HORMONES 2016, 15(2):186-196

Review

Effects of ghrelin in energy balance and body weight homeostasis

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ABSTRACT

Ghrelin is a gut peptide composed of 28 amino acids mostly secreted in the gastric fundus mucosa. It was isolated and described in 1999 by Kojima et al. and only three years later its specific receptor, GHSR1a, was also identified. Ghrelin, the endogenous ligand for the GH secretagogue receptor, is the only peripheral orexigenic hormone that activates the receptors to be found especially in the appetite center (hypothalamus and pituitary gland). Ghrelin is present in human plasma in two forms: an inactive form known as *deacylated ghrelin*, and an active form called *acylated ghrelin* synthesized under the action of ghrelin O-acyltransferase enzyme (GOAT). The literature even mentions an extremely complex ghrelin/GOAT/GHSR system involved in the regulation of human energy, metabolism and adaptation of energy homeostasis to environmental changes. In humans, there is a preprandial rise and a postprandial fall in plasma ghrelin levels, which strongly suggest that the peptide plays a physiological role in meal initiation and may be employed in determining the amount and quality of ingested food. Besides the stimulation of food intake, ghrelin determines a decrease in energy expenditure and promotes the storage of fatty acids in adipocytes. Thus, in the human body ghrelin induces a positive energy balance, an increased adiposity gain, as well as an increase in caloric storage, seen as an adaptive mechanism to caloric restriction conditions. In the current world context, when we are witnessing an increasing availability of food and a reduction of energy expenditure to a minimum level, these mechanisms have become pathogenic. As a consequence, the hypothesis that ghrelin is involved in the current obesity epidemic has been embraced by many scholars and researchers

Key words: Appetite, Energy balance, Ghrelin

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Received: 27-03-2016, Accepted: 16-05-2016

INTRODUCTION

Ghrelin is a gut peptide composed of 28 amino acids mostly secreted by the gastric fundus mucosa. It was isolated and described in 1999 by Kojima et al and

three years later its specific receptor, GH secretagogue receptor 1a (GHSR1a), was identified. Ghrelin, the endogenous ligand for GHSR1a, is the only peripheral orexigenic hormone that activates receptors localized in the appetite centers in hypothalamus. Ghrelin is present in human plasma in two forms: an inactive form known as *deacylated ghrelin*, and an active form, the *acylated ghrelin* synthesized under the action of ghrelin O-acyltransferase enzyme (GOAT). The literature additionally mentions an extremely complex ghrelin/GOAT/GHSR system involved in the regulation of human energy and metabolism and the adaptation of energy homeostasis to environmental changes. In humans, there is a preprandial rise and a postprandial fall in plasma ghrelin levels, which strongly suggest that the peptide plays a physiological role in meal initiation, while it is also employed in determining the amount and quality of ingested food. Besides the stimulation of food intake, ghrelin brings about a decrease in energy expenditure and promotes the storage of fatty acids in adipocytes. Thus, in the human body ghrelin induces a positive energy balance, an increased adiposity gain, as well as an increase in caloric storage, seen as an adaptive mechanism to caloric restriction conditions. In the current global context when we are witnessing an increasing availability of food and a reduction of energy expenditure to a minimum level, these mechanisms have become pathogenic. As a consequence, the hypothesis that ghrelin is involved in the current obesity epidemic has been embraced by many scholars and researchers. This review aims to analyze currently existing data on ghrelin involvement in regulating the human body energy balance.

