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REVIEW ARTICLE

THERAPEUTIC STRATEGIES IN CACHEXIA: CURRENT AND FUTURE DIRECTIONS

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SUMMARY

Cachexia is a complex syndrome. The main components of this pathological state are anorexia and metabolic abnormalities, such as glucose intolerance, fat depletion and muscle protein catabolism. The aim of the present article is to review the recent therapeutic approaches that have been designed to fight and counteract muscle wasting in different pathological states, such as cancer, AIDS and chronic heart failure.

INTRODUCTION: DEFINITION OF CACHEXIA

According to a recently published consensus (1), cachexia is a complex metabolic syndrome associated with underlying illness that is characterized by muscle loss with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss (corrected for fluid retention) in adults and growth failure (excluding endocrine disorders) in children. Distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism, cachexia is associated with increased morbidity and frequently with anorexia, inflammation, insulin resistance, increased muscle protein breakdown (1) and abnormalities in the metabolism of carbohydrates, lipids and proteins (2) (Fig. 1). The development of cachexia is perhaps the most common manifestation of severe diseases such as AIDS, chronic heart failure and cancer. Indeed, it occurs in the majority of cancer patients before death, and according to Warren (3), it is responsible for the death of 22% of cancer patients.

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Cancer cachexia is a multiorganic syndrome associated with cancer, characterized by body weight loss (at least 5%), muscle and adipose tissue wasting, and inflammation, often associated with anorexia (2). Interestingly, in studies performed before the era of highly active antiretroviral therapy (HAART), estimates of the prevalence of wasting as the first AIDS-defining diagnosis ranged up to 31% (4). Fatigue as a result of muscle wasting is an extremely common symptom in patients with cardiac cachexia; this condition is observed among a high percentage of chronic heart failure patients (5).

Although anorexia represents a very important factor in the development of cachexia, it should be pointed out that in many cases the use of total parenteral nutrition does not stop the loss of body weight (6). It seems, therefore, quite evident that metabolic disturbances present in the host (i.e., increased energy inefficiency, insulin resistance and abnormal carbohydrate metabolism, adipose tissue dissolution and hypertriglyceridemia, muscle wasting) have a definitive role in the development of cachexia (2).

Bearing in mind the fact that both anorexia and metabolic disturbances are involved, the development of different therapeutic strategies has focused on these two factors.

STUDIES ON FIGHTING ANOREXIA

Megestrol acetate

Megestrol acetate (*Megace®*) and medroxyprogesterone are synthetic, orally active derivatives of the naturally occurring hormone progesterone. In humans, these compounds have been found to improve appetite, caloric intake and nutritional status in several clinical trials (7-9) (Table I). In the case of megestrol acetate, the reason for the associated weight gain is mostly unknown, although it has been postulated that the effect is partially mediated by neuropeptide Y, a potent central appetite stimulant (10). On the other hand, medroxyprogesterone has been shown to reduce the in vitro production of serotonin and cytokines (IL-1β, IL-6 and TNF-α) by peripheral blood mononuclear cells (PBMCs) of cancer patients (11). All of these humoral factors have been implicated in the cachectic–anorexic response. Oral suspension of the progestational agent may be particularly useful in patients with far advanced disease, where taking larger amount of pills may lead to a decrease in patient compliance. Recent data from Tomíska et al. (12) showed that administration of an oral megestrol acetate suspension

