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Review

Mechanism and novel therapeutic approaches to wasting in chronic disease

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ABSTRACT

Cachexia is a multifactorial syndrome defined by continuous loss of skeletal muscle mass – with or without loss of fat mass – which cannot be fully reversed by conventional nutritional support and which may lead to progressive functional impairment and increased death risk. Its pathophysiology is characterized by negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. Muscle wasting is encountered in virtually all chronic disease states in particular during advanced stages of the respective illness. Several pre-clinical and clinical studies are ongoing to ameliorate this clinical problem. The mechanisms of muscle wasting and cachexia in chronic diseases such as cancer, chronic heart failure, chronic obstructive pulmonary disease and chronic kidney disease are described. We discuss therapeutic targets and such potential modulators as appetite stimulants, selective androgen receptor modulators, amino acids and naturally occurring peptide hormones.

Contents

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1. Introduction

Cachexia as a clinical entity is acknowledged as a complex syndrome in chronic disease, which is associated with poor outcomes [1]. The prevalence of cachexia ranges from 5% to 20% in chronic heart failure (HF) [2] to 60% in chronic obstructive pulmonary disease (COPD) and to as high as 85% in advanced cancer [3]. Interestingly, hormonal and inflammatory mechanisms differ between cachectic and non-cachectic patients, which may influence efficacy of disease therapy. Thus, patients at risk of developing cachexia should be identified as early as possible. The aim of this review is to provide insight into the mechanisms of cachexia development and to give an overview of novel therapeutic targets in the field of cachexia in chronic diseases.

2. Definition of cachexia

Cachexia is characterized by progressive weight loss affecting different body compartments, particularly muscle tissue and adipose tissue, although even bone mineral content may be affected. Use of the term cachexia is restricted to patients with involuntary weight loss associated with chronic or inflammatory disorders, and its presence has long been recognized as a *signum mali ominis* [4]. Several definitions have been used in different studies in the past, a fact that makes comparisons between studies and study outcomes challenging [5]. A group of international experts recently stated: "Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" [6]. Cachexia can finally be defined as a disease considered in adult patients with chronic illness, who experience a non-oedematous weight loss of 5% in 12 months or less [6]. It is associated with functional impairment and increased death risk across virtually all chronic disease states.

3. Mechanisms of wasting

An understanding of the hormonal and molecular effectors that maintain cachexia progression is pivotal in order to develop useful therapies. Cachexia can result from muscle pathology such as muscular dystrophy, muscle damage or systemic disease [7]. In some patients, cachexia may be intertwined with muscle wasting that resembles sarcopenia, however, the two terms must not be used synonymous [8]. Cachexia implies weight loss, while sarcopenia means loss of muscle mass without weight loss, because functional muscle may be replaced by adipocytes. Furthermore, there are differences in the underlying molecular mechanisms of the two clinical entities. For example, the importance of proteasome-mediated degradation of muscle fibres, the most important mechanism of muscle degradation in man, is established in cachexia, however, there is conflicting evidence for its role in sarcopenia [9]. Indeed, studies have implicated inflammatory cytokines as important humoral factors in the pathology of both sarcopenic and cachectic muscle wasting [8,9]. The ability of cachexia to induce sarcopenia underscores the potentially overlapping molecular mechanisms of the two syndromes. Both result in similar changes in the overall metabolic state of muscle fibres, leading to atrophy [8,9]. For the associated muscle wasting in cachexia various studies demonstrate that glucocorticoids, tumor necrosis factor (TNF), interleukin-6 (IL-6), and interferon-γ are important regulators that are primarily involved in activating the proteasome [10–12]. TNF, IL-1β, IL-6, and interferon-γ are thought to be the principal catabolic actors in skeletal muscle [13].