GHRELIN – A PERIPHERAL OREXIGENIC PEPTIDE WITH CENTRAL ACTION

It is known and has been abundantly demonstrated that in both animals and human subjects, ghrelin increases appetite and stimulates food intake in a GH-independent manner[1] through its specific receptor GHSR1a.[2] Numerous data in the literature have supported findings providing evidence that, besides exerting an orexigenic effect, this ghrelin/GOAT/GHSR system is involved in regulating energy metabolism and its adjustment to energy balance changes.[3] The circulating levels of ghrelin are elevated during fasting and before meals[4-6] and decline postprandially,[5-7] which implies that ghrelin plays a significant role in initiating food intake.[8] The increased level of ghrelin during fasting[9] is a unique phenomenon in human physiology, which contrasts with the secretion levels of most gut hormones that increase during nutrient intake and decrease during fasting.[8] Another peculiarity of ghrelin is that although it is a peripherally-secreted peptide in the gastrointestinal tract, it has major effects upon the central nervous system (CNS).[1] Ghrelin is synthesized and secreted primarily in the stomach[10] (oxintic mucosa X/A-like cells are immunoreactive cells for ghrelin, being more numerous in the gastric fundus and progressively decreasing towards the pylorus[11]), but low levels of ghrelin expression can also be found in other tissues such as the bowel, pancreas, kidney, ovary or brain.[12] Accordingly, positive immunoreactivity for ghrelin was described in the hypothalamic arcuate nucleus,[1] an extremely important region for appetite control, and in the internuclear space of the lateral hypothalamus, hypothalamic arcuate, ventromedial, dorsomedial and paraventricular nuclei and ependymal layer of the third ventricle.[13] To exert its orexigenic action, ghrelin reaches the hypothalamus in three different ways: systemically by crossing the blood-brain barrier, via the vagal afferents and via local hypothalamic synthesis and secretion, thereby exerting paracrine actions.[14]

In humans initiating meals voluntarily without time- and food-related cues, plasma ghrelin levels increase before meals and display a temporal profile similar to hunger scores,[15] once again confirming the hypothesis that ghrelin is a physiological meal initiator. Food intake or gastric/enteral feeding causes the suppression of circulating ghrelin levels.[16] Moreover, the composition of ingested foods appears to influence ghrelin secretion, albeit the published studies report conflicting results in this regard. In fact, two different situations have been observed: more significantly decreased levels of ghrelin after the ingestion of proteins and carbohydrates than those observed after the ingestion of lipids;[17,18] lower ghrelin levels after lipids that after carbohydrate or protein intake.[19]

However, most research teams have concluded that the circulating levels of ghrelin decrease after meals regardless of the type of nutrients consumed (carbohydrates and proteins still remaining the most

potent inhibitors),[20] these interprandial changes in circulating ghrelin levels being found only in normal weight individuals.[21] Ghrelin is the only currently known orexigenic gastrointestinal peptide which, in addition to appetite stimulation, increases the number of meals and also shortens latency to eat.[20] Ghrelin-induced hyperphagia was hence considered as one of the mechanisms involved in the development of overweight.

Recent studies have demonstrated that ghrelin also acts on the dopaminergic regions of the limbic system.[22] Moreover, ghrelin stimulates brain activity in certain regions involved in controlling eating behaviour, such as the amygdale and the orbitofrontal cortex.[23-25] Thus, besides the demonstrated classic effect of appetite stimulation through hypothalamic circuits, ghrelin may be involved in regulating eating behaviour.[16]

Ghrelin stimulates food intake in an acute manner, inducing meal initiation.[26] Initially, many experimental studies on laboratory animals showed that the administration of ghrelin increased the urge to eat and look for food,[27] without influencing the hedonic aspects of eating. But at the central level there are nuclei expressing ghrelin receptors that are associated with the intake of high-palatability foods. This may explain why in a food preference test the central administration of ghrelin shifts food choice towards a hyperlipid diet.[28] Therefore, ghrelin stimulates the intake of high energy density, high-fat, high-palatability foods, regardless of the type of nutrient normally preferred.[20] Ghrelin administration in laboratory mice caused increasing intake of palatable saccharin solutions and preference for food with saccharin.[29] In normal human subjects, ghrelin administration, besides increasing appetite and caloric intake, also stimulates imagination of favourite meals[30] and external visual stimuli represented by hedonic foods increases ghrelin levels.[31] In addition to meal initiation, ghrelin increases meal duration and size in the context of regularly scheduled meals.[32] The distribution of specific receptors for ghrelin as well as the study of MRI images confirm the hypothesis that ghrelin not only stimulates appetite but is also involved in regulating the hedonic aspects of eating: the preference for palatable foods, the motivation to obtain one's preferred foods, the reward value/effect of one's preferred foods and the actual purchase of foods.[33,34] Recent data indicate that ghrelin also influences behaviours related to motivational aspects of eating. Thus, currently existing evidence suggests that the ghrelin/GOAT/GHSR1a system is closely linked to pathways involved in reward aspects of food intake, additionally and partially separated from those determining food intake initiation.[35] Mediation of this eating behaviour response by ghrelin is accomplished through the dopaminergic neural network extending from the ventral tegmental area and other brain nuclei and finally resulting in food intake depending on its reward aspects.[36]