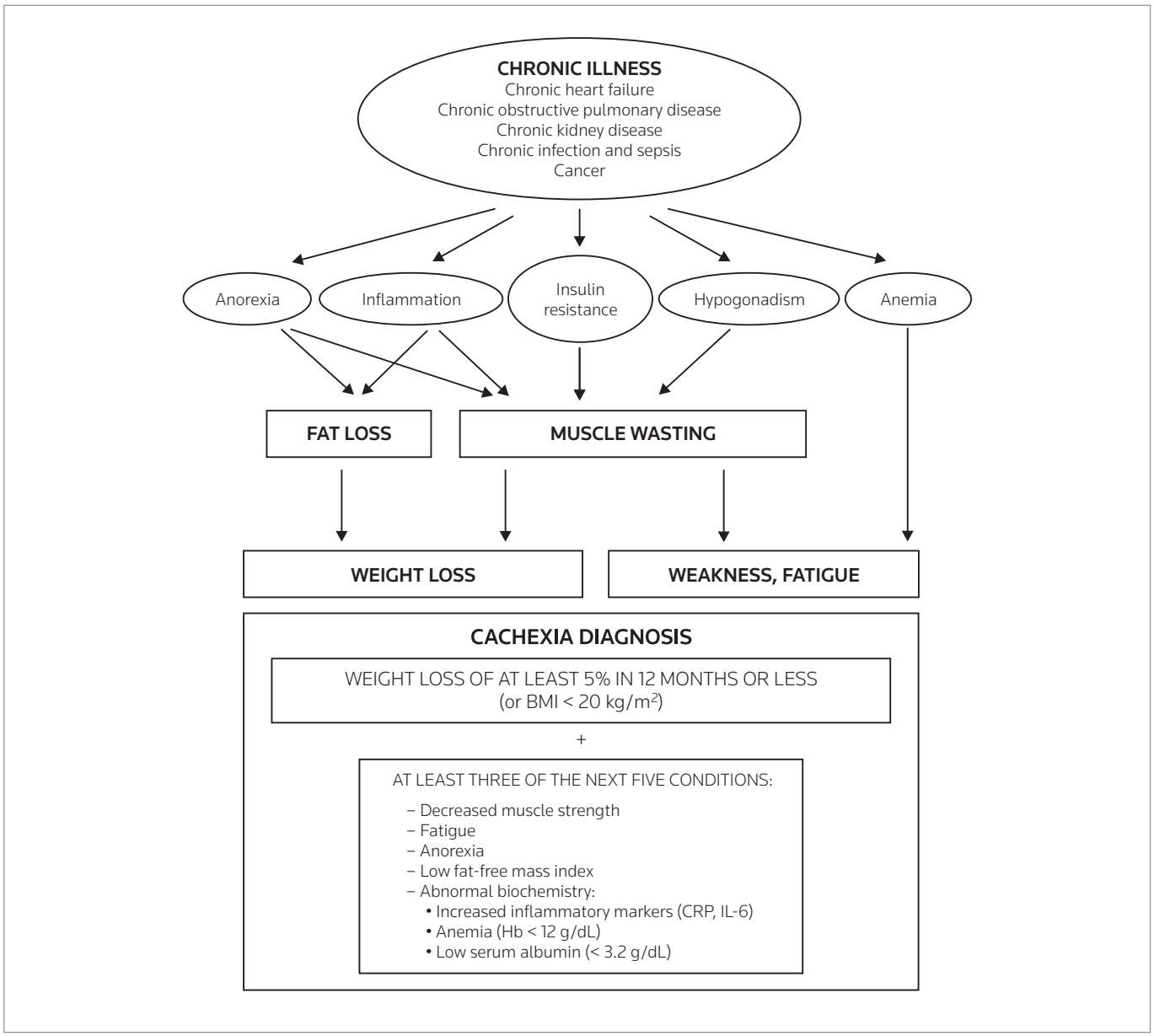

Figure 1. Conceptual representation of the definition of cachexia, which results from adaptation to an underlying illness such as cancer. The illness creates an environment that may be characterized by inflammation, loss of appetite (anorexia), low levels of testosterone and other anabolic hormones, and anemia. Decreased food intake and anorexia result in loss of body and muscle mass. In addition, inflammation, insulin resistance and low levels of anabolic hormones result in muscle wasting. BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin. Adapted from Evans, W.J., Morley, J.E., Argilés, J. et al. *Cachexia: A new definition*. Clin Nutr 2008, 27(6): 793-9, with permission from Elsevier.

improved appetite and quality of life in patients with far advanced cancer who were suffering from anorexia and weight loss.

Ghrelin

The orexigenic mediator ghrelin –a novel endogenous ligand for the growth hormone secretagogue (ghrelin) receptor– was recently reported to play a key role in increasing appetite, and therefore food intake. In addition to increasing food intake, an experimental study has shown that repeated administration of ghrelin improves cardiac structure and function and attenuates the development of cardiac cachexia in chronic heart failure. These results suggest that ghrelin has cardiovascular effects and regulates energy metabolism through ghrelin-dependent and -independent mechanisms. Thus, administration of ghrelin may be a new therapeutic strategy for the treatment of severe chronic heart failure (13). A randomized, placebo-controlled, double-blind phase II study using an oral ghrelin mimetic demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients (14).

Table I. *Selected promising cachexia treatments.*

Compound	Company	Structure	Indication	Development stage	Mechanism
Megace®	Bristol-Myers Squibb	Megestrol acetate	Cachexia	Clinical trials	Increases appetite
Megace® ES	Par Pharmaceutical	Megestrol acetate (*NanoCrystal®*)	AIDS cachexia	Clinical trials	Increases appetite
EPA	Nestle Abbott Danone	Eicosapentaenoic acid	Cancer cachexia	Clinical trials	Decreases muscle protein degradation
Dronabinol (*Marinol®*)	Unimed Pharmaceuticals	Cannabinoid derivative	AIDS cachexia	Clinical trials	Increases appetite
Oxandrolone (*Oxandrin®*)	Savient Pharmaceuticals	Anabolic steroid	Muscle wasting	Clinical trials	Increases muscle protein synthesis
Infliximab (*Remicade®*)	Schering-Plough Centocor	Peptide anti-TNF antibody	Cancer cachexia	Clinical trials	Blocks TNF-α
Formoterol	Acacia	β_2-Adrenoceptor agonist	Cancer cachexia	Preclinical	Decreases muscle protein degradation
R-1291	Rejuvenon	Peptide ghrelin analogue	Cachexia	Clinical trials	Increases appetite
AMG-745	Amgen	Peptide	Muscle wasting	Clinical trials	Suppresses myostatin
IL-15	Inmunex-Amgen	Peptide	Muscle wasting	Preclinical	Decreases muscle protein degradation
Ostarine®	GTx	Peptide	Cancer cachexia	Clinical trials	Androgen receptor

Cannabinoids

Cannabinoids, which are present in marijuana and its derivatives, have a definitive effect on weight gain and have therefore been used to increase food intake in cancer patients. The mechanism by which cannabinoids exert their effects has yet to be clarified. It was postulated that they may act via endorphin receptors or by inhibiting prostaglandin synthesis (15). Other reports suggest that the marijuana derivatives may act by inhibiting cytokine production/secretion (16-18). A recent clinical trial, however, showed very little efficacy for either orally administered cannabinoids or Δ-9-tetrahydrocannabinol in patients with cancer-related anorexia– cachexia syndrome (19).

