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Review Article

The Effects of Leptin and Ghrelin Hormones on Metabolism

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ABSTRACT

Leptin was first identified in 1994 by Zhang and colleagues as a signaling factor originating from adipose tissue. Its name is derived from the Greek word “leptos,” meaning “thin” or “slender”. While its primary site of secretion is white adipose tissue, leptin is also secreted in smaller amounts by brown adipose tissue, as well as by the placenta, skeletal muscle, stomach, mammary epithelium, and brain tissue. By acting at the hypothalamic level, leptin reduces appetite. Leptin is a 16-kilodalton, single-chain polypeptide hormone. Initially recognized for its role in satiety and energy balance, leptin was later identified as an anti-obesity factor that exerts feedback effects from adipocytes to the hypothalamus. It has been reported as a key physiological factor in mammals for preventing fat accumulation.Ghrelin, discovered in 1999 by Kojima and colleagues in the stomachs of mice, is a 28-amino acid oligopeptide hormone that stimulates the release of growth hormone. Although primarily secreted by stomach tissue, ghrelin is also produced by the brain, intestines, placenta, kidneys, pituitary gland, and pancreas. The name “ghrelin” is derived from the root “ghre,” meaning “grow,” in Indo-European languages, combined with “relin,” which implies secretion. Ghrelin is also referred to as the "appetite hormone. Isolated from mouse stomach tissue, this 28-amino acid peptide plays crucial physiological roles. Ghrelin has been reported to increase food intake, promote positive energy balance, and influence gastrointestinal motility, cell proliferation, bone metabolism, and reproduction.

Key words: Leptin, Ghrelin, Hormone, Metabolism

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INTRODUCTION

General Structure of Leptin and Ghrelin

Leptin is a peptide hormone with a molecular weight of 16 kDa, primarily recognized for its role in regulating body weight (Williams et al., 2002). Its structure resembles that of cytokines. In recent years, extensive research has been conducted on the synthesis, secretion, receptors, and effects of leptin. These studies have demonstrated that leptin influences appetite, hunger, energy expenditure, and reproduction (Wolinski et al., 2014).

The primary role of leptin in the body is to regulate food intake and energy metabolism via negative feedback to the brain, thereby preventing obesity. Moreover, leptin plays critical roles in regulating metabolism, reproduction, puberty, immunity, gastrointestinal functions, sympathetic nervous system activation, angiogenesis, and osteogenesis. Initially identified for its involvement in satiety and energy balance, leptin was later found to act as an anti-obesity factor with feedback effects from adipocytes to the hypothalamus (Zhang et al., 1994).

Leptin production and plasma levels in animals can vary depending on genetic factors such as species and breed, physiological factors like age, pregnancy, lactation, and feeding habits, as well as environmental conditions such as temperature and light (Williams et al., 2002).

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Ghrelin, primarily produced by X(A) cells in the fundus of the stomach with endocrine functions, is a 28-amino-acid lipopeptide hormone and the endogenous ligand of the growth hormone secretagogue receptor (Kojima et al., 1999). It is synthesized in the stomachs of humans and rodents, as well as in the abomasum and rumen tissues of cattle, playing a role in regulating food intake and energy balance in ruminants (Hayashida et al., 2001; Biçici and Karakurum; 2024).

Beyond the stomach, ghrelin is also synthesized in the hypothalamus, pituitary gland, salivary glands, thyroid, small intestine, kidneys, heart, alpha, beta, and epsilon cells of the pancreas, central nervous system, lungs, placenta, gonads, immune system, and mammary glands (Kojima et al., 1999).

Ghrelin's most significant effect is its strong stimulation of growth hormone secretion from somatotropic cells in the pituitary gland. In addition to this activity, ghrelin exhibits orexigenic effects, stimulates acid secretion, regulates gastric motility and pancreatic activity, affects sleep, contributes to cardiovascular functions, and exerts antiproliferative effects on various cells (Casanueva et al., 2004).

