RESEARCH ARTICLE

GHRELIN FOR REGULATING APPETITE AND ENERGY BALANCE: A SYSTEMATIC REVIEW

Gut hormones play a significant role in regulating feeding and energy balance. Almost all the gut hormones are responsible for reducing appetite i.e. they are anorectic, except for ghrelin which is responsible for increasing the appetite i.e. it has an orexigenic effect. Ghrelin is a 28-amino acid bioactive peptide hormone that was isolated from the stomach in 1999 by Kojima et al. A natural endogenous ligand of the growth hormone (GH) secretagogue receptor, it helps in the regulation of glucose and fat metabolism and regulation of energy balance. It also plays an essential role in regulation of appetite and bodyweight as well as modulation of gastrointestinal functions. The electronic databases, like CENTRAL, DARE, CDSR, Cochrane Methodology Reviews, MEDLINE, PUBMED and other resources, hard copies and unpublished works were searched. Pubmed keyword strategy was tailored to the other databases. The previous studies points out that Ghrelin is a hormone and the only known circulating orexigen produced in response to hunger. Although many substances play a role in the control of appetite, ghrelin is the only known peptide which increases appetite by sending signals of starvation from a stomach to the central nervous system. Besides playing a role in short-term regulation of food intake, ghrelin might also play a role in long-term regulation of energy balance. It also shows effects on the reward and motivation centers in the brain regions. Ghrelin has diverse roles. It also plays an essential role in regulation of appetite and bodyweight as well as modulation of gastrointestinal functions. As ghrelin is disturbed in obesity, it is important to reveal the mechanism of action for the purpose of developing novel therapeutic interventions.

Key Words: Obesity; Orexigenic; Ghrelin; Energy Balance; Leptin

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INTRODUCTION

An increasing number of people, including children are obese. The prevalence of obesity is increasing globally. Morbidity and mortality increase linearly with increase in body mass index (BMI).[1] The regulation of body weight is through complex systems. An important role in the regulation of food intake and body weight is played by two hormones; leptin and ghrelin both of which are formed in the periphery and relay information to the central nervous system, particularly to the hypothalamus.[2] In obese individuals, the circulating level of the orexigenic hormone ghrelin is decreased while anorexigenic hormone leptin is increased. Ghrelin is not solely expressed in stomach. It is also widely expressed in many organs such as brain, pituitary, heart and kidney.[3] As ghrelin is decreased in obesity, it is necessary to explore the mechanism of action of ghrelin for developing new therapeutic interventions. As increasing number of people are suffering from obesity, exploring the mechanisms by which this hormone regulates appetite and energy balance is a subject of intensive research.

Ghrelin is a fast-acting hormone and plays a significant role in meal initiation. It is regarded as the counterpart of leptin which when present at higher levels induces a feeling of satiation. Ghrelin is the only known circulating orexigen produced in response to fasting. The circulating ghrelin serves as a signal for the hypothalamus to stimulate the feeding. There is nearly a two-fold rise in plasma ghrelin levels before a meal and the levels fall within one hour after meal intake. In some bariatric surgeries performed in obese patients, resection of a part of a stomach reduces the level of ghrelin, which induces satiation and thereby reduces obesity. Ghrelin also plays a significant role in the regulation of secretion of GH. In addition, ghrelin also shows effect on inflammation and immune cell activation.[4] Although the major quantity of ghrelin originates in the stomach, other tissues, like pancreas, gonads, thyroid, hypothalamus, and placenta etc., also produce ghrelin but in minor quantity. The sources of ghrelin increases ghrelin secretion in a compensatory manner. For example, after gastrectomy, plasma ghrelin level is reduced only by 65%.[5] Ghrelin is mainly produced in the fundus of the stomach. By

resecting a portion of stomach, the majority of ghrelin-producing cells are removed, thereby reducing plasma ghrelin levels and subsequently produces satiety and promotes weight loss. Ghrelin levels may also be decreased as majority of ghrelin-producing cells isolated from contact with enteral nutrients, experience override inhibition. As per to this concept, an empty stomach and duodenum stimulates ghrelin production and paradoxically inhibits it when present continuously after gastric bypass. This phenomenon is similar to the paradoxical inhibition of gonadotropins (GnH) or growth hormone by continuous stimulation from GnRH or GHRH, respectively.[6]