Melanocortin MC_4 receptor antagonists

The melanocortin MC_4 receptor is involved in the anorexigenic cascade, leading to a decrease in neuropeptide Y, and therefore to a decrease in food intake. The use of antagonists of this receptor was proven to be effective in preventing anorexia, loss of lean body mass and basal energy expenditure in animals suffering from cachexia (20-22). No data on human subjects are currently available, but future clinical trials may prove the efficacy of this type of antagonist in the treatment of human cachexia.

Cyproheptadine

Considerable evidence, both in humans and animals, suggests that anorexia may be mediated by increased serotonergic activity in the brain (23, 24). Taking this into consideration, attempts to block serotonin (5-HT) activity during cancer cachexia have involved the use of cyproheptadine, a 5-HT receptor antagonist with antihistaminic properties, usually used for the treatment of allergies. Although initial clinical data suggested that it had appetite- and weight-enhancing effects in both patients without cancer and with cancer-related cachexia, it did not prevent progressive weight loss in individuals with advanced malignant disease (25). Future clinical trials of other antiserotonergic drugs are necessary to define the role of the serotonergic system in the development of cancer cachexia.

Insulin

Some of the main alterations associated with tumor burden include glucose intolerance, increased gluconeogenesis and Cori cycle activity (liver recycling of tumor-generated lactate), and accelerated lipolysis and protein catabolism. These metabolic changes are accompanied by insulin resistance and a blunted insulin-secretory response to hyperglycemia (2). Taking this into consideration, cachexia may be overcome by the use of exogenous insulin in the tumor-bearing host. Indeed, in animal studies insulin administration has improved the degree of food intake and muscle wasting (26, 27). Body composition analysis also indicated significant host preservation of nitrogen, fat and potassium (28). However, care should be taken with the use of insulin, since the body weight gain observed was associated with an increase in tumor weight (29). In the case of AIDS, Kabady et al. have reported that daily s.c. insulin administra-

tion also resulted in marked weight gain (30). The improvement in body weight was associated with increased nitrogen retention and positive energy balance. Therefore, the possibility that insulin administration may improve the metabolic disturbances and wasting associated with AIDS may warrant further evaluation.

Corticosteroids

This group of hormones was used as one of the first pharmacological approaches to treat cancer anorexia. Indeed, corticosteroids have been used to increase food intake in cancer patients, and a number of uncontrolled studies show that these hormones partially mitigate some cancer symptoms (e.g., anorexia and asthenia), giving the patients an increased sensation of well-being. Both dexamethasone and prednisolone have been used in different trials and appear to act as a result of their euphoriant activity or inhibition of prostaglandin metabolism (31). Although corticosteroid treatment has been associated with low toxicity in several trials, prolonged treatment appears to lead to weakness, delirium, osteoporosis and immunosuppression, all of which are commonly present in patients with advanced cancer (32).

Although the anti-inflammatory action of corticosteroids is well recognized and most likely occurs through the inhibition of TNF release (33), they have also been implicated in the TNF-induced muscle proteolysis that is characteristic of cachexia (34). In addition, it has been postulated that these hormones may be responsible for muscle wasting during sepsis (35). However, studies of the glucocorticoid receptor antagonist mifepristone (RU-486) in animals bearing cachectic tumors suggest that glucocorticoids are not involved in skeletal muscle wasting associated with cancer cachexia (36).

Although corticosteroids appear to improve the quality of life of terminal cancer patients and can be used as palliative therapy, unfortunately they do not seem to have any significant effect on the reduction of mortality (31).

Using nutrition

Enteral nutrition is a reasonable option as an alternative to the oral route in patients with a functional bowel. It can be useful in some patients with advanced head and neck tumors or esophageal carcinoma who are not able to swallow properly but still have an appetite and a good performance status (31).

Total parenteral nutrition has been extensively used in malnourished cancer patients who were unable to receive oral or enteral nutrition. Its clinical use, however, has been subject to conflicting results. While beneficial effects (e.g., wound healing, reduced sepsis, increased responsiveness to chemotherapy) of this type of nutritional therapy were demonstrated in some studies (37, 38), other trials, after evaluating the influence of total parenteral nutrition upon treatment sequelae, suggested that these benefits are limited to improvements of operative mortality and major surgical complications (39).

Concerning the potential differences between the two types of nutritional support, it must be pointed out that enteral feeding is above all more economical and randomized trials with patients undergoing major surgery indicate that the two types of nutrition similarly affect nitrogen balance, plasma proteins, body cell mass and body weight (6).

Altogether, the nutritional strategies represent "tools" for the treatment of anorexia and cachexia, and in combination with a pharmacological approach may lead to interesting and promising results in the near future.