Hence, at the mesolimbic level, ghrelin would produce increased hedonic aspects of eating and increase motivation to seek and procure food, initiating anticipatory activity and foraging behaviours.[35] Based on these aspects, some researchers have proposed the clinical use of ghrelin in cases in which increased levels of food intake may be beneficial, such as elderly patients with nutritional deficiencies[37] or with anorexia associated with different consumption diseases.[38]

Ghrelin is considered an orexigenic signal (gut-brain) for the control of appetite and energy balance in healthy individuals. GHSR1a, the ghrelin-specific receptor, binds acylated ghrelin and mainly induces the release of the growth hormone from the somatotropic cells in the anterior pituitary gland. Via the vagus nerve or directly at the central level, ghrelin activates the neurons in the arcuate nucleus (ARC nucleus) secreting orexigenic peptides—neuropeptide Y (NPY) and agouti-related peptide (AgRP)[39]—and inhibits the anorexigenic neurons secreting pro-opiomelanocortin and α-melanocyte-stimulating hormone. Orexigenic signals act via adenosine monophosphate-activated protein kinase (AMPK) and increase the dopaminergic transmission from the ventral tegmental area to the nucleus accumbens, enhancing the reward signals.[40] Therefore, the binding of ghrelin to its specific receptor GHSR1a will lead to an increase in intracellular calcium concentration, with consequent activation of CaMKK2 (calmodulin kinase-kinase 2), which will phosphorylate AMPK.[41] In its turn, AMPK will phosphorylate and inhibit acetyl-coenzyme A carboxylase, resulting in decreased levels of malonyl-CoA and subsequent activation of carnitine-palmitoyltransferase-1.[42] The end result of this long series of enzymatic reactions is increased mitochondrial β-oxidation, with the gen-

eration of reactive oxygen species and stimulation of uncoupling protein 2 (UCP2),[43] which will stimulate NPY/AgRP transcription.[44]

In pathologic states, ghrelin may be decreased (in obesity) or increased (in anorexia nervosa, cachexia or Prader-Willi syndrome), which promotes speculation about the therapeutic applications of both ghrelin agonists and antagonists in these states.[45] It is hence evident that the metabolic status plays a key role in ghrelin function. Ghrelin activates NPY/agouti-related protein (AgRP) neurons through fatty acid oxidation and maintains NPY/AgRP cell function during extended periods of negative energy balance. Meanwhile, ghrelin is also required to maintain normal blood sugar levels during severe caloric restriction. Ghrelin is a key modulator of energy metabolism during starvation or long periods of negative energy balance. Recent studies have shown that in patients with diet-induced obesity (DIO) there is resistance to ghrelin in the arcuate NPY/AgRP neurons. In this case, the level of circulating ghrelin, the overall level of ghrelin as well as that of the GOAT mRNA in the stomach and that of the GHSR in the hypothalamus are all decreased.[46]

GHRELIN – A REGULATOR OF GASTROINTESTINAL FUNCTIONS

Acylated ghrelin is a potent stimulator of gastric secretion and motility.[47] On the one hand, ghrelin stimulates the secretion of gastric acid and digestive enzymes in the digestive organs within the digestive/gastrointestinal (GI) tract (stomach, intestine, and pancreas).[48,49] On the other hand, ghrelin reduces the gastrointestinal transit time of ingested nutrients, accelerating gastric emptying and stimulating the motility in the small intestine and colon.[50] These prokinetic and prosecretory effects, coupled with the modulation of eating behaviour actually facilitate digestion and absorption processes.[8] However, by decreasing the intestinal transit time, ghrelin limits the feedback from digestive tract/GI satiety signals, which should determine termination of food intake.[20]

GHRELIN AND WEIGHT STATUS

The energy homeostasis/balance of the human body and therefore its weight stability is reached when there is a balance between energy intake and expenditure, the two arms of the energy balance. As a result, weight loss will occur when the caloric intake is decreased and/or the energy expenditure is increased, while weight gain will occur when the caloric intake is increased and/or the energy expenditure is reduced. Due to its appetite stimulating effect, ghrelin is an enteroendocrine peptide that induces weight gain and adiposity.[51,52] Interestingly enough, there is also a preferential effect on fat intake that has recently been demonstrated.[28] Additionally, ghrelin would seem to promote adipose tissue deposition,[39] reduced energy expenditure and more efficient storage of lipids.[39,53] It can be said that ghrelin acts to protect the energy resources of the body when these are available (defensive role, protecting against hypoglycaemia that may occur in conditions of prolonged caloric restriction),[54] to redirect the metabolism to storing excess calories for later use in case of food insufficiency. Some authors have suggested that ghrelin is the factor that modulates feeding behaviour towards energy accumulation,[50,55] which is not beneficial to the human body in the current circumstances, as we often witness at the individual level a positive energy balance oriented to excessive caloric intake associated with reduced energy expenditure mainly because of our present-day sedentary lifestyle. Thus, what should be a protective mechanism against starvation is currently a pathological mechanism geared towards obesity and its complications.