The secretion of ghrelin by the stomach depends mainly on the nutritional status of the body. Ghrelin levels demonstrate a preprandial increase and a postprandial decrease. Ghrelin levels also show a diurnal variation and are influenced by age, gender, BMI. Other hormones like growth hormone (GH) and insulin also affect the level of ghrelin Ghrelin secretion seems to higher in females compared with males.[7] Leptin has also been suggested to have modulate circulating ghrelin levels. It has been hypothesized that one of the mechanisms by which leptin induces satiety is by suppressing ghrelin secretion. However, leptin has also been shown to act as an upstream regulator of ghrelin in rodents.[8] Several studies in humans have produced conflicting results. Tschop et al. demonstrated that in obese patients fasting plasma ghrelin levels are negatively correlated with fasting plasma leptin levels.[9] However, in another study by Ikezaki et al. fasting plasma leptin and ghrelin concentrations were not correlated in obese children and adolescents.[10] Chan's study showed that administration of leptin to healthy subjects does not regulate the levels of ghrelin.[11] These results suggest that leptin alone does not play a role in the regulation of circulating ghrelin levels but that the leptin and ghrelin systems function independently in the control of energy homeostasis.

Objective: To explore and assess the role of ghrelin in regulating appetite and energy balance by reviewing the existing literature.

METHODOLOGY

Types of Studies: Randomized and non- randomized controlled trials as well as reviews and original articles investigating the role of ghrelin in regulating appetite and energy balance were included in the study.

Types of Participants: The role of ghrelin was observed in normal, cachexic as well as obese and anorexic people of both the genders and of any age or any ethnic group.

Types of Intervention: The effect of different analogues of ghrelin in any dose and any route of administration on appetite were assessed in the review. Studies assessing the effect of ghrelin in addition to other treatments as well as verses other treatments were also included in the review.

Search Methods for Identification of the Studies: The electronic databases, hard copies and unpublished works were searched. The Cochrane Library databases (Cochrane Central Register of Controlled Trials (CENTRAL), DARE, CDSR, Cochrane Methodology Reviews); MEDLINE (OVID); PUBMED , EMBASE were searched. The Database of Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED), National Research Register for Social Care, NIH (USA), Clinical Trials.gov, The Clinical Trials.gov, Center for International Rehabilitation Research Information and Exchange (CIRRI) were searched. Other sources searched include Google & Google Scholar and grey literature for unpublished work. We tailored the Pubmed keyword strategy to the other databases. The bibliographies of all the papers located were searched for further studies and experts in the field were contacted to identify further studies and for seeking more information on the topic. Hand searches were conducted for conference proceedings, medical journals and books. There were no language restrictions.

Data Collection: Two reviewers merged search results using reference management software, and removed obviously irrelevant reports and the duplicate records of the same reports. Titles and abstracts were then examined to remove obviously irrelevant reports. Full text of the potentially relevant reports were retrieved and examined for compliance of studies with eligibility criteria. Some of the authors were contacted to request further information. Final decisions were made on study inclusion by two authors. Disagreements between the reviewers about inclusion of studies was resolved by discussion with a third reviewer.

RESULTS

Our search identified 218 references from different databases and 6 references from additional sources. After removing duplicates 122 references remained which

were screened and 95 references were excluded. Full texts of 27 references were retrieved and screened for eligibility and after excluding 9 references, 18 were included in this review. (PRISMA Chart).

Effects of Ghrelin

Ghrelin circulates in two distinct forms, acylated ghrelin (AG) and unacylated ghrelin (UAG). Except for the deletion of Gln14, des-Gln14-ghrelin is identical to ghrelin. The acylation of ghrelin on the third serine residue is promoted by ghrelin O-acyltransferase which is necessary for the main endocrine functions of AG, including induction of food intake and regulation of energy homeostasis. Apart from its hormonal effects, AG has a broad range of peripheral functions, including roles in cardiovascular system, glucose metabolism, cell proliferation. Concentration of UAG in blood is more than that of AG but it is devoid of the typical AG-induced endocrine effects. However, it shares many of the AG peripheral functions. Obestatin (Ob) a 23-amino acid peptide is mainly produced in the stomach and is recently identified product of the ghrelin gene. Ob was claimed to be a physiological opponent of AG on food intake and gastrointestinal motility. However, its physiological role is still unclear. Several minor forms of human ghrelin has been isolated. All peptides found are either 27 or 28 amino acids in length and are obtained from the same precursor of ghrelin through two alternative pathways.