THERAPIES THAT COUNTERACT METABOLIC DISTURBANCES

Cytokines

Cytokines act on multiple target sites, such as bone marrow, myocytes, hepatocytes, adipocytes, endothelial cells and neurons, where they produce a complex cascade of biological responses leading to the wasting associated with cachexia. The cytokines that have been implicated in this cachectic response are TNF-α, IL-1, IL-6 and interferon gamma. Interestingly, these cytokines share the same metabolic effects and their activities are closely interrelated. In many cases they exhibit synergistic effects when administered together (40). Therefore, therapeutic strategies have been based on either blocking their synthesis or their action (41).

Thalidomide (α-*N*-phthalimidoglutaramide) is a drug unfortunately associated with tragedy. Indeed, its use as a sedative in pregnant women caused over 10,000 cases of severe malformations in newborn children. However, a certain revival has affected the drug since it was demonstrated to suppress TNF-α production in monocytes in vitro (42) and to normalize elevated TNF-α levels in vivo (43). A recent, randomized, placebo-controlled trial in patients with cancer cachexia showed that the drug was well tolerated and effective in attenuating loss of weight and lean body mass in patients with advanced pancreatic cancer (44).

A similar approach is the use of anticytokine strategies such as etanercept (a fusion protein directed against the p75 TNF-α receptor). Although its use has led to a poor clinical outcome in chronic heart failure and cancer (45), it decreased fatigue and improved the tolerability of anticancer therapy (docetaxel) in a pilot clinical study conducted by Monk et al. in patients with several advanced malignancies (46). Similarly, Steffen et al. have shown that anti-TNF treatment reduces rat skeletal muscle wasting in cardiac cachexia (47). A phase II trial using a TNF-α-directed monoclonal antibody (infliximab) to improve cachexia symptoms (lean body mass) in patients with pancreatic cancer was unsuccessful (48).

The degree of the cachectic syndrome is dependent not only on the production of the above-mentioned cytokines, known as catabolic proinflammatory cytokines, but also on the so-called anti-inflammatory cytokines (e.g., IL-4, IL-10 and IL-12). IL-15 has been reported to be an anabolic factor for skeletal muscle (49). This suggests that it is able to decrease protein degradation, reduce the rate of DNA fragmentation and increase *UCP3* expression in skeletal muscle, the most important trends associated with muscle wasting during cancer cachexia (50, 51). In vitro experiments carried out using both isolated incubated muscles and muscle cells in culture corroborate the in vivo observations and indicate that the cytokine acts directly on skeletal muscle (52). Although no clinical data are available, IL-15 treatment led to improved muscle mass and performance in an animal model of cachexia (50) (Table I).

Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs), present in large amounts in fish oil, have been proposed to be very active in reducing either tumor growth (53, 54) or the associated tissue wasting, particularly that of the adipose mass (55). In fact, the interest in omega-3 PUFAs originated from the observation that populations consuming a diet rich in such constituents showed the lowest incidence of certain types of cancer. An improvement in the lean body mass and quality of life was observed in a randomized, double-blind trial using a protein- and energy-dense oral supplement enriched in omega-3 fatty acids (56), provided that 2.2 g or more of eicosapentaenoic acid was consumed per day. However, recent data arising from a large, multicenter, double-blind, placebo-controlled trial indicate that eicosapentaenoic acid administration alone is not successful in the treatment of patients with advanced gastrointestinal or lung cancer who are losing weight (57). Moreover, a recent meta-analysis based on five studies concluded that there were insufficient data to establish whether oral eicosapentaenoic acid was superior to placebo. A combination of eicosapentaenoic acid, a protein energy supplement and the appetite stimulant megestrol acetate was compared with a protein energy supplement and megestrol acetate only in patients with advanced cancer who were also suffering from cachexia. The trial provided no evidence that eicosapentaenoic acid improves the symptoms of cancer cachexia (58). In chronic heart failure, fish oils improve body weight and produce anti-inflammatory effects by decreasing TNF-α production (59).

β_2-Adrenoceptor agonists

β_2-Adrenoceptor agonists are potentially very interesting since they have important effects on protein metabolism in skeletal muscle, favoring protein deposition. Apart from the older β_2-adrenoceptor agonists (e.g., clenbuterol), attention has recently been focused on newer drugs, such as formoterol. In particular, the administration of this β_2-adrenoceptor agonist in experimental animals proved to be very useful in reversing cancer-associated muscle wasting (60). In addition to its relatively low toxicity, formoterol is able to reverse the muscle-wasting process, both by activating the rate of protein synthesis and inhibiting the rate of muscle proteolysis. Northern blot analysis revealed that formoterol treatment decreased the mRNA content of ubiquitin and proteasome subunits in gastrocnemius muscles. This, together with the decreased proteasome activity observed, suggests that the main antiproteolytic action of the drug may be based on inhibition of the ATP/ubiquitin-dependent proteolytic system (60). Interestingly, formoterol was also able to reduce the increased rate of muscle apoptosis in tumor-bearing animals, and facilitated muscle regeneration by stimulating satellite cells. The results indicate that formoterol exerts a selective, powerful protective action on heart and skeletal muscle by antagonizing the enhanced protein degradation that characterizes cancer cachexia. Therefore, it may have potential as a therapeutic tool in pathological states wherein muscle protein hypercatabolism is a critical feature, such as cancer cachexia or other diseases associated with wasting (60, 61) (Table I).