Ghrelin acting through GHS-R theoretically causes weight gain based on the increase in height of individuals and/or lean tissue, similar to GH administration. Basically, the available data clearly demonstrate that central or peripheral administration of ghrelin increases the body fat mass,[26] adipogenesis and lipogenesis (by increasing PPARγ level), with concomitant reduction of lipolysis and use of lipids as energy substrates.[56] It is worth mentioning that these adipogenic effects appear to be independent from the orexigenic effect of ghrelin,[8,57] this being all the more interesting because of its influence on energy metabolism. Data derived from studies on laboratory animals show, in fact, an effect of stimulating differentiation and proliferation of preadipocytes.[58]

Plasma ghrelin levels are negatively correlated with body mass index and body fat percentage, being

considered a "reverse adiposity signal".[20] Accordingly, recent studies have demonstrated that obese people have low ghrelin levels,[59] while patients with anorexia have high plasma ghrelin levels[60] compared with healthy normal weight subjects. Moreover, variations in body weight (weight gain or loss) were observed to lead to compensatory responses of ghrelin levels.[56] For example, weight loss (whether resulting from reduced food intake or increased energy expenditure through physical activity) is accompanied by an increase in ghrelin level.[61] In its turn, weight gain (due to excessive caloric intake, high-fat diets, or else iatrogenic or pregnancy-related)[56,62] is accompanied by a decrease in ghrelin levels. Reduced ghrelin secretion in obese patients was found to be an adaptive mechanism to a long-term positive energy balance. Although circulating plasma ghrelin levels are low in obese people, a lack of postprandial ghrelin suppression was observed, which could contribute to increased food intake in these people.[49]

Obesity, especially diet-induced obesity (DIO), would produce resistance to ghrelin both peripherally and centrally. In the stomach, ghrelin-secreting cells stop responding to such stimuli as norepinephrine and glucose and central appetite can no longer be increased by the alteration of neural circuits regulating homeostatic feeding and reward processing pathways. Diets inducing weight loss reduce this resistance, pointing to possible defence mechanisms of body weight set-point established during times of food availability.[63] Voluntary weight loss secondary to low-calorie diets is accompanied by an increase in circulating ghrelin levels, leading to increased hunger sensation and therefore food intake.[64] As a result, attractive hypotheses have been put forward regarding the mechanism of repetitive weight gain in patients on cyclic diets, which can partially explain the present obesity epidemic.

It was noted that in obesity leptin levels are increased, while ghrelin levels are decreased,[60] which points to the adaptation of these two hormones to the positive energy balance and not necessarily their involvement in the determinism of obesity.

The conflicting results regarding ghrelin levels after metabolic surgery must be mentioned. In this situation, postsurgical weight loss caused different fluctuations in ghrelin levels: either an increase[65,66] or a decrease in plasma ghrelin[67,68] or, in some cases, no changes.[69] This variability in circulating ghrelin levels after metabolic surgery attracted the interest of numerous research teams in attempting to elucidate the mechanisms of postoperative weight loss. Several mechanisms have been proposed to explain these conflicting results:[70] either the differences in the surgical techniques employed that are related to the manipulation of the digestive tract and removal of certain portions involved or not in ghrelin secretion; or individual differences in the speed of postsurgical weight loss and in reaching a relatively stable body mass index. Recent data even demonstrate that high preoperative circulating ghrelin levels could identify patients with a susceptibility to weight regain1-2 years after metabolic surgery.[71] Further studies are needed to confirm/refute these hypotheses and to clarify the mechanisms of weight loss following metabolic surgery and, more crucially, the mechanisms for maintaining the new weight in the long term.