A large set of different transcription factors have recently been identified to play important roles in tissue wasting. Many of them are activated by pro-inflammatory stimuli. For example, different genetic studies [14,15] demonstrated the importance of the transcription factor protein Forkhead box O (FoxO) in the regulation of skeletal muscle mass. FoxO signalling is commonly activated during sepsis and in experimental models of cachexia [14]. Other studies buttress the view that increased FoxO signalling and the activation of the transcription factors nuclear factor κB (NF-κB),muscle ring-finger protein (MuRF1) and muscle atrophy F-box (MAFbx) in skeletal muscle play major roles during cachexia onset and progression [7,9,14]. MuRF1 and MAFbx are essentially involved in muscle atrophy development. Indeed, genes whose expression levels are commonly increased during multiple models of skeletal muscle atrophy, including cancer and sepsis, are MAFbx, MuRF1 and cathepsin, and there is evidence that each are FoxO target genes [14]. Inducers of MuRF1 and MAFbx expression are TNFa, IL-6 and IL-1, and NF-κB appears to be most important regulator of MuRF1 and MAFbx expression in the skeletal muscle. Apart from the proteasome, the endosome–lysosome system is involved in protein degradation in muscle. It largely relies on the activity of proteases and is comparatively non-selective [15]. Fig. 1 provides an overview of these interactions.

The development of anti-cachexia therapies may also tackle the induction of mechanisms of hypertrophy, during which, in skeletal muscle, general pathways of protein synthesis are being activated [7]. Myostatin, a transforming growth factor-β superfamily member is well characterized as a negative regulator of muscle growth and has been implicated in several forms of muscle wasting including severe cachexia [16,17]. Myostatin has become a main target for the development of drugs for cachexia and muscle wasting, because the identification of a myostatin mutation in a child with muscle hypertrophy, providing strong evidence that myostatin play an important role in regulating muscle mass in humans [18]. Characterization of myostatin signalling is therefore an intriguing respective in the development of treatments for cachexia [19]. Other studies have identified insulin-like growth factor-1 (IGF-1) as an interesting regulator of skeletal muscle growth and homeostasis and have created new interest in this mediator of anabolic pathways [20].

4. Clinical significance of cachexia in chronic diseases

4.1. Cancer cachexia

Cachexia is a clinical phenomenon frequently encountered in patients with cancer where prevalence is highly dependent on the underlying tumor type and stage in individual patient [3]. Indeed, with cachexia frequently associated cancers include gastric, pancreatic, lungs, prostate, or colonic, all of which show prevalence >50% in advanced disease stages [21]. In contrast, other tumors like non-Hodgkin's lymphoma, breast cancer, leukemias, or sarcomas are less frequently associated with body wasting; nonetheless, 30–50% of patients may still be affected in advanced disease [21].

As with most other chronic illnesses, the development of cachexia is frequently overlooked in the cancer patient. The three major pathophysiological factors i.e. altered energy intake, increased resting energy expenditure, and accelerated muscle and lipid catabolism [22] provide means for therapeutic interventions, although these may not be routinely pursued by clinical oncologists [23]. In addition, therapies targeting the tumor itself may play a role in the development of body wasting via loss of fat or muscle tissue during chemotherapy or mediated through anorexia [23]. The latter may be tackled with frequent small meals in pleasant surroundings, and attention should be given to food presentation and palatability [23]. Although anorexia versus cachexia may develop at the same time, it is a common misconception that anorexia

