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Ghrelin: A Review

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Abstract:
Ghrelin is a neuroendocrine hormone secreted mainly by P/D1 cells of gastric fundus. It may also be expressed in the pancreatic islets, hypothalamus, pituitary and several tissues in the periphery. Ghrelin is made of 28 amino acids and exists in two major forms: n-octanoyl modified ghrelin and des-acyl ghrelin. It acts as a ligand for the growth hormone (GH) secretagogue receptor and plays a major role in appetite stimulation. Apart from influencing the release of growth hormone from pituitary, it also functions on gastrointestinal system, cardiovascular system, energy balance and metabolism.

Key Words: Ghrelin, Growth hormone, appetite, food intake.

INTRODUCTION:

Ghrelin, a ligand for the growth hormone secretagogue (GHS) receptor (GHSR) [1], was discovered in 1999 after a research done on rat stomach produced an extract that activated the GHSR [1]. Ever since stomach has been recognized as the richest source of ghrelin produced chiefly by endocrine cells known as P/D1 cells[2, 3].The name ghrelin come from the root word "ghre",which means "grow" in Proto-Indi-European language. Ghrelin stimulates the secretion of GH, increases food intake and in turn produces gain in weight [4, 5]. Apart from its effect on GH, it has various important biological actions like regulation of cardiovascular functions [6, 7], stimulating gastric acid motility and secretion [8], modulating cell proliferation and survival [9], energy balance and metabolism. It is also associated with regulation of blood glucose, obesity and sleep wake cycle.

GHRELIN AND HORMONAL SECRETIONS:

Growth Hormone (GH) secretion by anterior pituitary is regulated by Growth Hormone Releasing Hormone(GHRH) and somatostatin which stimulate and increase its secretions respectively. Studies on artificial GHS have shown that ghrelin acts synergistically with GHRH to stimulate GH secretion from pituitary cells [1,10].Ghrelin induced GH secretions in humans is much stronger than GHRH[10].Studies conducted on anaesthetized rats have shown that both intravenous[11] and intracerebroventricular [1] administration of ghrelin increased rat plasma GH concentration, with the latter being more potent route. In high doses, ghrelin stimulates the secretion of prolactin, corticotropin, and cortisol.

EFFECT OF GHRELIN ON CARDIOVASCULAR FUNCTION:

The evidence for cardiovascular function of ghrelin has been found: expression of mRNA encoding both ghrelin and its receptors has been observed in the heart and aorta [12,13].Also the intravenous injection of ghrelin in human volunteers induces a decrease in blood pressure[13].In vitro studies revealed the inhibition of apoptosis of cardiomyocytes and endothelial cells by increased ghrelin levels[9]. An intravenous bolus of human ghrelin decreased the mean arterial pressure without changing the heart rate [13,14]. In addition ghrelin also increased the cardiac index and stroke volume indices. Ghrelin treated rats with chronic heart failure(CHF) showed an increase in cardiac output, stroke volume and left ventricular □P/□t-[max] compared with afflicted, but placebo-treated controls [21]. Elevated plasma ghrelin levels have also been found in humans suffering from CHF associated with cachexia[16]. Ghrelin expression has also been found in human placenta and some fetal tissues suggesting its role in cardiovascular adaptation during pregnancy [17].

EFFECT OF GHRELIN ON GASTROINTESTINAL FUNCTIONS:

Ghrelin is a gastric peptide released by oxyntic cells in stomach [1].The plasma levels of ghrelin rise prior to intake of food and decline rapidly when food is consumed [18].Exogenous administration of ghrelin also increases food intake [19] and it plays a role in meal initiation. The number of meals is said to be majorly effected in response to ghrelin administration [20]. Central and peripheral ghrelin administration results in increased expression of the orexigenic peptides NPY and AgRP within the arcuate nucleus of hypothalamus[21,22].The intravenous administration of ghrelin dose-dependently increases gastric acid secretion and stimulates gastric motility[23,24].The maximum response to ghrelin in terms of gastric acid secretion is almost as high as that shown by subcutaneous treatment with histamine[3mg/kg]. These responses to ghrelin were abolished by pre-treatment with either atropine or bilateral cervical vagotomy, but not by a histamine H2-receptor antagonist. Intracerebroventricular administration of ghrelin was shown to induce c-fos expression in the nucleus of solitary tract and dorsomotor nucleus of vagus nerve.

EFFECT OF GHRELIN IN FOOD INTAKE:

Ghrelin is known to transport hunger signals from periphery to the central nervous system. Research has shown that intravenous and subcutaneous injections of ghrelin in rodents resulted in increase in their food intake and thus increase in their body weight gain and decrease in fat utilization [5]. Immunohistochemical analyses indicate that ghrelin containing neurons are found in the arcuate nucleus (ARC) of hypothalamus[1]. This region of

hypothalamus is involved in appetite regulation. In fact, chronic intracerebroventricular injection of ghrelin increases cumulative food intake and decreases energy expenditure, resulting in body weight gain [5,19,25,26,27]. This orexigenic effect of hypothalamic ghrelin is regulated through a neuronal network. To stimulate the release of orexigenic peptides in ARC, ghrelin containing neurons send efferent fibers onto NPY- and AgRP-expressing neurons. It also sends efferent fibres to POMC neurons to suppress the release of anorexigenic peptides. Studies indicate that intracerebroventricular injection of ghrelin induces Fos expression in NPY-expressing neurons and increases the amount of NPY mRNA in the ARC[5,25,26].It also increases the AgRP mRNA level in the hypothalamus. The ARC is also a target of leptin , which is an appetite-suppressing hormone produced in adipose tissues [28,29]. Leptin directly inhibits the appetite stimulating effects of NPY and AgRP. Hypothalamic ghrelin augments NPY gene expression and blocked leptin-induced feeding reduction. Thus, ghrelin and leptin have competitive interactions and ghrelin is functionally a natural antagonist to leptin.