Erythropoietin

The administration of erythropoietin (EPO) results in a clinical benefit in cancer patients with subnormal or normal hemoglobin levels (62). Interestingly, Kanzaki et al. (63) showed that the positive therapeutic effects of EPO in tumor-bearing mice with cachexia are not only due to improved metabolic and exercise capacity via an increased erythrocyte count, but also to an attenuation of cachectic manifestations by a decreased production of the cachexia-inducing cytokine IL-6.

Angiotensin-converting enzyme inhibitors

In chronic heart failure, inhibition of angiotensin-converting enzyme (ACE) by administration of enalapril reduces the risk of weight loss and is linked to improved survival (64). Preliminary results demonstrate increased subcutaneous fat (increased skin fold thickness) and greater muscle bulk (increased mid–upper arm and thigh circumferences), together with a significant elevation in plasma albumin and hematocrit (65). In fact, ACE inhibitors like captopril seem to act by decreasing the production of TNF-α by mononuclear cells, suggesting a mechanism to account for the beneficial effects (related to body weight) observed in heart failure patients (66). The highly lipophilic ACE inhibitor imidapril hydrochloride attenuated weight loss in mice bearing MAC16 tumors, suggesting that angiotensin II may play a role in the development of cachexia in this model (66).

β-Adrenoceptor blockers

β-Adrenoceptor blockers can reduce body energy expenditure and improve the efficiency of substrate utilization. Interestingly, patients with chronic heart failure treated with these drugs show an increase in total body fat mass and partial reversal of cachexia (67).

Anabolic steroids

Although treatment with derivatives of gonadal steroids has important side effects, such as masculinization, fluid retention and hepatic toxicity, because they promote nitrogen protein accumulation, they could be used to counteract the progressive nitrogen loss associated with cachexia. Data from a double-blind, placebo-controlled trial of nandrolone decanoate in cachectic AIDS patients showed that the agent effectively increased lean body mass, improved quality of life and decreased the toxicity of AIDS therapy in these individuals (68). In a recent clinical trial conducted in healthy elderly subjects, the nonsteroidal selective androgen receptor modulator (SARM) ostarine successfully increased lean body mass and improved physical performance. For this reason, the potential of this class of drugs for use in cancer cachexia should be taken into consideration (69). Indeed, SARMs hold promise as a new class of function-promoting anabolic therapies for several clinical conditions associated with muscle wasting (70).

Growth hormone

Administration of growth hormone (GH) increases whole-body and skeletal muscle protein synthesis (71-73). Animal studies have shown that administration of recombinant rat GH to methylcholanthrene-induced sarcoma-bearing rats resulted in considerable stimulation of protein synthesis without changing tumor growth, protein degradation or host composition. Conversely, Wolf et al. (74) have reported improvements in whole-body protein balance in cancer patients

receiving GH. Very interestingly, the same research group (75) demonstrated that exogenous GH can attenuate weight loss and preserve host body composition in tumor-bearing rats undergoing chemotherapy with doxorubicin without stimulating tumor growth. Similar results have been obtained in AIDS patients (76), where GH treatment improved nitrogen balance and attenuated weight loss. Similarly, AIDS patients appear to suffer from GH resistance that can be reversed by low doses of recombinant insulin-like growth factor I (IGF-I) or GH administration. In both cases, protein accretion and nitrogen balance are improved (77). A pilot study involving GH administration to patients at the end stage of cardiac failure suggested that it has a beneficial effect on cardiac cachexia (78). However, the results of these case studies must be interpreted with caution, since spontaneous improvement in functional and hemodynamic capacity cannot be ruled out.

Insulin-like growth factor I

Insulin-like growth factor I (IGF-I), also known as somatomedin-C, mediates many of the anabolic properties of GH (79) and appears to be involved in the regulation of protein turnover (80). Other studies have shown an important role in muscle cell proliferation and differentiation (81). Interestingly, during catabolic states (such as sepsis) antagonism of IGF-I bioactivity has been reported (82). In the particular case of cardiac cachexia, decreased levels of circulating IGF-I have been reported in patients with tissue wasting and congestive heart failure (83). Since IGF-I stimulates amino acid uptake and protein synthesis (79), it is potentially a good candidate to counteract the changes that take place in skeletal muscle during cancer cachexia. In addition, IGF-I decreases lipolysis (79), a metabolic pathway that is activated in adipose tissue during cancer cachexia. In a study using a methylcholanthrene-induced rat sarcoma, Ng et al. (84) showed that IGF-I treatment by continuous s.c. administration resulted in preservation of lean tissue and an attenuation of muscle protein loss. Interestingly, the treatment did not stimulate tumor growth (as previously mentioned, IGF-I has mitogenic properties in certain cell types) but, conversely, the proportion of aneuploid and S-phase cells in tumors was reduced, implying additional beneficial effects of IGF-I treatment (84). In spite of the complexity of the IGF-I protein family (which includes IGF-I-binding proteins that counteract the action of the growth factor), it seems that overexpression of IGF-I leads to a phenotype that is characterized by both increased muscle mass and increased muscle regeneration capacity. Bearing this in mind, gene therapy approaches involving local IGF-I increases in cachectic skeletal muscle may prove advantageous and cardiotrophic effects of growth factors would be avoided. Future research in this area is therefore promising (85).