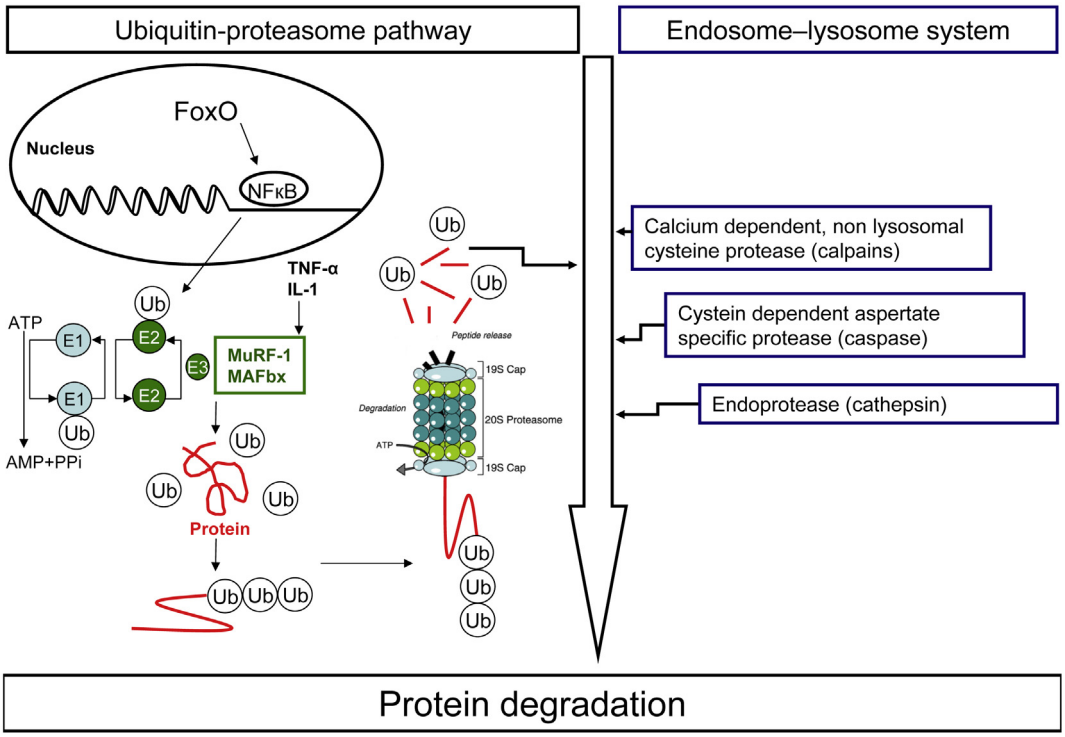

Fig. 1. Mechanism of wasting. The ubiquitin (Ub) proteasome pathway starts with increased Forkhead box O (FoxO) signalling and increased transcription factor nuclear factor κB (NFκB) expression. Ubiquitin is first bound to the Ub-activating enzyme (E1), transferred to the Ub-conjugating enzyme (E2), and catalysed by the action of Ub-ligase enzyme (E3). Two muscle-specific Ub-ligases are muscle ring-finger protein (MuRF) and muscle atrophy F-box (MAFbx). Catabolic cytokine tumor necrosis factor-alpha (TNFα) and interleukin 1 (IL-1) are inducers of MAFbx mRNA expression in skeletal muscle. Proteins are unfolded and fed into the proteasome in an ATP-dependent process. The ubiquitinated proteins are then disassembled into their constituent peptides.

causes cachexia. This is not the case, because mere supply of calories cures anorexia but is not sufficient to treat cachexia. Some drug classes that have been evaluated in their capacity to correct poor appetite include progestin, glucocorticoids and cannabinoids, but without major breakthrough [24]. Indeed, approved treatments for cachexia are available only for the treatment of cachexia associated with acquired immunodeficiency syndrome (AIDS), and treatment regimens remain a matter of the attending physicians personal experience and are in most cases off-label. Research, however, is ongoing and includes smaller clinical trials and animal experiments. Gramigano et al. [25] showed that L-carnitine administration (6 g/day for 30 days) is effective at improving fatigue and increasing lean body mass and appetite in 12 patients with advanced cancer.

Another interesting candidate for the treatment of cancer cachexia is IGF-1, a protein with similarity to insulin, which transmits growth hormone signalling. Using a rat model, Schmidt et al. [20] showed that IGF-1 treatment (0.3 mg/kg/day) in tumor bearing rats does not promote tumour growth but loss of body weight was attenuated (from 211 ± 3 g to 168 ± 10 g in16 days, $p < 0.05$) and survival was improved. In addition, the authors suggested improved quality of life as assessed by measurement of spontaneous movement. Clinical research on cancer cachexia includes investigations of possible mechanisms and mediators as well as randomized clinical trials of anti-cachexia therapies [20,26,27]. Outcomes of drug trials in cancer cachexia focus on symptomatic and quality-of-life advantages since the survival of cachectic cancer patients is usually limited to weeks or months due to the incurable nature of the underlying malignancy [28,29].

