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A hypothesis for a possible synergy between ghrelin and exercise in patients with cachexia: Biochemical and physiological bases ☆

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ABSTRACT

This article reviews the biochemical and physiological observations underpinning the synergism between ghrelin and ghrelin agonists with exercise, especially progressive resistance training that has been shown to increase muscle mass. The synergy of ghrelin agonists and physical exercise could be beneficial in conditions where muscle wasting is present, such as that found in patients with advanced cancer. The principal mechanism that controls muscle anabolism following the activation of the ghrelin receptor in the central nervous system involves the release of growth hormone/insulin-like growth factor-1 (GH/IGF-1). GH/IGF-1 axis has a dual pathway of action on muscle growth: (a) a direct action on muscle, bone and fat tissue and (b) an indirect action via the production of both muscle-restricted mIGF-1 and anti-cachectic cytokines. Progressive resistance training is a potent inducer of the secretion the muscle-restricted IGF-1 (mIGF-1) that enhances protein synthesis, increases lean body mass and eventually leads to the improvement of muscle strength. Thus, the combination of ghrelin administration with progressive resistance training may serve to circumvent ghrelin resistance and further reduce muscle wasting, which are commonly associated with cachexia.

Introduction

Cachexia is a multifactorial syndrome characterized by significant losses of skeletal muscle mass, fat stores, appetite, and performance as well as by chronic inflammatory and metabolic abnormalities [1]. Cachexia, therefore have major negative consequences on patients' morbidity, mortality, quality of life and their ability to undergo potentially curative treatments. At the present time, there is no single drug or intervention that is totally effective in counteracting the multitude of physiological systems affected by cachexia [2,3]. Thus, multiple systemic approaches consisting of pharmacological (e.g., different drugs that address the numerous pathophysiological abnormalities of cachexia) and non-pharmacological interventions (e.g., exercise programs that provide a "whole body" systemic adaptation of the neuromuscular, endocrine, immune, cardiovascular, and respiratory systems) should be investigated.

There is a host of new investigational drugs currently being tested in Phase 1, 2 and 3 trials [4]. Among these include ghrelin, a protein hormone produced primarily by the stomach with primary targets in the anterior pituitary (e.g., production and release of growth hormone: GH) and the hypothalamus (production of Neuropeptide Y) and with secondary peripheral actions on insulin-like growth factor-1 (IGF-1) release from the liver [5]. Due to its anti-cachectic and orexigenic actions, ghrelin has been proposed in the treatment of cachexia related diseases, including congestive heart failure, COPD, renal failure, and cancer [6]. Preliminary results using ghrelin and its agonists are indeed promising as both murine and human models showed increased in lean (muscle) mass, and reductions in some of the multiple symptoms including improvement in appetite [7–8]. Regular physical exercise, in particular, progressive resistance training (PRT) has been used effectively over the last 65 years to increase muscle mass, not only in the athletic population, but also in many clinical oncology populations, including patients with breast, colon, and prostate cancers [9]. This form of training has been proposed as a potentially effective intervention in terms of attenuating muscle wasting and suppressing the pro-inflammatory drive brought on by cachexia [10]. Furthermore, PRT is shown to stimulate GH and IGF-1, two protein hormones known for their anabolic stimulus to assist in the muscle protein synthetic process. Coincidently, ghrelin is most likely active in the muscle synthesis process by similar biological and physiological pathways. Thus, it stands to reason that combined pharmacological (e.g., ghrelin) and non-pharmacological (e.g., PRT) approaches could result in a synergistic action on building muscle mass and perhaps "arresting" or overcoming the increased

☆ A preliminary hypothesis was presented in September 2012 at the Cachexia Congress in Boston (MA, USA) with the title, Effect of ghrelin agonists on muscle mass and function: synergism with exercise?

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muscle catabolism that is typically prevalent in cachexia [11]. This brief review highlights the biochemistry of ghrelin and its central and peripheral physiological actions. In addition, this review identifies the relationship between PRT and its anabolic action on muscle mass synthesis with a primary focus on the actions of GH and IGF-1. The review concludes with a rationale of combining ghrelin administration with PRT as a probable and effective pharmacological and non-pharmacological treatment to alleviate significant losses in muscle mass due to cachexia.

Hypothesis (Figure 1)

General overview of ghrelin

Ghrelin is a 28 amino-acid peptide with hormonal function secreted primarily from the stomach wall cells in response to mechanical (e.g., when the stomach is empty), neuronal (e.g., vagal nerve activation) and physiological stimuli (e.g., high blood concentration of releasing factors) [12]. In humans, the ghrelin gene is located in chromosome 3 between the loci p25 and 26. The main mRNA codifies for the 117 amino-acid preproghrelin, which is then enzymatically cleaved to produce ghrelin and obestatin. Ghrelin and obestatin are unique in that they are two hormones with different functions that arise from the same gene. They are two antagonistic peptides in the regulation of growth hormone (GH) secretion and food intake. There are several ghrelin isoforms found in humans that have been identified in pathologies linked to an unbalanced energy homeostasis [13]. Once released, ghrelin passes the blood–brain barrier (BBB) and targets the hypothalamus (Fig. 1), where it binds with the growth hormone secretagogue receptor (GHSR), a seven-trans-membrane domain receptor (7TMR) [14]. GHSR was first observed in somatotropic cells in the anterior pituitary gland, where they constitute more than 40% of the total gland mass [15]. The effect of the GHSR stimulation is the release of growth hormone (GH or somatotropin). GH binds selectively to the growth hormone receptor (GHR) and acts as a physiological agonist [15–16]. GHR is expressed in skeletal muscle, bones, adipose tissue, liver, heart and kidney. Activation of GHR induces the synthesis of insulin-like growth factor type 1 (IGF-1) in most tissues, with the liver being the organ that contributes the major part to circulating IGF-1 levels. IGF-1 is bound to IGF-binding protein (IGFBP), which prolongs IGF-1 half-life and regulates its availability for target tissues. There are also various non-hormonal stimuli that affect the frequency and magnitude of the GH pulse such as gender, age, adiposity, circadian rhythm during the sleep and awake phases, diet and exercise [17].

