Decreased ghrelin levels: the cause of obesity and weight regain?

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“…our research group recently found that baseline plasma ghrelin levels could explain the variability in body weight regain after an energy restriction treatment.”

Ghrelin is a circulating orexigenic hormone which is implicated in both the short-term control of food intake at single meals and in long-term body weight regulation. Due to the potent orexigenic action of this hormone, it would be expected that obese subjects would show elevated ghrelin levels that could contribute to pathogenesis of obesity. However, it was observed that ghrelin is downregulated in human obesity and fasting plasma ghrelin concentrations were negatively correlated with body weight, percentage body fat, BMI and fat mass, as well as with leptin and insulin [1]. This downregulation was proposed to represent a physiological adaptation to the positive energy balance associated with obesity [1].

In the same line of obesity, our research group recently found that baseline plasma ghrelin levels could explain the variability in body weight regain after an energy restriction treatment. Thus, after a weight reduction induced by an 8-week balanced hypocaloric diet, subjects who regained at least 10% of the lost weight 6 months later appeared to have lower fasting plasma ghrelin levels at all times during the study than those that maintained body weight. These finding was accompanied by higher fasting plasma leptin levels in the weight regain group compared with the maintained group of patients [2]. These counterintuitive findings of ghrelin and leptin suggest that weight regain may be associated with some central or peripheral resistance to both hormones, in the same way as obesity [2]. Indeed, a recent study demonstrated that obesity causes central ghrelin resistance in hypothalamic neuropeptide Y and agouti-related peptide circuits [3]. It was postulated that the hypothalamus senses excessive positive energy balance or calorie intake and responds by suppressing the neuroendocrine ghrelin axis by reducing the acylated and des-acylated forms of plasma ghrelin, suppressing the ghrelin and Goat mRNA in the stomach and the growth hormone secretagogue receptor mRNA levels in the hypothalamus of diet-induced obesity mice compared with controls [3]. These results, together with a previous study demonstrating that ghrelin increases UCP2, suggest that the primary role of ghrelin is to prevent starvation rather than promote obesity since UCP2 enhances peripheral fat oxidation and as a result prevents excessive fat deposition [4]. Besides being an important hormone that promotes food intake, ghrelin has potent lipogenic action [5] and preproghrelin-derived peptides have a role in adipogenesis through an autocrine/paracrine mechanism [6]. However, these actions appear to be mediated mainly in the absence of UCP2. The acute actions of ghrelin on food intake require uncoupling protein UCP2 for a complete food intake response and chronic ghrelin treatment either via osmotic minipumps or daily intraperitoneal injections, which favor lipogenesis and induce more potentiated body weight gain in UCP2-knockout mice than in UCP2 wild-type mice [4].

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The role of ghrelin in appetite and food intake is well established. Therefore, approaches for interruption of ghrelin signaling have been widely tested, from pharmacologic agents to surgical strategies [7]. However, there is currently no ghrelin antiobesity drug on the market due to lack efficacy and lack of sustained weight loss [7]. Bariatric surgery is an increasingly popular treatment option for individuals with extreme obesity and significantly decreases ghrelin levels after surgery [8]. Although for some individuals the weight loss and improvement in comorbidity and mortality is successful, a significant minority of patients experience suboptimal outcomes including less than expected weight loss and premature weight regain [9]. The reasons for these outcomes are not well understood and behavioral and physiological processes have been proposed [9]. However, greater decreases of postoperative ghrelin levels could be involved in the long-term weight maintenance success in the same line of findings after a diet-induced weight loss [2] or after intragastric balloon treatment [10] by which higher ghrelin levels were related to greater treatment efficiency.

Ghrelin is a ubiquitously expressed hormone with endocrine, cardiovascular, immunological, reproductive and behavioral effects, playing an important role in the physiological functions of the organism [11,12]. In this context, rather than its demonstrated activity as a potent circulating orexin, controlling energy expenditure, adiposity and growth hormone secretion, ghrelin also has a functional role in regulation of immune responses [13]. Recently published reports demonstrated anti-inflammatory effects of ghrelin in vitro and in vivo at the systemic level and in skeletal muscle [14]. Ghrelin administration following high-fat feeding results in a novel model of weight gain with low inflammation, high mitochondrial enzyme activities and normalized triglycerides in skeletal muscle, which suggests a potential positive metabolic impact of ghrelin in fat-induced obesity [14]. Moreover, it was demonstrated that ghrelin inhibits the expression of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α and other leptin-induced cytokine expression [15] and also reduces the phagocytic activity and modulates free radical production, adherence and migration of peritoneal macrophages [16]. This fact is reinforced by the aforementioned relationship between ghrelin and UCP2, a mitochondrial protein important for reducing reactive oxygen species, and therefore it maintains a healthy phenotype and extends life span [4].

Obesity is characterized by a state of chronic low-grade inflammation, which is a putative link between this metabolic disorder and its comorbidities [17]. The susceptibility to regain the diet-induced weight loss has also been associated with an advanced proinflammatory state [18]. Therefore, the differential levels found in ghrelin and leptin levels between subjects prone to regain the weight loss and those able to maintain it are consistent with this advanced proinflammatory state because leptin has been proposed as a proinflammatory adipokine and ghrelin appears to have anti-inflammatory and antioxidant properties [2]. In fact, ghrelin levels increase after a caloric restriction treatment to induce weight loss and it has been widely demonstrated that this therapy improves the oxidative and proinflammatory stress associated with obesity [17,19,20]. Moreover, it was recently proposed that a healthy neuropeptide system is needed as neuropeptides such as ghrelin are intrinsic modulators of the immune response and that a failure in the neuropeptide/receptor signaling system affects the maintenance of immune homeostasis [13].

Taking these observations together, ghrelin appears to play a role in maintaining a balance in the physiological functions of the organism to guarantee a healthy life span, which could be negatively influenced by the interruption of ghrelin signaling. Therefore, the decrease in ghrelin could be a cause of obesity and related to the development of obesity comorbidities by inducing deregulation in the body system and energy homeostasis as well as in inflammation and oxidative stress protection.

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