4.2. Cachexia in chronic kidney disease

Cachexia is highly prevalent in moderate to advanced stages of chronic kidney disease (CKD) including up to 75% of patients undergoing maintenance hemodialysis [30]. Although the International Society of Renal Nutrition and Metabolism has suggested that the term cachexia be reserved for only the most severe forms of protein-energy wasting [31], earlier stages of wasting syndrome are very common in CKD and – as in other chronic diseases – embrace increased resting energy expenditure, decreased protein stores characterized by low serum albumin, and loss of body weight and muscle mass [32]. The differentiation of malnutrition from cachexia or its earlier stages known as protein-energy wasting is pivotal for the prompt recognition and effective treatment of CKD patients, and the two terms must not be mixed or even used as synonyms. Malnutrition is a consequence of inadequate intake of nutrients and manifests as weight loss associated with protective metabolic responses [33].

Kim et al. showed in 5/6 nephrectomised rats consuming a high-fat diet that the animals gained weight normally, and that they displayed reduced proteinuria, suppressed oxidative stress and inflammation in the remnant kidney compared to healthy control rats and compared to nephrectomised rats consuming regular food [34]. The authors suggested that down-regulation of pro-inflammatory, pro-oxidant, profibrotic and pro-apoptotic pathways, may in part be due to the moderate reduction in protein intake and diminished catabolism of endogenous proteins. Indeed, inflammation in patients with chronic kidney disease has been shown to lead to muscle wasting through increased protein catabolism, decreased protein synthesis, or impaired muscle

progenitor cell proliferation [34]. It is therefore not astonishing that, cardio-renal syndromes and cachexia use common pathophysiologically mechanisms and Cicoira et al. [35] hypothesize that the presence of one of these conditions may favour the worsening of the other.

4.3. Cachexia in chronic obstructive pulmonary disease

Dyspnea and fatigue cause the hypoxic inactivity, a major clinical feature of COPD that on top of common pathophysiological mechanisms contributes to body wasting and cachexia [36–38]. In a retrospective study of 968 patients with COPD, Lainscak et al. showed, that body size has important clinical implications in terms of mortality [39]. Patients were divided by body mass index (BMI) into four groups (group I with BMI < 21.55, group II: 21.55–25.08, group III: 25.08–29.05, group IV: > 29.05 kg/m^2) and 430 patients died (mortality 44%) over a mean follow-up of 3.26 years, with highest BMI quartile being associated with lowest risk of mortality. Malnutrition or risk of malnutrition as defined using the Mini Nutritional Assessment questionnaire is also common in COPD patients to affect 69% of patients [40]. It is therefore important to screen for malnutrition as it was predicting short-term hospitalizations beyond the body composition parameters.

Although COPD affects whole body, skeletal muscle appears to have a central role [41], and body fat starts to receive attention [42]. Novel data are available for intramuscular myostatin expression which is accelerated in patients with COPD. Ju and Chen [43] demonstrated that serum myostatin levels were significantly elevated in 71 patients with stable COPD compared to 60 healthy controls (12 ± 4 ng/ml vs. 8 ± 2 ng/ml, $p < 0.01$). The myostatin levels correlated inversely with total-body skeletal muscle mass and body mass index (all $p < 0.001$). A correlation existed between serum myostatin and TNFα levels in all patients with COPD ($p < 0.05$). The interventions in COPD therefore aim to maintain the muscle bulk and associated functions beyond ability to move [44].

4.4. Cachexia in heart failure

The clinical effects of cachexia on morbidity and mortality of patients with chronic HF has only recently been recognized [2]. In total, it can be expected that 16% of ambulatory patients with heart failure are affected by involuntary weight loss that fulfils the criteria of cachexia [26]. The catabolic/anabolic imbalance as well as general overactivity of the immune system have been described in patients with cardiac cachexia [45]. Levine et al. [46] were the first to observe high levels of circulating TNFα in patients with chronic HF. They measured serum levels of TNFα in 33 patients with chronic HF compared to 33 healthy controls. Mean serum levels of tumor necrosis factor were increased in patients with HF (115 ± 25 U/ml) compared to healthy controls (9 ± 3 U/ml, $p < 0.001$).

