Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2017; 9(1): 51-54

DOI number: 10.25258/ijpcr.v9i1.8263

ISSN- 0975 1556

Research Article

Ghrelin and Obesity-An Update

Gandhi M[1], Swaminathan S[2]

[1]Department of Biochemistry, Vels University, Chennai-600117 and Lab Technologist, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram Chennai-600095.
[2]Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai-600095.

Available Online: 25th January, 2017

ABSTRACT
Ghrelin as human natural hormones is involved in fundamental regulatory process of eating and energy balance. It is a stomach derived hormone that acts as at the ghrelin receptor in multiple tissues throughout to the body. Its properties includes increasing appetite, decreasing systemic inflammation, decreasing vascular resistance ,increasing cardiac output, increasing glucose and IGF-1 levels, Hence it may play a significant role in Diabetes mellitus. Many studies have linked ghrelin to obesity and this paper is an attempt to bring out recent findings on the role of ghrelin in Diabetes Mellitus, particularly type2 Diabetes mellitus.

Keywords: Ghrelin, Obesity, Diabetes mellitus.

INTRODUCTION

Ghrelin is a peptide hormone comprising 28 amino acids from a 94 long amino acid precursor proghrelin. It is an orexigenic hormone. It is produced by x/A cells of oxyntic glands present in the mucosal layer of the fundus region of stomach. Traces of ghrelin are also produced in the pancreas, hypothalamus and kidney glomeruli. It is an appetite stimulating hormone which sends "feed me" message to brain and it is part of the built in defence mechanism to protect against famine and starvation. The factors that cause increased secretion of ghrelin includes dieting exercise, during starvation and famine and when ghrelin level increases, metabolism drops leading to hungry mood and more eating habits. Ghrelin signals the nutrient availability from the gastrointestinal tract to the central nerves system. Ghrelin does more to exert it's probably sentinel role allowed "human energy". For clinical applications, not only the natural ghrelin and its variants but also several modified or artificial molecules acting at ghrelin associated receptors are developed, but current clinical applications are related to clinical trials only. Several clinical trials are involving focussing mainly on chronic renal failure, cancer, chronic obstructive pulmonary disease, end stage renal disease, and cystic fibrosis. Ghrelin of late plays a significant role in obesity and type2 Diabetes mellitus.

Literature Review

Ghrelin is a 28-amino acid peptide secreted mainly from the X/A-like cells of the stomach. Ghrelin is found in circulation in both a des-acyl (dAG) and acyl form (AG). Acylation is catalysed by the enzyme ghrelin O-acyltransferase (GOAT). AG acts on the growth hormone secretagogue receptor (GHSR) in the central nervous system (CNS) to promote feeding and adiposity, and also acts on GHSR in the pancreas to inhibit glucose-stimulated insulin secretion. These well-described actions of AG have made it a popular target for obesity and type 2 diabetes (T2DM) pharmacotherapies[1]. Ghrelin regulates homeostatic food intake, hedonic eating, and is a mediator in the stress response. In addition, ghrelin has metabolic, cardiovascular, and anti-aging effects. Among the obese subjects, plasma ghrelinconcentrations were negatively correlated with insulin resistance, but were not significantly correlated with blood pressure, heart rate or telomere length. Total plasma ghrelin and its associations with food intake, hedonic eating, and stress are decreased in obesity, providing evidence consistent with the theory that central resistance to ghrelin develops in obesity and ghrelin's function in appetite regulation may have evolved to prevent starvation in food scarcity rather than cope with modern food excess. Furthermore, ghrelin is associated with metabolic and cardiovascular health, and may have anti-aging effects, but these effects may be attenuated in obesity[2].

Adipose tissue macrophages (ATMs) have emerged as a major pathogenic factor for obesity and insulin resistance. High fructose corn syrup (HFCS) has detrimental effects on metabolism, suggesting that dietary guidelines on HFCS consumption for Americans may need to be revisited. GHSR deletion mitigates the effects of HFCS on adipose inflammation and insulin resistance, suggesting that GHSR antagonists may represent a novel therapy for insulin resistance[3]. Exercise increased postprandial fullness in the T2DM group ($P < 0.05$), while plasma ghrelin levels were unaffected. Our data suggest that the presence of T2DM likely drives suppressed ghrelin levels and poor appetite regulation, but a single exercise bout is sufficient to restore oral glucose-induced fullness independently of ghrelin[4]. Ghrelin could be blocked by GHSR antagonist [d-Lys-3]-GHRP-6 or BIM28163. RIA