One exception that is frequently mentioned in the literature is that of patients with Prader-Willi syndrome who, although obese, have circulating ghrelin levels much higher compared to normal weight individuals (a condition termed by some authors "hereditary hyperghrelinemia").[8] Moreover, these patients do not present the postprandial ghrelin kinetics: the circulating level is not reduced after food intake or the decline is much less compared to obese or normal weight individuals.[60] The above initial data produced enthusiasm among some authors who have suggested that these may explain, at least partially, the increased appetite (almost uncontrollable) of these patients and the high incidence of obesity. However, although research has continued, the consequences of high levels of ghrelin in these patients are still unclear and controversial. Nevertheless, recent studies confirm that total levels of plasma ghrelin are highest in children with Prader-Willi syndrome early in life when they are characterized, during the nutritional phases, by reduced appetite and reduced food intake, i.e. long before the onset of hyperphagia,[72] while changing plasma ghrelin levels were not associated with a transition to the hyperphagic phase.[73] It is noteworthy that both studies mentioned analyzed total plasma and not acylated ghrelin. However, other hypotheses

have arisen to explain the increased appetite of these patients and excessive weight gain which propose that it concerns alterations of cortical and subcortical regions involved in reward aspects of eating along with other neural circuits (abnormal or delayed development of effective pathways of this hormone, altered sensitivity of the neural transmission).[73,74]

GHRELIN AND INTERMEDIARY METABOLISMS

Ghrelin is a gastrointestinal peptide with a major role in the regulation of glucose homeostasis as an integral part of body energy metabolism. Both ghrelin and its receptors are also present in pancreatic islet cells,[75] implying that ghrelin exerts paracrine and autocrine actions in the pancreas.[76] Consequently, the interest of many research teams has been directed towards investigating the role of ghrelin in the regulation of glucose homeostasis. In this regard, *in vitro* and *in vivo* studies involving both animals and humans were conducted to elucidate the ghrelin-insulin-glucagon interactions. As to the action of ghrelin on plasma insulin levels, the results are also contradictory, with some studies showing that ghrelin stimulates insulin secretion in the presence of hyperglycemia[9,77,78] and others finding no change in insulinemia under normoglycemic conditions.[79-81] There are also studies that demonstrate the hyperglycemic effect of ghrelin secondary to decreased insulin secretion,[79,82] thus indicating that ghrelin may be a diabetogenic factor.[83] However, the various effects of ghrelin on insulin secretion reported in the literature seem to correlate with the individual level of glycemic control.[84,85] If we look at the studies in their entirety, the published results demonstrate that acute administration of physiological and pharmacological doses of ghrelin inhibits glucose-dependent insulin secretion,[80,86] while supraphysiological doses of ghrelin may even decrease peripheral insulin sensitivity.[87] The long-term effects of ghrelin on carbohydrate metabolism have undergone fewer studies in humans. The use of a ghrelin mimetic for 1 year resulted in increased basal glucose level and decreased insulin sensitivity estimated by the Quicki index.[88] In its turn, circulating ghrelin levels are influenced by insulinemia levels. A recent study in healthy volunteers demonstrated that acylated ghrelin levels are low under hyperinsulinemia conditions, followed by a subsequent increase in plasma ghrelin levels.[89] The authors even suggested that this fluctuation in ghrelin levels in response to acute hyperinsulemia would contribute to a rise of hunger sensation and therefore of food intake which are indeed observed after episodes of hypoglycemia.[89]

Studies in animal models have demonstrated that ghrelin increases hepatic glucose production[62] by activating the gluconeogenic processes and/or via GH (which in its turn causes an increased hepatic glucose production).[57] Concomitantly, ghrelin blocks the ability of insulin to suppress endogenous glucose production.[62] Additionally, ghrelin inhibits the secretion of adiponectin (acting as an insulin sensitizer) and stimulates the secretion of counterregulatory hormones (glucagon, cortisol, GH, adrenaline). Data in the literature have also indicated the existence of a feedback loop between ghrelin and glucagon.[57] Thus, ghrelin directly stimulates glucagon secretion from pancreatic α cells (via GHS-R),[90] while glucagon stimulates ghrelin secretion under nutrient-deficient conditions.[91] Studies on laboratory animals have revealed that under the action of acyl-ghrelin, fat is stored not only in adipose tissue but also the liver,[39] where an increase in triacylglycerol content and genes involved in hepatic lipogenesis was found.[92]

A recent study published by Gagnon *et al*. brought up for discussion a new aspect of ghrelin involvement in glucose regulation, the authors demonstrating that ghrelin increases the secretion of GLP-1 (glucagon like peptide 1), thereby improving glucose tolerance.[93] They concluded that ghrelin is a "GLP-1 secretagogue".[93]

All these results emphasize the complexity of the relationship between ghrelin and pancreatic β-cell; however, this is a topic that is still open for research. For this reason, although initial data related to ghrelin involvement in appetite control have attracted a great amount of interest as a potential therapeutic option in weight control, most researchers are cautious about its actual use until the involvement of ghrelin in carbohydrate metabolism has been elucidated.