Ghrelin is the first identified circulating hormone that promotes feeding following peripheral administration. The rate at which peripheral ghrelin passes the blood−brain barrier has shown to be very low and thus peripheral ghrelin must activate the appropriate hypothalamic regions via an indirect pathway. The presence of ghrelin receptors on vagal afferent neurons in the rat nodose ganglion suggests that ghrelin signals from the stomach are transmitted to the brain via the vagus nerve [30,31].Moreover, ghrelin activates the vagus system by inducing c-Fos in the dorsomotor nucleus of the vagus[32]. As noted above, vagotomy actually inhibits the ability of ghrelin to stimulate food intake [30]. A similar effect was also observed when capsaicin was applied to vagus nerve terminals to induce sensory denervation. Fasting-induced elevation of plasma ghrelin is completely abolished by subdiaphragmatic vagotomy or atropine treatment [33]. In summary, ghrelin is secreted primarily from stomach in response to hunger and starvation, circulates in the blood, and serves as a peripheral signal, conveying the central nervous system (via vagus nerve) to stimulate feeding.

Meals and ghrelin:

Ghrelin is secreted in a pulsatile manner, peaking at 2000 h, rising before meals and returning to basal levels after food ingestion. Plasma ghrelin levels increases by about two folds immediately before each meal and fall to minimum levels within 1 h after eating [18, 34]. The clear preprandial rise and postprandial fall in plasma ghrelin levels support the hypothesis that ghrelin is an initiation signal for meal consumption. Research studies have shown preprandial increase in ghrelin levels in humans that initiated meals voluntarily without any time- and food-related cues. Furthermore, the postprandial suppression of plasma ghrelin level is proportional to the ingested caloric load [35], further reinforcing that ghrelin is a hunger signal.

Ghrelin gene expression and appetite:

The gene expression of ghrelin in the stomach is increased by fasting and decreased by administration of leptin and interleukin (IL)-1 [36,37,38]. It promotes a positive energy balance by increasing food intake, decreasing energy expenditure and blocking IL-1 -induced anorexia. All these facts suggest a possible clinical use of ghrelin for pathological anorexia that occurs as a side effect of some drugs and surgical operations and as a symptom of cancer and AIDS.

Ghrelin and gastric bypass surgery:

Obesity is a global epidemic caused by chronic impaired balance between energy supply and its expenditure. It leads to gathering of excessive fat tissues in the body. As ghrelin is functionally associated with energy homeostasis, it is intimately related to obesity. Gastric bypass operations are often performed to treat severe obesity [39,40]. This procedure reduces the space for food in gastric lumen and hence reduces the total calorie intake. Statistics show that in the United States, a total of 40,000 people are estimated to have been treated with a gastric bypass in 2000 , and 75,000 in 2001. However, the exact mechanism of action of this operation is still unclear.

Recent research has revealed that ghrelin may contribute to the body weight reduction that occurs post gastric bypass. The patients receiving the procedure and having successful weight loss were examined for their plasma ghrelin levels[41,42,43]. It was found that total ghrelin secretion was reduced by up to 77% compared with normal-weight control groups and by up to 72% compared with matched obese groups [41]. Moreover, the normal meal-related fluctuations and diurnal rhythm of ghrelin level were absent in these patients. The mean plasma ghrelin concentration decreased significantly after gastric bypass surgery and may have been responsible for their lack of hyperphagia and contributed to their weight loss. The mechanism for decreasing plasma ghrelin level in gastric bypass patients is still unknown and one hypothesis is that direct contact between gastric mucosa and food is important for the production and secretion of ghrelin [44].

OTHER FUNCTIONS OF GHRELIN:

Studies have suggested that ghrelin leads to increased gastrointestinal motility and (possibly) increased gastric acid secretion, which may play a physiological role in preparing the gastrointestinal tract to process food.[24,36,45-48]. In terms of gastric acid secretion, the maximum response to ghrelin is almost as high as that elicited by subcutaneous treatment with histamine (3 mg/kg). Pretreatment with either atropine or bilateral cervical vagotomy, abolished these responses to ghrelin but not by a histamine H_2- receptor antagonist.

There are many evidences on the regulation of insulin secretion by ghrelin[49-52]. It was reported by Date et al. that ghrelin stimulates insulin release in the presence of high levels of glucose (8.3 mM/l) that could independently cause insulin release from cultured islet cells [49]. In contrast to this, ghrelin had no effect on insulin release

in the context of a basal level of glucose (2.8 mM/l). Ghrelin has also shown to reduce insulin secretion and induce hyperglycemiain humans[53].The role played by ghrelin on insulin secretion is still a matter of debate among researchers and further research in the field is required.

After the discovery of ghrelin, it was realized that the stomach plays a major role not only for digestive functions but also for the regulation of energy metabolism and secretion of GH.

In addition to the appetite-related neuronal pathways activated by ghrelin, ghrelin receptors are present in many areas of brain that can affect mood and emotions, and, indeed, it was found that ghrelin may interfere with the regulation of the stress response, mood, and anxiety.

Ghrelin and its agonists may also modulate immune functions by enhancing immune cell proliferation and inhibiting the secretion of proinflammatory cytokines from immune cells [54-56].

The novel octanoylated structure of ghrelin represents a new finding in biochemistry. The newly identified enzyme that catalyzes the acyl-modification of ghrelin, GOAT, provides an important clue in the secretory machinery of ghrelin. The mechanism of ghrelin synthesis still remains unclear and hopefully will be elucidated by future research.

CONCLUSION:

A critical review of the newly discovered chemical messenger ghrelin and its numerous actions is provided

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