Besides pro-inflammatory mediators, hormonal players such as leptin appear to play prominent roles. Leptin, the product of the Ob(Lep) gene, is a 167 amino acid hormone that is produced by adipose tissue, and its serum levels are known to be positively correlated with fat mass. Leptin acts on receptors in the hypothalamus of the brain where it inhibits appetite. Murdoch et al. [47] studied plasma leptin levels of 51 patients with chronic HF and 26 healthy controls. Among patients with chronic HF, plasma leptin levels were significantly lower in 29 cachectic patients (mean: 6.2 ± 0.6 ng/ml) than in 22 non-cachectic patients (mean: 16.9 ± 3.6 ng/ml) or with ischaemic heart disease (mean: 16.8 ng/ml) with normal left ventricular function. Lower leptin levels seem to be not correlated with aetiological factor in cachexia with chronic heart failure. Thus the authors concluded that cardiac cachexia is not caused by enhanced leptin release.

Sarraf et al. showed that TNFα has influence on circulating leptin concentrations in mice [48]. These workers measured leptin levels after 7 h of fasting and treatment with a single intraperitoneal injection of lipopolysaccharide, or multiple cytokines at doses that are known to confer anorectic effects. The authors found that leptin levels are significantly increased by lipopolysaccharide, TNFα, and IL-1 in a dose-dependent fashion. One possible explanation for both the low leptin concentrations and increased metabolic rate in cachectic patients with chronic HF is activation of the sympathetic nervous system [47], because leptin counteracts the effects of neuropeptide Y (NPY), a hormone that promotes food intake in the hypothalamus.

Adiponectin seems to play another interesting part in the pathophysiology of cachexia in HF. Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Araujo et al. [49] assessed adiponectin levels in BMI-matched cachectic ($n = 33$ patients) and non-cachectic ($n = 33$) patients with chronic HF to verify the hypothesis that a higher capacity for adiponectin production in cachectics may contribute to the wasting process. They showed a marked difference in adiponectin levels in cachectic (25.0 ± 12.3 μg/ml) and non-cachectic patients (14.7 ± 8.8 μg/ml), with higher levels in the cachectic group. Thus they speculated that adiponectin may play a causative role in the weight loss process and cachexia development in patients with chronic HF.

Van Berendoncks et al. [50] showed a significant decrease in the expression of the adiponectin receptor (AdipoR1) on the level of the skeletal muscle in patients with chronic HF, making a case for the existence of functional adiponectin resistance, which might provide one explanation for the compensatory rise in adiponectin levels. Adiponectin was found to be decreased in obesity. Adiponectin is the only adipose-specific protein known to date that is negatively regulated in obesity [51].

It needs to be established whether markers such as adiponectin or leptin may serve as surrogate biomarkers for the detection of an anabolic–catabolic dysbalance or even of the wasting process itself [52]. The wasting process in patients with chronic HF is an important risk factor and the assessment of cachectic status and should be included in other studies [2,12,53].

5. Novel therapeutic avenues in cachexia

Several factors have complicated the development of effective therapies for cachexia, particularly the multifactorial pathogenesis of the disease and the fact that the players involved in the pathophysiology of cachexia are rather pleiotropic, thus making drug development difficult. The focus of most clinical therapies has therefore been on nutritional interventions so far. Moreover, there has been little consensus on primary end points for clinical trials, which has hampered the assessment of the efficacy of treatments between studies [28]. Several clinical trials are underway to clearly determine the therapeutic benefit of new drug candidates.

5.1. Appetite stimulants

Several classes of drugs have been evaluated in their capacity to correct poor appetite, including progestin (a synthetic progesterone derivative), megestrol acetate, glucocorticoids, and cannabinoids [24]. A subgroup of appetite stimulants such as ghrelin and ghrelin agonists act by increasing the release of the appetite-inducing NPY in the hypothalamus or by blocking the appetite-reducing melanocortin receptors [30].

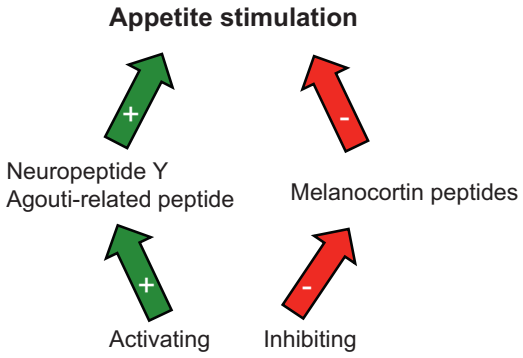

Fig. 2. Basic mechanism of appetite stimulation. Appetite stimulants act by inducing neuropeptide Y (NPY) and agouti-related peptide (AGRP) or by blocking melanocortin receptors.

