Maturitas 75 (2013) 199–206

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Mechanism and novel therapeutic approaches to wasting in chronic disease

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ARTICLE INFO

Article history:
Received 15 March 2013
Accepted 20 March 2013

Keywords:
Cachexia
Wasting
Therapy

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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http://dx.doi.org/10.1016/j.maturitas.2013.03.014

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