**Author for Correspondence: glorynathan@gmail.com*

and real-time polymerase chain reaction data showed that the levels of ghrelin in the plasma, stomach and ghrelin mRNA in the Arc increased at first but decreased later and the expression of GHSR-1a mRNA in the Arc maintained a low level in DM rats. The present findings indicate that ghrelin could regulate the activity of Gastric distension sensitive neurons and gastric motility disorder in diabetes[5].
Postprandial ghrelin suppression may be part of the mechanism that contributes to diabetes remission after Roux-en-Y gastric bypass surgery[6]. Much attention is focused on the enzyme called GOAT, which mediates the physiological functions of ghrelin. Acyl-ghrelin and des-acyl-ghrelin appear to have opposite glucoregulatory effects. The regulation of acylation by GOAT seems therefore to play a role in mediating glucose metabolism. The modulation of GOAT or ghrelin signaling may be a clinically relevant strategy to treat obesity and metabolic diseases such as T2DM[7]. During severe calorie restriction, Ghrelin increases blood glucose concentrations in order to maintain glucose homeostasis. In diet-induced obesity, ghrelin exacerbates hyperglycemia and promotes a diabetic phenotype[8].
Ghrelin is a peptide hormone from stomach with growth hormone releasing activity. It is also able to modify glucose and insulin metabolism, blood pressure levels, abiogenesis, and inflammatory processes in experimental conditions. Whether ghrelin has arole in the development metabolic syndrome and the associated diseases, is not known. This review will report the evidence for the role of ghrelin in the clustering of the components of the metabolic syndrome [9]. Ghrelin is a 28-amino-acid peptide that displays a strong growth hormone- (GH) releasing activity through the activation of the GHSR. Low plasma ghrelin levels are associated with elevated fasting insulin levels and insulin resistance, suggesting both physiological and pathophysiological roles for ghrelin. For this reason, at least theoretically, ghrelin and/or its signalling manipulation could be useful for the treatment or prevention of diseases of glucose homeostasis such as type 2 diabetes[10]. Postprandial desacyl ghrelin levels can be a sensitive biomarker of carbohydrate metabolism. The combination of white rice with barley plays a beneficial role in preventing and treating T2DM, obesity and other metabolic diseases[11.]
Patients with diabetes with gastroparesis showed no decrease of plasma ghrelin after glucose loading, unlike patients without gastroparesis or healthy controls. Diabetes mellitus with autonomic neuropathy, but not those without it, also showed no decrease of plasma ghrelin after glucose loading. Diabetic gastroparesis may be related to ghrelin associated neurohormonal abnormalities, but the pathophysiological meaning of this abnormal ghrelin response needs further clarification[12]. The incidence of postprandial antropyloric coordination was significantly increased in streptozotocin (STZ) rats, compared with that of control rats ($P < 0.05$). Treatments with anti-ghrelin antibodies suppressed this enhanced antropyloric coordination in STZ rats. Our study suggests that elevated endogenous ghrelin enhances antropyloric coordination, which accelerates gastric emptying in the early stages of diabetes[13]. Leptin could be of importance for suppression of basal ghrelin during moderate weight gain in normoinsulinemic subjects, whereas hyperinsulinemia but not leptin is responsible in more severe obesity. Postprandial suppression of ghrelin is attenuated by as yet unknown mechanisms that are related to body weight but not to insulin or T2DM[14].
At present, it is not clear whether nutrients suppress the plasma ghrelin concentration directly or indirectly by stimulating insulin secretion.1). Insulin is essential for meal-induced plasma ghrelin suppression, 2). Basal insulin availability is sufficient for postprandial ghrelin suppression in type 1 diabetic subjects, and 3). Lack of meal-induced ghrelin suppression caused by severe insulin deficiency may explain hyperphagia of uncontrolled type 1 diabetic subjects[15]. Experimental studies have suggested that ghrelin plays a role in glucose homeostasis and in the regulation of blood pressure (BP). Low ghrelin is independently associated with type 2 diabetes, insulin concentration, insulin resistance, and elevated BP. Therefore, it might have some role in the etiology of type 2 DM and the regulation of BP. The ghrelin Arg51Gln mutation is associated with low plasma ghrelin concentrations[16]. Measurement of salivary ghrelin and its relationship to other salivary parameters might help to provide insight into the role of ghrelin in diabetes[17.]
Enhanced Neuropeptide Y and reduced alpha-melanocyte stimulating hormone expression are secondary to the release of ghrelin, which should be considered the underlying trigger of hyperphagia associated with uncontrolled diabetes[18.] Exercise performed the night before a meal suppresses acylated ghrelin concentrations in Normal weight(NW) individuals without altering perceived hunger or fullness. In Obese individuals, despite no changes in acylated ghrelin concentrations, exercise reduced the fullness response to the test meal. Acylated ghrelin and perceived fullness responses are differently altered by acute aerobic exercise in NW and Obese individuals[19]. Additional source of ghrelin and probably changes in activity of ghrelin o-acylotransferase, are responsible for the high concentration of ghrelin in the obese woman[20]. The number of ghrelin immunoreactive cells was significantly reduced in obese patients with higher compared to lowerbody mass index (BMI). Also, the ghrelin-acylating enzyme ghrelin-O-acyltransferase decreased with increasing BMI[21].
The prominent role of the ghrelinergic system in the regulation of feeding gives rise to it as an effective target for the development of successful antiobesity pharmacotherapies that not only affect satiety but also selectively modulate the rewarding properties of food and reduce the desire to eat[22]. The pathophysiological mechanism responsible for GH hyposecretion in obesity is probably multifactorial, and there is probably a defect in ghrelin secretion. Ghrelin is the only known circulating orexigenic factor, and has been found to be reduced in obese humans. Ghrelin levels in blood decrease during periods of feeding. Due to its orexigenic and metabolic effects, ghrelin has a potential benefit in antagonizing protein breakdown and weight loss in catabolic conditions