A basic understanding of the mechanisms of feeding is required to understand the different therapeutic approaches, however, it needs to be acknowledged that an increase in food intake may compensate some weight loss, but a shift in tissue distribution, particularly in the loss of muscle may still be present. The two distinct subsets of neurons that control food intake are the neurons that produce NPY, which stimulate feeding, and melanocortin peptides, which act as inhibitors of eating (Fig. 2). Typically, when one of these players is activated, the other is inhibited. Whilst circulating leptin and insulin decrease appetite by inhibition of NPY- or agouti-related peptide (AgRP), melanocortin-producing neurons in the arcuate nucleus region of the hypothalamus stimulate it [30]. During weight loss NPY expressing neurons are activated, and melanocortin-producing neurons are inhibited, which are responses that stimulate eating and promote the recovery of depleted stores until sufficient food becomes available. Ghrelin activates NPY and AgRP thus yielding stimulation of food intake [30].

Early animal studies had suggested beneficial effects of appetite stimulants in tumor-bearing rats [54]. Several studies in cancer patients showed encouraging results. Megestrol acetate is a synthetic derivative of progesterone and has been most extensively researched in this regard. For example, Mantovani et al. [55] studied a total of 332 patients with different solid tumors and weight loss of at least 5% in the previous 3 months. Most patients presented with stage IV disease. Patients were randomly assigned to one of 5 treatment groups, receiving on a daily basis either (i) megestrol acetate, (ii) eicosapentaenoic acid, (iii) L-carnitine, (iv) thalidomide, or (v) a combination of the four substances. Only the combined therapy in the last group showed an increase in lean body mass by 2.1 ± 2.1 kg as assessed by Dual-Energy X-ray Absorptiometry (DEXA) scan after a follow-up of 4 months. Whilst the latter study used a dose of megestrol acetate of 320 mg daily, other researchers have used even higher doses demonstrating other effectiveness. For example, Jatoi et al. [56] used liquid suspension of megesterol acetate (600 mg/day) alone and in combination with eicosapentaenoic acid (1.09 g/day) in 421 patients with cancer-associated wasting. They found no statistically significant difference in weight change between treatment groups after 4 and 8 weeks. Loprinzi et al. [57] analysed 12 Patients with metastatic breast cancer with a high dose of 800 mg/day megesterol acetate. This study showed that both fat and lean body mass increased with megestrol acetate treatment. However, when analysing data from studies with appetite stimulants, it has to be kept in mind that stimulation of nutritional intake in cancer patients using megestrol acetate does not primarily restore lean body mass, but rather adipose tissue and water [57]. In addition vast arrays of drugs using different pharmacological approaches are currently under investigation in phase II clinical trials.

5.2. Selective androgen receptor modulators

Few studies investigated the anabolic effect of testosterone in cachexia to demonstrate a generally favorable effect of this agent to enhance body weight, lean body mass, and muscle strength [58–61]. Therapy, however, has many adverse effects including prostate hyperplasia, left ventricular hypertrophy and systolic and diastolic dysfunction [59], inflammation, coagulation, and platelet aggregation.

Selective androgen receptor modulators (SARM) belong to a relatively new class of therapeutics that possesses anabolic properties. Since 2008, the entire class of androgen receptor modulators has been prohibited in sports according to the regulations of the World Anti Doping Agency [62]. The first orally active nonsteroidal androgen receptor agonist LG121071 was described in 1999 [63]. An orally available derivative, LGD-2226, was later developed in 2001 [64]. Structural modifications led to the discovery of the first generation of the SARM family [65]. Lead compounds bind to androgen receptor with high affinity and demonstrate much improved pharmacokinetic profile and tissue selectivity in animal models [66]. Also LGD-3303 has SARM properties that are independent of its pharmacokinetic profile and suggesting that the principle mechanism for tissue-selective activity is the result of altered molecular interactions at the level of the androgen receptor [67].