Ghrelin mRNA has been detected in nearly all tissues, with the highest levels observed in the fundus of the stomach. This is followed by the jejunum, duodenum, antrum of the stomach, lungs, pancreas, venous system, gallbladder, lymph nodes, esophagus, left colon, buccal mucosa, pituitary gland, mammary gland, kidneys, ovaries, prostate, right colon, ileum, liver, spleen, fallopian tubes, lymphocytes, testes, adipose tissue, placenta, adrenal glands, muscles, bladder, atrium of the heart, thyroid gland, myocardium, and skin (Hayashida et al., 2001).

Ghrelin has been reported to increase food consumption and promote a positive energy balance. Additionally, it influences gastrointestinal motility, cell proliferation, bone metabolism, and reproductive activities (Zizzari et al., 2011).

Relationship Between Leptin and Ghrelin

Leptin, secreted by adipose tissue, and ghrelin, secreted by the stomach, are significant hormones discovered in recent years that play critical roles in energy balance regulation.

Leptin and ghrelin operate within the organism based on the "Yin-Yang" principle. In other words, the concentrations of ghrelin and leptin are controlled via a feedback mechanism involving Y neurons in the hypothalamus, which helps regulate body weight. The levels of these hormones are influenced by factors such as hunger-satiety, glucose levels, diet, insulin, gut hormones, parasympathetic activity, age, pregnancy, obesity, gender, polycystic ovary syndrome, energy levels, insulin resistance, diabetes mellitus, GH deficiency, acromegaly, hypo- and hyperthyroidism, the neonatal period, and certain neuroendocrine gastrointestinal tumors. Intracerebroventricular administration of leptin has been observed to increase arterial pressure, whereas administration of ghrelin reduces it (Nagaya et al., 2001).

Recent studies suggest that leptin, in conjunction with ghrelin, a hormone produced by the gastrointestinal system, regulates energy metabolism by influencing specific neurons in the central nervous system. Unlike leptin, ghrelin is reported to have appetite- and fat-increasing properties (Yiş et al., 2005).

Effects of Leptin and Ghrelin on Metabolism

Effects on Food Intake

Feeding is a fundamental behavior necessary for survival. Appetite regulation is considered to be under the control of the brain, particularly through the complex mechanisms of the central nervous system and the hypothalamus. Removal of the lateral hypothalamus results in hypophagia, leading to severe weight loss and eventual death. Conversely, removal of the ventromedial hypothalamus causes hyperphagia, leading to increased feeding frequency and food intake, resulting in significant weight gain and severe obesity. Thus, feeding behavior is regulated by a balance of stimulatory and inhibitory forces in the hypothalamus (Kojima et al., 1999).

One of ghrelin's earliest discovered effects is its relationship with growth hormone (GH). Intravenous administration of ghrelin in humans and dogs stimulates GH release. Ghrelin increases GH secretion in a dose-dependent manner in both in vitro and in vivo conditions (Date et al., 2000).

Ghrelin's appetite-stimulating effect is as potent as neuropeptide Y (NPY), which is known to be the strongest appetite stimulator. Ghrelin promotes feeding behavior by activating NPY/AgRP neurons in the hypothalamus. NPY (neuropeptide Y) and agouti-related protein (AgRP) are produced by the same neuronal population in the arcuate nucleus (ARC). Their appetite-stimulating effects are directly inhibited by leptin. Leptin suppresses ghrelin-induced food intake, whereas ghrelin reverses leptin's appetite-suppressing effect. This indicates that ghrelin antagonizes leptin's role in the regulation of the NPY/AgRP system (Hosoda et al., 2002).

Leptin prevents excessive weight gain by inhibiting anabolic signaling pathways that promote weight gain in the brain and activating catabolic signaling pathways that increase energy expenditure. In addition to leptin, the gastrointestinal system sends signals to the brain to regulate meal size and frequency. Some of these signals are mechanical impulses resulting from gastrointestinal tract distension, while the majority are transmitted via the afferent branches of the vagus nerve. The first and most critical hormonal satiety signal transmitted through the vagus nerve is cholecystokinin (CCK). Leptin also works in synergy with CCK and enhances sensitivity to it, reducing meal size (Daniel et al., 2002).

Effects on Energy Metabolism

In recent years, it has been suggested that leptin, along with the ghrelin hormone produced by the gastrointestinal system, plays a role in regulating energy metabolism by influencing specific neurons in the central nervous system. Unlike leptin, ghrelin is reported to have appetite- and fat-increasing properties (Yiş et al., 2005).