In AIDS patients, Lieberman et al. (77) have studied the effects of a combination therapy based on both GH and IGF-I. Although the treatment resulted in a transient increase in nitrogen retention, further randomized, placebo-controlled human studies are necessary to support these encouraging results.

Melanocortin

Recent studies have shown the existence of reciprocal links between cytokine activity and immunomodulating neurohormones or neuropeptides. In particular, the pineal hormone melatonin appears to influence cytokine activity during tumor growth. Lissoni et al. (86) evaluated the effects of melatonin therapy in patients with solid metastatic tumors, demonstrating that there is indeed an inhibitory effect of melatonin on TNF-α release, since the treatment resulted in a considerable decrease in the circulating levels of this cytokine.

In another study (87), the same research group investigated the relationship between melatonin, TNF-α and cancer-related weight loss in a group of 100 untreatable patients with metastatic solid tumors, and showed that weight loss was lower in the melatonin-treated group as compared with the cohort receiving placebo, therefore concluding that the pineal hormone may be effective in the treatment of neoplastic cachexia by decreasing the TNF-α concentration in blood.

Another clinical study (88) clearly shows that the concomitant administration of melatonin and cisplatin plus etoposide may improve the efficacy of chemotherapy in terms of survival time. Additionally, melatonin treatment appears to reduce the toxicity of chemotherapy in patients who are in poor clinical condition (88).

Insulin/glucagon ratio

Cancer cachexia is associated with a decreased insulin/glucagon ratio. Some studies have postulated that the decrease in this hormone index is largely responsible for the progressive catabolism in cancer cachexia. Taking this into consideration, Bartlett et al. (89) studied the effects of somatostatin, insulin and GH as a combined therapy with the aim of increasing the insulin/glucagon ratio in animals inoculated s.c. with the spontaneously metastasizing mammary adenocarcinoma MAC-33. In the animals receiving the combined therapy, host carcass weight, hamstring muscle weight and protein content were increased as compared to tumor-bearing animals receiving no treatment (89). Insulin treatment alone leads to limited success in treating cancer cachexia due to the fact that it induces hypoglycemia, and subsequently, glucagon secretion. The advantage of the inclusion of somatostatin in the treatment is based on the fact that it leads to a decrease in the levels of glucagon. It is therefore becoming increasingly evident that a single pharmacological strategy is unlikely to reverse cachexia completely, and that future attempts to revert the progressive catabolism present in the tumor-bearing host will involve combinations of several drugs.

Amino acids

Peripheral muscle proteolysis, as occurs in cancer cachexia, serves to mobilize amino acids required for the synthesis of liver and tumor proteins (2). Therefore, the administration of exogenous amino acids may theoretically serve as a protein-sparing metabolic fuel by providing substrates for both muscle metabolism and gluconeogenesis (90, 91). Based on this, the branched-chain amino acids (BCAAs) leucine, isoleucine and valine have been used in parenteral nutrition with the aim of improving nitrogen balance and, particularly, muscle protein metabolism. Based on a prospective, randomized, crossover trial in patients with advanced intra-abdominal adenocarcinoma, Tayek et al. (92) concluded that BCAA-enriched total parenteral nutrition resulted in an improved protein accretion and albumin synthesis. Similarly, studies in tumor-bearing animals show that high BCAA concentrations in total parenteral nutrition have beneficial effects on host protein metabolism (93).

Cangiano et al. (94) have proposed that BCAA administration would also serve to counteract the anorexia associated with tumor growth. The authors postulated that increased hypothalamic serotonergic activity is one of the pathogenic mechanisms leading to the development of cancer anorexia. In fact, free tryptophan (the precursor of brain 5-HT) is increased during cancer (95, 96) and BCAA may act by competing for the same transport system as tryptophan across the blood–brain barrier (97). This hypothesis has been tested in anorectic cancer patients receiving oral BCAA supplementation, with encouraging results, since the treatment decreased the severity of anorexia in the treated patients (94). Recent studies have demonstrated that dietary supplementation with a specific combination of proteins, leucine and fish oil improves muscle function and daily activity and the immune response in cachectic tumor-bearing mice (98, 99). In addition, β-hydroxy-β-methyl butyrate derived from leucine catabolism used as a supplement in tumor-bearing rats prevents cachexia by modifying nuclear factor NF-kappa-B (NF-κB) expression (100).