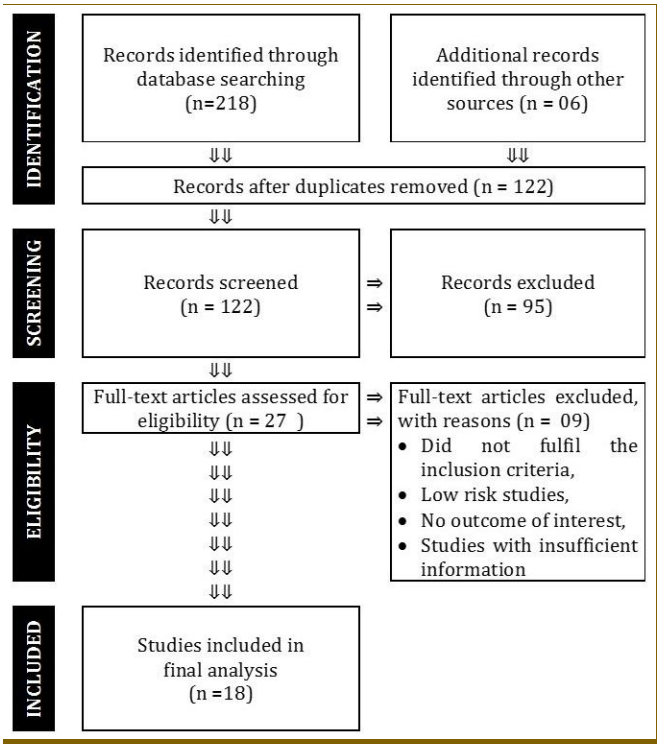

Figure-1: PRISMA Flow Diagram

The effects of ghrelin on energy homeostasis are largely mediated by the hypothalamus. Korbonits et al. projected three different pathways for the orexigenic effects of ghrelin on the brain.[12] First, ghrelin produced in stomach is released into the bloodstream and then it may cross the blood brain barrier and bind to its specific receptors in the hypothalamus. Second, ghrelin may enter the brain via the vagal nerve and nucleus of tractus solitarus. Third, ghrelin is produced locally in the hypothalamus, where it may directly affect the various hypothalamic nuclei. The specific receptor for ghrelin is a G protein-coupled receptor, known as the growth hormone secretagogue receptor. It is present in high density in the hypothalamus, pituitary as well as vagal afferent cell bodies and vagal afferent endings throughout the gastro-intestinal tract.[13] Ghrelin binds to the GHSR1 a splice-variant of this receptor which. Once ghrelin reaches hypothalamus by these three mechanisms, it activates ghrelin receptor and initiates signaling cascade thereby causing changes in food intake.

Ghrelin has a stimulatory effect on the neurons which express for NPY, AgRP and orexin.[14] On the other hand, it has an inhibitory effect on the neurons producing corticotrophin releasing hormone and also on POMC neurones. Thus, ghrelin inhibits the hypothalamic neurons containing different neuropeptides, resulting in orexigenic effects on energy homeostasis. Ghrelin also modulates the expression of different hypothalamic peptides and attenuates leptin-induced suppression of food intake and body weight.[15]

In humans; circulating levels of ghrelin are increased by fasting and in patients with cachexia and anorexia nervosa whereas plasma ghrelin levels are decreased in obese subjects and states of acute caloric intake. In rodents, peripheral administration of ghrelin stimulates an acute increase in food intake and reduces the utilization of fats and thereby decreases the energy expenditure and induces adiposity in them.[16]

Several studies in animal models and few human clinical trials have demonstrated the efficacy of ghrelin or ghrelin receptor (GHS-R) agonists in the treatment of cancer cachexia. However, further large-scale, long-term multi-centric randomized clinical trials are needed to confirm sustained effects. Recently, Rikkunshito, a Japanese traditional medicine has been shown to stimulate endogenous secretion of and thereby increase the food intake.[17] Clinical trials have demonstrated that ghrelin incr that the effectiveness of ghrelin in increasing lean

body mass and activity in cachexia caused by chronic heart failure, chronic respiratory disease, anorexia nervosa, functional dyspepsia, and cancer. Ghrelin functions as anabolic, orexigenic, and anti-inflammatory agent. So administration of ghrelin may be able to improve quality of life in cachectic patients. Besides playing a role in short-term regulation of food intake, ghrelin might also play a role in long-term regulation of energy balance.

