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Review

Control of food intake and muscle wasting in cachexia☆

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ABSTRACT

Cachexia is characterized by anorexia, weakness, weight loss, and muscle wasting. Anorexia and muscle wasting are the key features of cachexia and they affect mortality, morbidity, and quality of life. Consistent studies have found that feeding-regulating peptides such as melanocortin, ghrelin, and leptin are related to muscle metabolism, and the balance of catabolism and anabolism in muscle is regulated in the hypothalamus, which also regulates appetite and energy expenditure. In cachexia, proinflammatory cytokines, such as TNF-α, IL-1, IL-6 and Angiotensin II induce muscle atrophy. The mechanism is suggested via upregulation of MuRF1 and MAFbx. In contrast, the orexigenic peptide, AgRP and ghrelin have the effect to decrease proinflammatory cytokines and increase body weight, food intake, and muscle mass.

The understandings of the pathological mechanism of anorexia and muscle metabolism in view of the crosstalk between brain and muscle will open the new way for the management of cachexia. In this review, we describe recent experimental and clinical studies that have examined the regulation of food intake and muscle wasting in cachexia.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

1. Introduction

Food intake is controlled by a complex network that depends on the central regulation of energy homeostasis. Signals that regulate food intake are ultimately integrated or coordinated by central mechanisms, particularly those in the hypothalamus. Many factors must be considered in the hypothalamic regulation of food intake, and the interactions between adiposity and the central neuropeptidergic cascade downstream of leptin are increasingly being studied.

Cancer cachexia is the main cause of death in approximately 20% of cancer patients (Inui and Meguid, 2003). Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (Evans et al., 2008). Cachexia is highly associated with anorexia, weakness, weight loss, muscle wasting, and inflammation. Those phenotypes of cachexia affect mortality, morbidity, and quality of life (Lainscak et al., 2008).

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

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

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

2.1. Melanocortins

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

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

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

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

2.2. Leptin

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

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

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

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

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

2.3. Ghrelin

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

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

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