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Research review

Exercise and ghrelin. A narrative overview of research ☆

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ABSTRACT

Since its discovery in 1999, ghrelin has been implicated in a multiplicity of physiological activities. Most notably, ghrelin has an important influence on energy metabolism and after the identification of its potent appetite stimulating effects ghrelin has been termed the '*hunger hormone*'. Exercise is a stimulus which has a significant impact on energy homeostasis and consequently a substantial body of research has investigated the interaction between exercise and ghrelin. This narrative review provides an overview of research relating to the acute and chronic effects of exercise on circulating ghrelin (acylated, unacylated and total). To enhance study comparability, the scope of this review is limited to research undertaken in adult humans and consequently studies involving children and animals are not discussed. Although there is significant ambiguity within much of the early research, our review suggests that acute exercise transiently interferes with the production of acylated ghrelin. Furthermore, the consensus of evidence indicates that exercise training does not influence circulating ghrelin independent of weight loss. Additional research is needed to verify and extend the available literature, particularly by uncovering the mechanisms governing acute exercise-related changes and characterising responses in other populations such as females, older adults, and the obese.

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Introduction

After an arduous search, in 1999 Kojima and colleagues reported the purification and identification of an endogenous ligand able to bind to the orphan growth hormone secretagogue receptor (GHSR-1a) and stimulate growth hormone (GH) secretion via a novel independent pathway (Kojima, 2008; Kojima et al., 1999). The researchers termed this peptide 'ghrelin' as a tribute to its potent GH-RELeasing action (Kojima, Hosoda, Matsuo, & Kangawa, 2001). Unbeknown at the time, the importance of ghrelin in metabolism would turn out to be much more wide ranging than initially recognised.

Ghrelin is a 28 amino acid peptide produced primarily from P/D_1 cells in the stomach fundus, with much lesser amounts being synthesised in the intestine, pancreas and other peripheral organs

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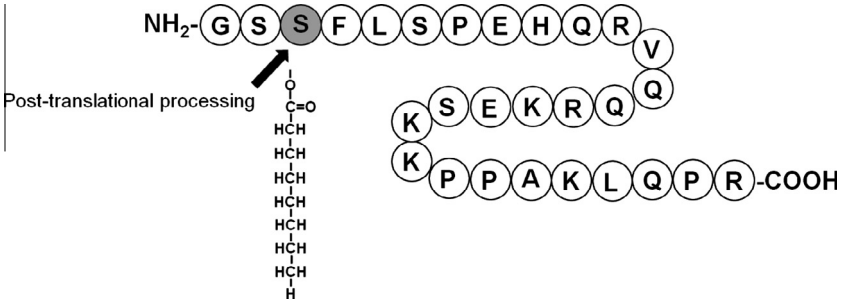

Fig. 1. Post-translational processing yielding acylated ghrelin via addition of medium chain fatty acids to serine-3. Adapted from Kojima et al. (1999).

including the testis, heart, adipose tissue and skin (Gutierrez et al., 2008; Stengel & Taché, 2012). Upon fasting, and/or low circulating levels of glucose and insulin, ghrelin is secreted into the circulation where it is present in two forms, acylated and unacylated (~1:4 ratio) (Stengel, Goebel, Wang, & Taché, 2010). Acylated ghrelin is made explicit by the post-translational addition of a medium chain fatty acid, typically octanoate or decanoate, to its third amino acid residue (serine), a modification catalysed by ghrelin O acyltransferase (GOAT) (Gutierrez et al., 2008; Yang, Brown, Liang, Grishin, & Goldstein, 2008) and which is essential for ghrelin to bind to the GHSR-1a to exert its primary hormonal and metabolic actions (Kojima & Kangawa, 2005) (Fig. 1).

The biological activities of ghrelin are multifaceted which is consistent with the widespread distribution of its receptor in the brain e.g. hypothalamus, (Schellekens, Dinan, & Cryan, 2010) and peripheral tissues e.g. vagal afferents, adipose tissue, spleen, myocardium, thyroid, adrenal gland (Stengel & Taché, 2012). In addition to its well defined role as a regulator of GH secretion, ghrelin is also understood to harbour complex roles in glucose metabolism (Delhanty & van der Lely, 2011), gastrointestinal (Levin et al., 2006; Tack et al., 2006), reproductive (Muccioli et al., 2011), immune (Taub, 2008) and cardiovascular (Nagaya et al., 2001; Vlasova, Järvinen, & Herzig, 2009) function. Unquestionably however, the most notable discovery has been the identification of ghrelin's central role in appetite regulation and energy homeostasis whereby ghrelin remains the only known circulating peptide which stimulates appetite and feeding. Research surrounding this unique characteristic of ghrelin has captured significant attention.