GHRELIN AND ENERGY EXPENDITURE

Besides its major influence on energy intake, ghrelin exerts important effects on energy expenditure. Studies on laboratory mice have shown that administration of

anti-ghrelin antibodies increases energy expenditure,[57] this demonstrating the complex role they play in the adjustment of body energy balance by acting on both components (both caloric intake and reduced energy consumption). Ghrelin receptor GHS-R is an important regulator of thermogenesis.[57] The ablation of this receptor increases energy expenditure by increasing thermogenesis in brown adipose tissue (by uncoupling oxidative phosphorylation from electron transport chain due to increased UCP1expression),[52,94] which is independent of food intake or physical activity.[57] This finding has significant practical implications since it has been proposed that GHS-R antagonists may represent a new therapeutic class effective in obesity[94] and not requiring restrictive diets or physical activity.

In addition to decreased thermogenesis, ghrelin also decreases energy expenditure by reducing the activity of the sympathetic nervous system (SNS), especially in brown adipose tissue.[95]

Another aspect, possibly less studied, is that of ghrelin as a potential clinical marker of catabolism.[60] This hypothesis was based on the findings that increased circulating ghrelin levels are found in patients with cachexia associated with chronic heart failure, liver cirrhosis or neoplastic disease, and in patients with chemotherapy-induced anorexia (all these conditions being characterized by hypercatabolism).[62] It had been experimentally demonstrated that GH secretagogues have the ability to reverse the catabolic effects and to improve the somatotroph axis alterations and protein catabolism in patients with severe, prolonged diseases characterized by hypercatabolism.[96] Due to its anabolic effects, GH has already been used to prevent muscle loss associated with surgical stress, sepsis, HIV/AIDS and malignancies.[97] In this respect, ghrelin, or any other compound stimulating GH secretion, would improve the therapeutic outcomes in these patients, particularly in elderly patients in whom the association of reduced GH secretion, reduced muscle mass and anorexia is often present. Studies aimed at evaluating the efficacy of ghrelin treatment in patients with anorexia-cachexia syndrome associated with neoplastic disease are needed, as a so-called resistance to ghrelin has been suggested.

In conclusion, circulating ghrelin level in humans are low under conditions of positive energy balance,

Table 1. The main effects of ghrelin that can influence energy metabolism

Food intake[1,35]	↑ appetite/↑ food intake
	↑ hedonic aspect of eating
	↑ motivation to obtain food
	↑ food seeking behaviours
Gastrointestinal function[47-50]	↑ gastric motility
	↑ gastric acid secretion and digestive enzymes
Adipose tissue [26,39,53,58]	↑ lipogenesis
	↑ adipogenesis (↑ differentiation and proliferation of preadipocytes)
	↓ lipid oxidation
Intermediary metabolisms[57,62,79,82,90,92,93]	↓ insulin secretion
	↑ hepatic gluconeogenesis
	↓ insulin sensitivity
	↑ glucagon secretion
	↑ hepatic lipogenesis
	GLP-1 secretagogue
Energy expenditure[52,57,94,95]	↓ energy expenditure
	↓ thermogenesis in BAT
	↓ sympathetic nervous system in BAT

either in acute conditions (food intake) or chronic conditions (obesity). Elevated circulating ghrelin levels are found in fasting conditions and in patients with anorexia of various causes. One can therefore conclude that ghrelin levels correlate inversely with body energy stores. The increased levels of ghrelin right before meals suggests that it is a *meal initiator* or *hunger signal*, being involved in meal duration and size and in the hedonic aspects of nutrition. The administration of ghrelin generates a positive energy balance and increases adiposity while reducing energy expenditure. However, ghrelin seems to exert more complex effects (summarized in Table 1), playing a major role in the modulation of intermediary metabolisms and their integration into the metabolic economy of our body. Simultaneously, ghrelin has a central role in controlling the energy balance, integrating the peripheral signals and central effectors that determine our eating behaviour.

FUNDING

This research was financed by the "Grigore T. Popa" University of Medicine and Pharmacy by contract no. 30887/30.12.2014.

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