea effect; ③, blockers of the Cori cycle; ④ ⑤, blockers of fat and muscle tissue wasting; ⑥, appetite stimulants with or without antinausea effect; and ⑦, antianxiety/depressant drugs. These agents should be selected on an individual basis according to the cause of cachexia or the state of the patient. *The precise actions of statins on skeletal muscle still remain controversial. First-line treatments, glucocorticoids ① ⑥, progesterones ① ⑥; second-line treatments, cannabinoids ⑥, cyproheptadine ⑥, branched-chain amino acids ⑤ ⑥, metoclopramide ② ⑥, eicosapentanoic acid ① ④ ⑤, 5′-deoxy-5-fluorouridine ①, melatonin ①, thalidomide ①, β2-adrenoceptor agonists ⑤, non-steroidal anti-inflammatory drugs ① ⑥, others, anabolic steroids ⑤, pentoxifylline ①, hydrazine sulfate ③, statin ① ⑤*, angiotensin-converting-enzyme inhibitor inhibitor ⑤, selective androgen receptor modulator ⑤, ghrelin agonists ① ② ③ ④ ⑤ ⑥.

treatment (123). The multicomponent herbal medicines capable of targeting multiple sites could be useful for future drug discovery. Mechanistic studies and identification of active compounds could lead to new discoveries in biological and biomedical sciences.

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Conflict of interest statement

None declared.

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