Yarrow et al. [68] demonstrated that trenbolone, a potent testosterone analogue, exhibits selective androgen receptor modulators-like properties in orchiectomized rats. Intramuscular trenbolone (7.0 mg/week) vs. vehicle (sesame oil) maintained prostate mass and haemoglobin at the level of intact animals and reduced fat mass. A double-blind, placebo-controlled phase II clinical trial with SARM agent GTx-024 (enobosarm) in 120 healthy elderly men and women showed (3 mg of GTx-024) improvement in total lean body mass and physical function [69]. Importantly, in this study the effect was presented without the adverse consequences often seen with testosterone and other anabolic steroids. This observation may have potential implications for the use of SARMs in patients with cachexia. The mechanism through which steroidal and nonsteroidal SARMs produce selective tissue-specific anabolic responses has not been fully elucidated. However future studies will be necessary to evaluate the mechanism and long term effect of SARMs in patients with cachexia.

5.3. Amino acids

Protein depletion is a hallmark feature of cachexia [70]. L-carnitine a trimethylated amino acid roughly similar in structure to choline. In most studies, a dose between 2 and 6 g L-carnitine/day was adopted [70]. A phase III, randomized study showed that the treatment of amino acids and appetite stimulation agents in 60 patients with cancer-cachexia syndrome influence lean body mass (arm 1: L-carnitine 4 g/day + celecoxib 3 g/day, arm 2: L-carnitine 4 g/day + celecoxib 3 g/day + megestrol acetate 3.2 g/day). All patients received as basic treatment polyphenols 3 g/day, lipoic acid 3 g/day, carbocysteine 2.7 g/day and Vitamin E, A, C. After 4 months of treatment lean body mass assessed by DEXA increased significantly in both arms (arm 1: baseline 38.6 ± 9.5 kg and after treatment 41.0 ± 9.2 kg, $p = 0.03$, arm 2: baseline 41.3 ± 7.5 kg vs. after treatment 43.8 ± 6.4 kg, $p = 0.04$) as well as physical performance assessed by 6 minute walk test. This further demonstrated that a multi-targeted approach is may be the way forward in the field of cachexia research.

5.4. Anabolic catabolic transforming agents

The catabolic/anabolic imbalance that occurs in cachectic patients was in the focus of recent research. A small molecule

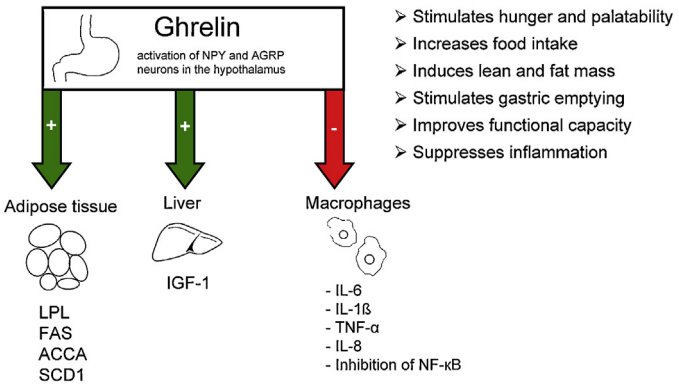

Fig. 3. Effects of ghrelin. Effects of ghrelin are based on activation of agouti-related peptide (AGRP) and neuropeptide Y (NPY). Ghrelin stimulates lipoprotein lipase (LPL), fatty acid synthase (FAS), acetyl-CoA carboxylase α (ACCA) and steaoryl-CoA desaturase-1 (SCD1) in adipose tissue. In liver, ghrelin stimulates insulin like growth factor-1 (IGF-1). In macrophages, ghrelin inhibits nuclear factor κB (NF-κB), interleukin 6 (IL-6), interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNFα) and interleukin 8 (IL-8).

termed MT-102 has both anti-catabolic and pro-anabolic activity. MT-102 was tested in the Yoshiada hepatoma rat model, which induces severe cachexia over a short period of time [71]. Tumor-bearing rats treated with 3.0 mg/kg/d MT-102 showed a gain of lean mass and body weight as well as an improved outcome. Based on these pre-clinical results, the ACT-ONE clinical trial, a multicentre, randomised, double blind, placebo-controlled, dose-finding utilizing MT-102 has recently commenced. This trial recruits cachectic patients with stage III and IV non-small cell lung cancer or colorectal cancer [29].