such as cancer cachexia, renal and cardiac disease, and age-related frailty. Theoretically ghrelin receptor antagonists could be employed as anti-obesity drugs, blocking the orexigenic signal. By blocking the constitutive receptor activity, inverse agonists of the ghrelin receptor may lower the set-point for hunger, and could be used for the treatment of obesity. In summary, ghrelin secretion is reduced inobesity, and could be partly responsible for GH hyposecretion in obesity; ghrelin antagonist or partial inverse agonists should be considered for the treatment of obesity [23].

Ghrelinergic system as an effective target for the development of successful anti-obesity pharmacotherapies, which not only affects appetite but also selectively modulates the rewarding properties of food and impact on psychological well-being in conditions of stress, anxiety and depression[24]. Ghrelin was shown to be synthesized in the cardiovascular system, heart muscle cells, tails of the sperms, hair follicles, lacrimal glands, tongue, and teeth of rats for the first time in this study and ghrelin syntheses in these tissues were found to decrease in obesity. Nutritional obesity is among the most common causes of obesity and the findings we have obtained through diet-induced obesity will contribute to the illumination of the etiopathology of obesity[25].

Higher growth hormone was associated with lower ghrelin in lean individuals. Results suggest that glucoregulatory homeostasis is altered with increasing levels of obesity and that these alterations may mediate the response of cortisol and ghrelin in response toResistance exercise[26]. Ghrelin exerts potent anti-inflammatory effects in macrophages and functions as a mediator of the beneficial effects of exercise training[27]. During severe calorie restriction, ghrelin increases blood glucose concentrations in order to maintain glucose homeostasis. In diet-induced obesity, ghrelin exacerbates hyperglycemia and promotes a diabetic phenotype[28]. Altered ghrelin levels have also been observed in Cushing's syndrome and thyroid disease probably due to the secondary insulin resistance in these subjects[29].

Ghrelin play an important role in obesity-pain relationship and/or regulate other systems that are related to pain pathway. Based on the above analyses, we propose a hypothesis that the diminution of the susceptibility to pain in lean subjects/animals may be induced by the increase in endogenous ghrelin activity, or increased of the susceptibility to pain in obese subject/animals may be induced by the decrease in endogenous ghrelin activity[30]. Acylated ghrelin also induced hepatic steatosis, increasing lipid droplet number and triacylglycerol content by a GHS-R (1a)-dependent mechanism. Our data imply that, during periods of energy insufficiency, exposure to acylated ghrelin may limit energy utilization in specific WAT depots by GHS-R (1a)-dependent lipid retention[31]. Serum factors and physiological states influence the rate at which ghrelin is transported across the blood-brain barrier[32]. An increased fat mass per se does not exert an inhibitory effect on ghrelin homeostasis during ingestion of the HF diet. Additionally, the magnitude of change in plasma ghrelin in response to fasting was not blunted, indicating that a presumed, endogenous signal for activation of ingestive behavior remains intact, despite excess stored calories in HF-fed rats[33.]