Role of ghrelin agonists

Central effect of ghrelin

This paragraph only mentions some of the most important roles of ghrelin in the central nervous system (CNS). The aim of this work is not to discuss the biological meaning of cell signaling redundancy and/or the interrelation between cytokines and hormones and their pharmacological significance. Our goal is to give to the reader the molecular basis to understand the medical hypothesis discuss herein.

Once the stomach wall cells produce ghrelin, the latter reaches the hypophysis and binds to the ghrelin receptor of somatotroph cells to induce the release of growth hormone (GH or somatotropin) [90,93]. GH secretion occurs in a pulsatile pattern and is regulated by other hypothalamic hormones [16]. Other than ghrelin, it is well known that GH-releasing hormone (GHRH) induces GH secretion, but binds over a different receptor than that of ghrelin [19]. On the contrary, the hormone somatostatin (somatotropin release inhibiting factor or SRIF) inhibits the secretion of GH. Ghrelin is able to inhibit the release of somatostatin centrally and peripherally and vice versa [85,88]. Ghrelin is also able to bind to specific neurons in the hypothalamus (Arcuate Nucelus), triggering the GHRH liberation to potentiate the action of ghrelin to produce a peak of GH [95]. Specifically, GHRH binds as direct agonist on the GHRH receptor situated in the membrane of the somatotroph cells, but does not bind on ghrelin receptors as direct agonist. Indeed, GHRH acts as an allosteric modulator on the ghrelin receptor to potentiate the action of ghrelin into somatotroph cells [86,91].

Ghrelin activates two main pathways in the hypothalamus: the GH/IGF-1 axis and the orexin cells. From the hypothalamus, ghrelin goes into the hypophysis by way of the median eminence [20]. Both receptors are expressed in the somatotropic cell membranes and once activated, they work jointly to produce and liberate the growth hormone (GH) in the blood stream [21]. GHRH receptor starts its intracellular downstream via cAMP. Oppositely, the ghrelin receptor acts on the liberation of Ca^{2+} as second messenger [86,87]. Recently, researchers have discovered neurons that secrete ghrelin into the hypothalamus that act to potentiate the effect of ghrelin produced by stomach wall cells [18]. However, the most significant organ for the production and regulation of ghrelin is still the stomach [89,92]. In the hypothalamus, ghrelin activates the NPY cells that start a series of events that act positively on the NPY gene expression and negatively on the activation of melanocortins neurons [22]. Physiological effects attributed to NPY release include: stimulation of food intake [23], inhibition of anxiety in the CNS [24], modulation of circadian rhythm [25], release of pituitary hormones (e.g., luteinizing hormone) [26], modulation of hippocampal activity in terms of adaptive behavior and long-term memory [27], decrease of pain transmission [28], increase in vasoconstriction [29] and inhibition of insulin release [30]. Increased circulating ghrelin levels are also positively correlated with increased sex hormones levels [96]. This clinical correlation can be also used as pharmaceutical intervention to ameliorate function of advanced cancer patient in case of moderate or severe hypogonadism [97]. Difference in pharmacodynamics of ghrelin and other ghrelin agonists have been reported [94].

Peripheral effects of ghrelin: biochemical aspects

GH stimulates the synthesis of IGF-1 in most tissues [31]. The liver is the organ chiefly responsible for the production of serum IGF-1. GH administration causes rapid upregulation of IGF-1 mRNA and protein in the liver. Unlike GH, serum IGF-1 levels are quite stable in healthy humans and show little day-to-day intra-individual variability. Serum IGF-1 levels above or below the normal age-corrected range is a good indicator of GH dysfunction [32]. The effects of IGF-1 are mediated mainly by the type 1 IGF receptor (IGF1R). This has tyrosine activity and signals through the phosphatidylinositol 3 kinase (PI3 K)/AKT pathway. IGF-1 also binds to the insulin receptor (IR) but with much lower affinity than the IGF1R. The IR and IGF1R are dimeric transmembrane receptors and can form functional hybrids. The role of hybrid receptors in cellular responses remains unclear. GH secretion is regulated by negative feedback since elevated serum IGF-1 inhibits GH secretion [33]. The GH receptor (GHR) is ubiquitously expressed [34]. Physiologists have been able to identify a GHR in the skeletal muscle membrane, but it is still under investigation because its role in myocyte metabolism is not clear [35–37]. GHR is a transmembrane receptor that undergoes dimerization after binding of GH. The phosphorylation of receptor associated Janus 2 (JAK2) leads to the formation of a docking site for members of the signal transducers and activator of transcription (STAT) family of protein transcription factors [38]. The JAK/STAT signaling pathway is

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