Glutamine-enriched solutions have also been used in total parenteral nutrition with the aim of enhancing immunoregulation of tumor growth (101) and compensating for the tumor's uptake of the amino acid. Indeed, tumor cells are major glutamine consumers (for both protein synthesis and oxidation) (102) and therefore lead to host glutamine depletion (103), which results in a decreased host immune response and gastrointestinal mucosal integrity (101). In patients undergoing bone marrow transplants for hematological malignancies, glutamine supplementation was found to be beneficial, improving nitrogen balance and reducing the incidence of clinical infection as compared with the standard parenteral nutrition therapy (104). It could be argued that glutamine supplementation may facilitate tumor growth, since it is one of the preferred substrates for fast-growing tumors. However, evidence obtained in experimental models demonstrates that glutamine supplementation improves the tumoricidal effectiveness of methotrexate while reducing its toxicity (105). As Laviano et al. (106) suggest, this could be due to the glutamine-induced increased number of tumor cells in the S-phase, the phase of the cell cycle during which they are more susceptible to chemotherapy.

Increasing evidence suggests that abnormal cysteine and glutathione metabolism plays a decisive role in the development of catabolic conditions and associated immunological dysfunction (107). Indeed, the increased glycolytic activity and lactate production during cancer (108) cause an acidification of the muscle cells, which may result in decreased transport of glutamate and therefore impaired glutathione metabolism (107). The acidification is aggravated by the fact that the temporary increase of intracellular pyruvate causes an increased enzymatic activity of cysteine/pyruvate transaminase, and consequently, increased cysteine degradation into sulfate and protons (107). Increased intracellular sulfate levels have indeed been found in skeletal muscle of tumor-bearing mice (109). This was associated with a decrease in the glutathione level in the skeletal muscle tissue, indicating that cysteine catabolism was increased at the expense of glutathione biosynthesis at this time (107). Bearing all this in mind, Dröge et al. (107) suggest that *N*-acetylcysteine can be used to increase cysteine availability during the treatment of catabolic states such as cancer cachexia. In fact, preliminary studies support a positive role for this amino acid derivative in HIV-infected patients.

Hydrazine sulfate

Among the compounds that counteract metabolic changes, it is particularly interesting to take into consideration hydrazine sulfate, an inhibitor of gluconeogenesis from lactate and amino acids. Gold (110) introduced its use as an anticancer treatment based on his theory that the abnormalities in carbohydrate metabolism (including increased gluconeogenesis and enhanced Cori cycle activity) are the central causes of tumor-induced cachexia. Based on Gold's hypothesis, a study conducted in patients with small cell lung carcinoma indicated that hydrazine treatment can improve parameters of carbohydrate metabolism and prolong survival (111). Similarly, after performing a double-blind trial in malnourished lung cancer patients, Tayek et al. (112) concluded that the administration of the drug reduced amino acid flux, favorably influencing the metabolic abnormalities associated with cachexia. Further clinical studies are being performed to evaluate the utility of this low-toxicity drug in cancer cachexia.

Prostaglandin and nitric oxide synthase inhibitors

The effects of prostaglandins on cell growth have been studied both in vitro (113) and in vivo (114, 115), and it has been proposed that cell growth may be controlled by the interconversion of different types of prostaglandins. In fact, large amounts of these compounds are found both in tumor tissue and plasma from cancer patients (116). Taking all this into consideration, several studies have examined the role of cyclooxygenase (COX) inhibitors on tumor growth and cachexia. The results obtained are clearly contradictory. While Homem-De-Bittencourt et al. (117) reported that indomethacin, ibuprofen and aspirin markedly inhibited tumor growth and reduced anorexia in rats bearing Walker 256 carcinosarcoma, McCarthy and Daun (118) (using the same rat tumor model) also reported a decrease in tumor weight, but this was not associated with a reduction in anorexia or body weight loss. Hussey and Tisdale (119) have recently studied the effects of the COX-2 inhibitor meloxicam on tumor growth and cachexia in the murine adenocarcinoma MAC16. The results suggest that the inhibitor is able to effectively attenuate cachexia, possibly by exercising a direct effect on skeletal muscle protein degradation.

Inhibition of nitric oxide production by specific blockade of nitric oxide synthase (NOS) resulted in decreased muscle wasting in a model of cachexia. Interestingly, the decrease in body weight, muscle wasting and skeletal muscle molecular abnormalities were prevented by the use of both *N*-nitro-L-arginine (an NOS inhibitor) and antioxidants (120). Therefore, further studies in other tumor models are needed before any serious conclusions can be drawn about the beneficial effects of prostaglandin inhibitors in cancer cachexia.

ATP and creatine

Weight maintenance is a balance of energy supplements. In fact, during catabolic conditions, illness often increases energy demands. It is for this reason that administration of adenosine 5′-triphosphate (ATP), a directly hydrolyzable source of energy, could potentially tip the balance towards weight gain and preservation of lean body mass. Data from several clinical trials support this observation (121-123).

Using a similar principle, perhaps more directly linked with skeletal muscle, creatine administration may result in an increase in skeletal muscle phosphocreatine content, which in turn may protect the tissue during catabolic conditions. Indeed, Gordon et al. (124) have reported that administration of creatine supplements to patients with chronic heart failure increases not only the levels of creatine phosphate in skeletal muscles, but also muscle performance. This new therapeutic approach merits further attention.