There is an extensive body of literature demonstrating that ghrelin administration augments food intake and over time leads to gains in body weight/adiposity (Asakawa et al., 2003; Nakazato et al., 2001; Shintani et al., 2001; Wren et al., 2000, Wren, Small, et al., 2001). In humans, the appetite stimulating properties of ghrelin were first identified when hunger was reported as a side effect during an investigation examining the influence of ghrelin administration on GH dynamics (Arvat et al., 2001). Thereafter, in a landmark study, Wren, Cohen, et al. (2001) published findings demonstrating a striking increase in hunger perceptions and *ad libitum* energy intake in response to intravenous ghrelin infusion. These results have subsequently been confirmed by other investigators in both lean and obese individuals (Druce et al., 2005, 2006). The diurnal circulating profile of ghrelin is also consistent with the notion that ghrelin influences appetite and feeding with circulating levels peaking before meal times and falling thereafter in proportion to the amount of ingested energy (Callahan et al., 2004; Cummings et al., 2001). Ghrelin has subsequently been labelled the 'hunger hormone' (Higgins, Gueorguiev, & Korbonits, 2007).

The impact of ghrelin on energy metabolism extends beyond appetite regulation. Specifically, ghrelin promotes weight gain and adiposity by reducing energy expenditure (Pfluger et al., 2008) and fat oxidation (increases the respiratory exchange ratio) (Wortley et al., 2004), whilst promoting fat storage and the motivation to seek out energy dense food (Shimbara et al., 2004). In humans, circulating concentrations of ghrelin are inversely associated with body mass index and multiple measures of adiposity (Shiiya et al., 2002). Ghrelin levels are reduced in obese individuals (Cummings et al., 2002; Tschöp et al., 2001; Vendrell et al., 2004) which may at least partly be mediated by impaired insulin sensitivity/hyperinsulinemia (McLaughlin, Abbasi, Lamendola, Frayo, & Cummings, 2004). Augmented ghrelin therefore does not appear to be a mechanism which perpetuates obesity. Conversely, an attenuated postprandial suppression of ghrelin has been reported in obese individuals requiring a higher energy ingestion before a post-meal suppression is observed (English, Ghatei, Malik, Bloom, & Wilding, 2002; Le Roux et al., 2005). This may contribute to impaired satiety signalling in obesity and the propagation of positive energy balance.

In addition to its role in mediating the homeostatic control of energy balance, recent research has identified a role of ghrelin in the hedonic component of eating behaviour with studies showing that ghrelin increases the preference for foods with high palatability or high fat content (Egecioglu et al., 2010; Perello et al., 2009). This effect appears to be mediated by the activation of key brain regions associated with pleasure and reward (amygdala, orbitofrontal cortex, anterior insula and striatum) (Malik, McGlone, Bedrossian, & Dagher, 2008).

With the recognition of the apparent centrality of ghrelin in the control of appetite and energy metabolism it was not long before interest developed concerning the impact of exercise on ghrelin. Exercise influences diverse aspects of energy homeostasis and metabolism including appetite, energy expenditure, substrate utilisation or partitioning, body weight and composition. A decade ago the first studies investigating the impact of exercise on ghrelin appeared in the literature (Dall et al., 2002; Kallio et al., 2001) and since this time there has been an explosion of research within the area. This review aims to provide a narrative overview of studies that have examined both the acute and chronic impact of exercise on circulating levels of ghrelin in adult humans. At this point it is important to emphasise that ghrelin, in the general sense, is composed of two peptide variants, namely acylated and unacylated (Kojima et al., 1999; Yang, Brown, Liang, Grishin, & Goldstein, 2008). References to 'ghrelin' typically refer to total ghrelin i.e. measurements based on assays which detect both circulating forms. This distinction is critical given that the physiological actions of acylated and unacylated ghrelin vary considerably. Acylated ghrelin binds and signals through the GHSR-1a to induce GH secretion and to stimulate appetite and feeding. Unacylated ghrelin cannot bind to this receptor, and although it was initially thought of as inactive, it is now known to possess diverse metabolic effects (e.g. effects on insulin sensitivity, glucose and lipid metabolism), some of which may modulate the effect of acylated ghrelin (Delhanty, Neggers, & van der Lely, 2012). Of particular