Ghrelin enhances the deposition of lipids in visceral tissues and increases the chances of developing insulin resistance. Ghrelin favors the overexpression of the fatty genes that bring about the retention of lipids thereby leading to hypertension or T 2DM. These effects of ghrelin on lipid metabolism promotes the development of metabolic syndrome.

Ghrelin has emerged as the first identified circulating hunger stimulating peptide. Ghrelin and synthetic ghrelin mimetics (the growth hormone secretagogues) increase food intake and increase fat mass by an action exerted at the level of the hypothalamus.[18] They activate the orexigenic neuropeptide Y (NPY) neurons in the arcuate nucleus.[19] Ghrelin also activates the mesolimbic cholinergic-dopaminergic reward link, a circuit that communicates the natural rewards, such as food, as well as of addictive drugs, such as ethanol. There is also strong evidence that ghrelin has a peripheral appetite modulatory effect on satiety by affecting the mechano-sensitivity of gastric vagal afferents, making them less sensitive to distension resulting in over eating. A pre-meal rise of human plasma ghrelin, suggests a possible role of ghrelin as a hunger signal triggering meal initiation. In rodents, fasting and hypoglycemia increase ghrelin levels, whereas intake of food, especially carbohydrates (dextrose), decreases ghrelin secretion.[20]

In humans, circulating levels of ghrelin bears a negative correlation with the basal metabolic index. The levels of ghrelin increase when obese subjects lose weight, and decrease when the patients of anorexia nervosa gain weight. This shows that the levels of ghrelin alter in response to diet to maintain body weight.[21,22] Circulating levels of ghrelin reduce after gastrectomy, which contributes to the weight-reducing effect of this procedure. Alterations in other gut peptides involved in regulation of appetite may also contribute to this effect. Ghrelin, a hormone which regulates hunger, is mainly produced in the fundus of the stomach. By resecting the fundus, the major portion of the ghrelin-producing cells are removed, thus reducing plasma ghrelin levels and subsequently hunger and weight loss.[17] Ghrelin levels decreases because the majority of ghrelin- producing cells, isolated from contact with enteral nutrients, undergo override inhibition.[18] An empty stomach and duodenum, stimulates the production of ghrelin and after gastric bypass, ghrelin production is paradoxically inhibited. This phenomenon is similar to the paradoxical inhibition of gonadotropins by continuous signaling from GnRH.[19]

Ghrelin also shows its effects on brain regions involved in reward and motivation.[22] It has been observed that after an infusion of ghrelin, the reward centers respond more strongly to pictures of food. A study has demonstrated that ghrelin promotes hunger and appetite by increasing reward signaling in the nucleus accumbens.

Ghrelin increases the appeal of high-calorie foods over low-calorie foods. The ghrelin secreting cells of the stomach show a circadian rhythm and coordinate the anticipation of food with metabolic cycles. Ghrelin is released from the stomach into the circulation prior to mealtime. It triggers food-seeking behavior and moderates the normal eating habits. It shows that the stomach tells the brain when to eat, and thus maintaining a regular meal plan regulates the release of ghrelin by the stomach.[14] Ghrelin plays an important role in food intake that is driven by the pleasure of food rather than by hunger for food. Thus future therapies for obesity could be improved with drugs that suppress ghrelin's effects on the reward system.[15]

CONCLUSION

Ghrelin, a hormone produced principally by the stomach, is the only known circulating orexigen produced in response to hunger. It circulates in the blood and serves as a signal to stimulate feeding. The effects of ghrelin on energy balance are at least in a large part mediated by the hypothalamus. Besides playing a role in short-term regulation of food intake, ghrelin also play a role in long-term regulation of energy balance. Ghrelin modulates the expression of various hypothalamic peptides and attenuates leptin-induced reduction in food intake and body weight. It also has specific effects on many brain regions implicated in reward and motivation. Very less information is available and this has to be investigated in order to develop therapeutic drugs.

Implications for Practice: There is not enough evidence to support the use of ghrelin in patients with cachexia or

anorexia nervosa or its inhibitors in tackling obesity. However the sparse existing data indicate that these patients might benefit from ghrelin analogues.

Implications for Research: Further good quality randomized controlled trials assessing the effect of ghrelin on appetite are required. The role of ghrelin as a therapeutic agent for cachexia, anorexia nervosa, obesity and other metabolic diseases needs to be explored.

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