OTHER NEW PROMISING THERAPEUTIC STRATEGIES

Myostatin, a transforming growth factor β (TGF-β) superfamily member, has been well characterized as a negative regulator of muscle growth and development. Myostatin has been implicated in several forms of muscle wasting, including the severe cachexia observed as a result of conditions such as AIDS and liver cirrhosis. McFarlane et al. (125) have demonstrated that myostatin induces cachexia through an NF-κB-independent mechanism by antagonizing hypertrophy signaling through regulation of the c-AKT/forkhead box protein O1 pathway. Myostatin-targeting strategies are therefore promising and should be considered in future clinical trials involving cachectic patients (126).

The corticotropin-releasing factor receptor CRF_2 has many biological activities, including modulation of the stress response, and has been involved in the prevention of skeletal muscle wasting resulting from a variety of physiological stimuli. Indeed, the use of CRF_2 agonists has proven to be successful in partially blocking muscle wasting in several models of experimental cachexia (127, 128). However, a lack of clinical data exists.

As previously stated, enhanced protein degradation in skeletal muscle during cachexia involves activation of the ubiquitin/proteasome system in muscle. Therefore, inhibitors of this proteolytic system (e.g., peptide aldehyde, lactacystin and β-lactone, which can effectively block up to 90% of the degradation of normal proteins and short-lived proteins in the cells) are potential drugs for the treatment of muscle wasting (129). However, the toxicity of such compounds is fairly high, since they are not specific inhibitors of the proteolytic system in muscle tissue (130). Bearing this in mind, a substance that can specifically block myofibrillar protein degradation in skeletal muscle is still awaiting discovery. From this point of view, the discovery of specific muscle ubiquitin-protein ligases (atrogin-1 and MuRF1) (131) is particularly interesting since a tissue-specific inhibition of ubiquitin/proteasome proteolysis could be achieved if inhibitors of these ligases were discovered.

COMBINED APPROACHES

From all the data presented, one can speculate that a single therapy may not be completely successful in the treatment of cachexia. Treatments involving different combinations are more likely to be effective. A very interesting phase II study showed that administration of antioxidants, pharmaconutritional support, a progestagen and a COX-2 inhibitor was effective and safe in patients with different types of advanced cancer who were suffering from cachexia (132). Based on the results of the phase II trial, a randomized phase III study was started in 2005 with the aim of including more than 300 cachectic cancer patients and is still in progress. These data clearly reinforce the use of these multitargeted therapies in the treatment of the cachexia–anorexia syndrome in different clinical conditions such as cancer, AIDS and chronic heart failure.

CONCLUSIONS

In the opinion of the authors, nutritional strategies are not sufficient to reverse the cachectic syndrome. Indeed, patients on total parenteral nutrition are still subject to significant wasting, therefore emphasizing the role of metabolic abnormalities in cachexia. It is perhaps for this reason that any therapeutic approach based on increasing food intake must be combined with a pharmacological strategy to counteract metabolic changes. Moreover, timing is very important and has to be seriously considered when designing the therapeutic approach. A very important aspect to be taken into consideration when treating cancer patients is that any nutritional/metabolic/pharmacological support should be started early in the course of the disease, before severe weight loss occurs.

The loss of muscle mass is a hallmark of cancer cachexia and is essentially caused by an increased degradation of myofibrillar proteins (especially myosin heavy chain), sometimes accompanied by a decrease in protein synthesis. The enhanced protein degradation is caused by an activation of the ubiquitin-dependent proteolytic system. Therefore, therapeutic approaches based on the neutralization of the enhanced myofibrillar protein degradation should be encouraged.

Another important problem associated with the design of an ideal therapeutic approach is that no definite mediators of cachexia have yet been identified. The therapy of wasting during cachexia has concentrated on either increasing food intake or normalizing the persistent metabolic alterations that take place in the patient. Therefore, it is difficult to apply a therapeutic approach based on the neutralization of the potential mediators involved in muscle wasting (i.e., TNF-α, IL-6, interferon gamma, proteolysis-inducing factor), because many of them are simultaneously involved in promoting the metabolic alterations and anorexia present in cancer patients. Thus, it is obvious that a good understanding of the molecular mechanisms involved in the signaling of these mediators may be very positive in the design of a therapeutic strategy (Table I). This is especially relevant because different mediators may share the same signaling pathways. Up to the present, few studies have described the role of cytokines and tumor factors in the signaling associated with muscle wasting.

In conclusion, because both tumoral and humoral (mainly cytokines) factors triggering cachexia may share common signaling pathways, it is not very likely that a single drug will block the complex processes involved in cachexia. In addition, some of the mediators proposed for the wasting syndrome also play a role in the regulation of body weight in absolutely opposite states, such as obesity. In conclusion, the future treatment of the cachectic syndrome will no doubt combine nutritional support with different pharmacological approaches to efficiently reverse the metabolic changes described above and, at the same time, ameliorate anorexia in the patients. Defining this therapeutic combination of drugs is an exciting project that will stimulate many scientific efforts.

At present, a good recommendation would be a combination of nutritional support, an appetite-stimulating agent (e.g., megestrol

acetate) and an anticatabolic compound, either a nutraceutical (i.e., eicosapentaenoic acid) or a drug.

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DISCLOSURES

The authors state no conflicts of interest.

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