Although much more exploration is needed, we placed more emphasis on reviewing studies during different physiological states when conclusions are less dependent on measurement of ghrelin. Despite these shortcomings, we conclude that there is ample evidence indicating ghrelin participates in regulating energy balance[34]. This reduced weight gain was associated with decreased adiposity and increased energy expenditure and locomotor activity as the animals aged. Despite the absence of ghrelin, these Ghrl-/- mice showed a paradoxical preservation of the GH/IGF-1 axis, similar to that reported in lean compared with obese humans [35].

CONCLUSIONS

This review article on ghrelin and obesity has brought the research work done in this during the last 10 years bringing into focus the recent developments. Most of the findings on to use of ghrelin are on only at the clinical trial level and more such works have to be done before actually implementing its use on Diabetic patients. More research works are necessary in this field before it is actually recognised as a marker for treating DM patients.

REFERENCES

1. Heppner KM,Tong J, Regulation of glucose metabolism by the ghrelin system multiple players and multiple actions. Eur J Endocrinal, 2014; Apr 8.
2. Buss J, Havel PJ, Epel E, Lin J, Blackburn E, Daubenmier J. Associations of ghrelin with eating behaviors, stress, metabolic factors, and telomere length among overweight and obese women preliminary evidence of attenuated ghrelin effects in obesity?. Appetite. 2014;76:84-94.
3. Ma X, Lin L, Yue J, Pradhan G, Qin G, Minze LJ, Wu H, Sheikh-Hamad D, Smith CW, Sun Y.Ghrelin receptor regulates HFCS-induced adipose inflammation and insulin resistance. Nutr Diabetes. 2013.
4. Knudsen SH, Karstoft K, Solomon TP. Impaired postprandial fullness in Type 2 diabetic subjects is rescued by acute exercise independently of total and acylated ghrelin. J ApplPhysiol. 2013; 1:115(5):618-25.
5. Xu L, Qu Z, Guo F, Pang M, Gao S, Zhu H, Gu F, Sun X. Effects of ghrelin on gastric distention sensitive neurons in the arcuate nucleus of hypothalamus and gastric motility in diabetic rats. eptides. 2013; 48:137-46.
6. Samat A, Malin SK, Huang H, Schauer PR, Kirwan JP, Kashyap SR. Ghrelin suppression is associated with weight loss and insulin action following gastric bypass surgery at 12 months in obese adults with type2 diabetes. Diabetes ObesMetab. 2013; 15(10):963-6.
7. Otto-Buczkowska E, Chobot A.Role of ghrelin and leptin in the regulation of carbohydrate metabolism. Part I. Ghrelin.Postepy Hig Med Dosw (Online).2012 ; 26;66:795-8.