Leptin concentration correlates with the amount of energy stored in fat and the body's energy balance. Plasma leptin levels are higher in obese individuals compared to lean ones, drop rapidly during fasting, and rise again after feeding (Ahima et al., 2000).

Leptin has a short-term stimulatory effect on lipid oxidation in skeletal muscles. It reduces lipid stores in skeletal muscles by increasing fatty acid catabolism. Intravenous leptin administration decreases triacylglycerol secretion in the liver while enhancing fatty acid oxidation. In the liver, it reduces triglyceride content and boosts fatty acid oxidation. Additionally, by activating the sympathetic nervous system and increasing thyroid hormones, leptin enhances thermogenesis and acts as a regulator of energy metabolism (Suzuki et al., 2007).

Ghrelin plays roles in growth hormone release, energy balance, food intake, and body weight regulation. It is described as a hormone that prevents energy depletion and cachexia. Its serum levels rise before each meal, stimulating appetite (Soriana et al., 2004). Studies in mice have shown that fasting increases ghrelin secretion, while carbohydrate intake suppresses it (Cummings ve ark 2001). Ghrelin's effects on energy homeostasis occur primarily in the hypothalamus of the central nervous system, indicating that its impact extends beyond the peripheral tissues where it is produced (Rindi et al., 2002).

Over the past 15 years, significant progress has been made in understanding the effects of leptin and ghrelin on energy balance, neuroendocrine function, and various physiological processes. Insights into the biology of leptin and ghrelin under normal and pathological conditions can aid in the diagnosis and treatment of obesity and related metabolic diseases (Ahima et al., 2000).

Effects on the Cardiovascular System

Ghrelin mRNA has been detected in the heart and aorta. Intracerebroventricular (ICV) injection of ghrelin into the nucleus tractus solitarius in rats suppresses sympathetic activity, leading to reductions in blood pressure and heart rate, a mechanism opposite to that observed with leptin (Zhang et al., 1994). Additionally, ghrelin administration in rats increases left ventricular stroke volume. In hypophysectomized rats, ghrelin administration has been associated with healthy heart development. Ghrelin also counteracts the vasoconstrictive effects of endothelin-1 in arteries, indicating a role in vascular homeostasis (Morton et al., 2001).

Effects on the Immune System

Leptin plays a regulatory role in immune system functions (Barb et al., 2001). It stimulates leukocyte synthesis and enhances the erythropoietic effects of erythropoietin on red blood cells. Like bacterial antigens, leptin activates macrophages, increases their phagocytic activity, and stimulates the secretion of both pro-inflammatory and anti-inflammatory cytokines from macrophages (Hekimoğlu, 2006).

Recent studies have uncovered the functional roles of ghrelin and other growth hormone secretagogues within the immune system, especially under conditions of inflammatory stress and injury. Over the past decade, numerous reports have described ghrelin as a potent anti-inflammatory agent, showing promise as a therapeutic substance for treating inflammatory diseases and injuries in both in vivo and in vitro settings. Additionally, ghrelin has been shown to support lymphocyte development in primary lymphoid organs (bone marrow and thymus) and reverse age-related thymic involution (Patel et al., 2011).

DISCUSSION

The interplay between leptin and ghrelin highlights a complex regulatory mechanism governing energy metabolism and physiological functions. While leptin primarily acts as a satiety signal to reduce food intake and prevent excessive fat accumulation, ghrelin functions as an appetite stimulant, promoting energy storage and

positive energy balance. This "Yin-Yang" dynamic suggests a finely tuned feedback system within the hypothalamus to maintain energy homeostasis. Leptin's role extends beyond metabolism, influencing immune responses and cardiovascular regulation by activating sympathetic pathways and modulating cytokine release. Conversely, ghrelin not only stimulates growth hormone secretion but also exhibits anti-inflammatory properties and supports cardiovascular and immune health. These findings underscore the therapeutic potential of targeting leptin and ghrelin pathways for managing obesity, metabolic disorders, and inflammatory diseases. Further research into these hormones' interactions may offer insights into novel treatment strategies for metabolic and systemic disorders.

CONFLICT OF INTEREST

There is no conflict of interest.

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