5.5. Naturally occurring peptide hormones

Hormones that regulate food intake can be separated into those that act rapidly to influence individual meals and those that act more slowly to promote the stability of body fat stores [30]. Ghrelin is a growth hormone secretagogue and is secreted mainly from the stomach into the bloodstream under fasting conditions (Fig. 3). Physiologically, ghrelin induces the release of growth hormone, regulates appetite and has anti-inflammatory properties [2]. Ghrelin effects on food intake or body weight are mediated through the activation of specific AgRP-, NPY-neurons in the hypothalamus [72]. In rat hypothalamic synaptosomes Brunetti et al. [73] found that ghrelin did not modify dopamine or norepinephrine release, but inhibited serotonin release. The appetite-stimulating activity of ghrelin could be mediated by inhibition of serotonin release.

Ghrelin may be influence left ventricular dysfunction and attenuate the development of cardiac cachexia. For testing this hypothesis Nagaya et al. analysed the influence of ghrelin in rats with produced chronic HF [74]. Myocardial infarction was produced in male wistar rats ($n = 31$ infarct rats) and randomly divided into 2 groups to receive either ghrelin ($n = 16$) or placebo ($n = 15$) for 3 weeks. Similarly, 26 sham-operated rats were randomized to receive ghrelin ($n = 13$) or placebo ($n = 13$). Rat ghrelin 100 mg/kg was injected subcutaneously in both chronic HF rats and sham-operated rats. The results of this study showed that treatment with ghrelin increased posterior wall thickness, inhibited the progressive LV enlargement, and thereby reduced the LV wall stress in rats with chronic HF [74]. With this rat model it was shown that ghrelin has cardiovascular effects, including increased cardiac output and decreased blood pressure.

Thus, supplementation of ghrelin could be a new therapeutic approach in the treatment of cardiac cachexia and should be tested in large randomized trials [75,76]. Moreover, administration of ghrelin or ghrelin agonists has been shown to decrease expression of inflammatory cytokines in monocytes and T-cells [76]. Thus, ghrelin exhibits anticachectic actions via both growth hormone-dependent and -independent mechanisms [77]. Plasma ghrelin levels are elevated in cachectic patients possibly through a compensatory mechanism due to the catabolic/anabolic imbalance [77].

Pape et al. [78] showed in a study of 7 malnourished patients with COPD that subcutaneous injections of recombinant growth hormone (0.05 mg/kg daily) caused substantial weight gain (mean 2.23 ± 0.45 kg, $p < 0.001$) after 3 weeks of treatment. Also they showed an improved nitrogen balance (3.49 ± 0.46 g/day) during the first week of treatment. Thus they concluded that growth hormone administration might be a useful adjunct of malnourished COPD patients and should be tested in large, placebo controlled, randomised studies. A promising approach is the orally active ghrelin receptor agonist anamorelin which is under development for the management of non-small lung cancer associated cachexia/anorexia [28,79]. Thus naturally occurring peptide hormones such as ghrelin and ghrelin receptor agonists are may be a promising approach for the treatment of cachexia in different diseases.

6. Conclusion

The most important point about cachexia is to create awareness for its presence and development and to teach clinicians in its early recognition. Therapies against muscle wasting during cachexia have concentrated on either increasing food intake or normalizing the persistent metabolic alternations that take place in the patient. By contrast, patients with cachexia fail to adapt metabolism to spare protein stores, resulting in a persistently negative nitrogen balance that cannot be corrected with nutrition alone. Approval of drugs for the treatment of cachexia is currently only available for AIDS-associated cachexia. Drugs include, for example megesterol acetate [80] and growth hormone somatropin [81]. Other candidate targets for therapeutic interventions include transcription factors and their stimulators, neurohormonal antagonists, and anti-inflammatory drugs. To date, we are left with little guidance how to treat our cachexia patients, until results of ongoing studies are available, aggressive therapy of cachexia inducing illness and comorbid conditions appears as best possible practice [82].

Contributors

Nicole Ebner wrote the first draft of the manuscript and all authors provided guidance and assistance in the writing and editing of the manuscript; and gave sagely advice. All authors have seen and approved the final version of the draft.

Competing interests

There are no conflicts of interests.

Provenance and peer review

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