Ghrelin and Leptin in Fasting

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Animals and humans when exposed to conditions of energy deficit make compensatory changes in the efficiency of energy utilization and activity to conserve energy for essential functions, thereby maintaining homeostasis. The decrease in whole body energy expenditure stems from changes in metabolism at the cellular level. Cellular metabolism is modified in response to activation of neural and hormonal regulatory systems, such as down-regulation of sympathetic outflow to major organs, e.g. heart, increased sympathetic outflow to white adipose tissue (to mobilize lipids) and changes in secretion of ghrelin and leptin [1].

Ghrelin is an appetite-stimulating peptide secreted mainly by the stomach and acts as a ligand for the growth hormone (GH) secretagogue receptor [2]. Ghrelin is secreted in a pulsatile manner, peaking at 2000 h, rising before meals and returning to baseline levels after food ingestion. Since ghrelin discovery in 1999, it has been studied as a potential anti-obesity therapeutic target because central and peripheral ghrelin administration increases appetite and promotes food intake in rodents and humans and, in long run, induces adiposity in rodents [3]. This implies its importance in feeding behaviour and provides a link between the stomach and brain in the regulation of energy homeostasis. Acylated ghrelin, having an n-octanoyl moiety attached to the serine at position 3, is the most active form of ghrelin and accounts for only 5%–10% of the total circulating ghrelin. The enzyme responsible for ghrelin acylation has been recently discovered. The enzyme, ghrelin-O-acyltransferase (GOAT) is a member of the membrane-bound acyltransferase family of proteins, and information regarding the regulation of its expression is limited. Acylated ghrelin stimulates food intake and induces weight gain [4].

In addition to the orexigenic effects of ghrelin, several other potential functions of ghrelin have been recently elucidated, including its role in gastrointestinal motility, gastric acid secretion and various cardiovascular, immunological, reproductive and behavioural processes [5].

Leptin is a satiety hormone, secreted in proportion to adipose tissue, informing the hypothalamus of the status of energy stores [6]. Leptin plays a crucial role in body weight homeostasis by regulating food intake and energy expenditure. Leptin receptors are expressed in several areas of the brain and mediate the central actions of leptin. High leptin levels signal the presence of sufficient energy stores to certain sites in the central nervous system, which respond by reducing appetite and increasing energy expenditure to prevent obesity [7]. In addition, leptin can promptly signal the shift between sufficient and insufficient energy intake. For example, leptin levels rapidly fall with the onset of starvation, disproportionally to changes in adipose tissue mass. The fall in leptin levels is a signal for the brain to initiate adaptive responses to starvation. It has been proposed that this dual leptin restraint is the major regulatory arm of the feedback communication between the periphery and the hypothalamus for weight homeostasis [8].

Immunoneutralization of circulating plasma ghrelin with specific IgG anti-ghrelin antibodies causes a marked increase in plasma leptin and decrease in food intake. In contrast, exogenous leptin reduced ghrelin and attenuated food intake, and these effects can be reversed by the administration of specific IgG anti-leptin antibodies [8]. These results clearly support the hypothesis that ghrelin negatively controls plasma release of leptin and *vice-versa* that leptin has a counter-regulatory influence on ghrelin release and action.

In the present issue of the journal, Syed et al conjunctively measured ghrelin, leptin and free fatty acid (FFA) in 18-hour fasted mice [9]. They found that FFA concentration was approximately two-fold higher in fasted mice than that in control mice, and that ghrelin significantly increased, whereas leptin levels were considerably lower in fasting mice. Such changes could be interpreted as compensatory mechanisms for conserving energy under conditions of unavailability of food.

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Although energy balance is tightly regulated, eating disorders are a major cause of morbidity and mortality in modern societies. Anorexia nervosa (AN) is an often fatal eating disorder in which the affected individual severely restricts food intake and increases energy expenditure despite progressive emaciation. In patients with AN, higher circulating ghrelin levels with lower leptin levels are observed [10]. Recently, increased levels of ghrelin because of increases in inactive, i.e. nonacylated ghrelin, have been observed in patients with AN. However, acylated ghrelin infusions fail to induce appetite in patients with AN and only tend to increase drowsiness. Understanding the biological mechanisms that induce appetite and saturation will not necessarily provide the sole key to sufficiently treat complex diseases such as AN.

Obesity is one of the most common metabolic diseases which associated with high levels of leptin. Although previous studies demonstrate that leptin can be a most effective pharmaceutical preparation for treating obesity in leptin-deficient states [11], the administration of exogenous leptin fails to reduce adiposity significantly in most cases of human obesity that are characterized by increased adipocyte leptin content and high circulating leptin levels, reflecting a state of leptin resistance. Theoretically, weight loss achieved by lifestyle modifications or currently available anorectic medications should restore leptin sensitivity, and thereafter leptin treatment might help maintain weight loss. In addition, the development of a ghrelin antagonist, or the development of a mechanism to inhibit ghrelin release to control appetite, may be an important pharmaceutical development for the management of obesity.

Mammals that hibernate (grizzly bears or golden mantled ground squirrels) are unique models for studies on food intake and body condition because of their circannual cycles of obesity and anorexia. Control of the food intake pathway in hibernators is not completely understood, but hormones such as ghrelin, leptin, insulin and adiponectin may play an important role in the seasonal changes in food intake observed in these animals. Therefore, investigations of these animals may reveal crucial information regarding ghrelin and leptin that can be translated into novel and effective strategies or therapies for easy maintenance of a healthy body weight.

While there is a general lack of knowledge on how different diets, physical activities, mental conditions, gender and/or ageing influence the central and peripheral energy control of these hormones on-going and future research is likely to elucidate the physiological role played by ghrelin and leptin.

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