8. Briggs D, Andrews ZB. A recent update on the role of ghrelin in glucose homeostasis.Curr Diabetes Rev. 2011;7(3):201-7.
9. Ukkola O. Ghrelin in Type 2 diabetes mellitus and metabolic syndrome. Mol Cell Endocrinol. 2011; 20; 340(1):26-8.
10. Sangiao-Alvarellos S, Cordido F.Effect of ghrelin on glucose-insulin homeostasis therapeutic implications. Int J Pept. 2010.
11. Sakuma M, Yamanaka-Okumura H, Naniwa Y, Matsumoto D, Tsunematsu M, Yamamoto H, Taketani Y, Takeda E.Dose-dependent effects of barley cooked with white rice on postprandial glucose and desacyl ghrelin levels. J ClinBiochem Nutr. 2009; 44(2):151-9.
12. Asai S, Katabami T, Obi N, Matsui T, Kato H, Obi R, Ogawa Y, Kawata T, Takama H, Ohta A, Tanaka Y.No ghrelin response to oral glucose in diabetes mellitus with gastroparesis. Endocr J. 2009; 56(1):79-87.
13. Ariga H, Imai K, Chen C, Mantyh C, Pappas TN, Takahashi T.Does ghrelin explain accelerated gastric emptying in the early stages of diabetes mellitus?. Am J Physiol RegulIntegr Comp Physiol. 2008; 294(6):R1807-12.
14. Erdmann J, Lippl F, Wagenpfeil S, Schusdziarra V. Differential association of basal and postprandial plasma ghrelin with leptin, insulin, and type 2 diabetes. Diabetes. 2005;54(5):1371-8.
15. Murdolo G, Lucidi P, Di Loreto C, Parlanti N, De Cicco A, Fatone C, Fanelli CG, Bolli GB, Santeusanio F, De Feo P.Insulin is required for prandial ghrelin suppression in humans. Diabetes. 2003; 52(12):2923-7.
16. PoykkoSM, Kellokoski E, Horkko S, Kauma H, Kesaniemi YA, Ukkola O.Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes. 2003; 52(10):2546-53.
17. Aydin S. A comparison of ghrelin, glucose, alpha-amylase and protein levels in saliva from diabetics. J BiochemMol Biol. 2007; 31:40(1):29-35.
18. Dong J, Peeters TL, De Smet B, Moechars D, Delporte C, VandenBerghe P, Coulie B, Tang M, Depoortere I.Role of endogenous ghrelin in the hyperphagia of mice with streptozotocin-induced diabetes. Endocrinology. 2006; 147(6):2634-42.
19. Heden TD, Liu Y, Park Y, Dellsperger KC, Kanaley JA. Acute aerobic exercise differentially alters acylated ghrelin and perceived fullness in normal-weight and obese individuals. J ApplPhysiol 2013; 1:115(5):680-7.
20. Kasacka, Arciszewski M, Łebkowski W.Extraordinary level of hormone and number of ghrelin cells in the stomach and duodenum of an obese woman.ActaHistochem. 2014; 116(1):230-4.
21. Stengel A, Hofmann T, Goebel-Stengel M, Lembke V, Ahnis A, Elbelt U, Lambrecht NW, Ordemann J, Klapp BF, Kobelt P.Ghrelin and NUCB2/nesfatin-1 are expressed in the same gastric cell and differentially correlated with body mass index in obese subjects. Histochem Cell Biol. 2013; 139(6):909-18.
22. Schellekens H, Dinan TG, Cryan JF.Ghrelin at the interface of obesity and reward.VitamHorm. 2013; 91:285-323.
23. Alvarez-Castro P, Pena L, Cordido F.Ghrelin in obesity, physiological and pharmacological considerations. Mini Rev Med Chem. 2013; 13(4):541-52.
24. Schellekens H, Finger BC, Dinan TG, Cryan JF.Ghrelin signalling and obesity at the interface of stress, mood and food reward.PharmacolTher.2012; 135(3):316-26.
25. Aydin S, Sahin I, Ozkan Y, Dag E, Gunay A, Guzel SP, Catak Z, Ozercan MR. Examination of the tissue ghrelin expression of rats with diet-induced obesity using radioimmunoassay and immunohistochemical methods. Mol Cell Biochem. 2012; 365(1-2):165-73.
26. Thomas GA, Kraemer WJ, Comstock BA, Dunn-Lewis C, Volek JS, Denegar CR, Maresh CM.Effects of resistance exercise and obesity level on ghrelin and cortisol in men. Metabolism 2012; 61(6):860-8.
27. Kizaki T, Maegawa T, Sakurai T, Ogasawara JE, Ookawara T, Oh-ishi S, Izawa T, Haga S, Ohno H.Voluntary exercise attenuates obesity-associated inflammation through ghrelin expressed in macrophages. BiochemBiophys Res Commun 2011; 413(3):454-9.
28. Briggs DI, Andrews ZB.A recent update on the role of ghrelin in glucose homeostasis. Curr Diabetes Rev. 2011;7(3):201-7.
29. Scerif M, Goldstone AP, Korbonits M.Ghrelin in obesity and endocrine diseases. Mol Cell Endocrinol. 2011; 20:340(1):15-25.
30. Guneli E, Gumustekin M, Ates M. Possible involvement of ghrelin on pain threshold in obesity. Med Hypotheses. 2010; 74(3):452-4.
31. Davies JS, Kotokorpi P, Eccles SR, Barnes SK, Tokarczuk PF, Allen SK, Whitworth HS, Guschina IA, Evans BA, Mode A, Zigman JM, Wells T.Ghrelin induces abdominal obesity via GHS-R-dependent lipid retention. MolEndocrinol. 2009;23(6):914-24.
32. Banks WA, Burney BO, Robinson SM.Effects of triglycerides, obesity, and starvation on ghrelin transport across the blood-brain barrier. Peptides. 2008; 29(11):2061-5.
33. Qi X, Reed JT, Wang G, Han S, Englander EW, Greeley GH Jr. Ghrelin secretion is not reduced by increased fat mass during diet-induced obesity. Am J Physiol RegulIntegr Comp Physiol. 2008; 295(2):R429-35.
34. Heiman ML, Witcher DR.Ghrelin in obesity. MetabSyndrRelatDisord. 2006;4(1):37-42.
35. Wortley KE, del Rincon JP, Murray JD, Garcia K, Iida K, Thorner MO, Sleeman MW. Absence of ghrelin protects against early-onset obesity. J Clin Invest. 2005; 115(12):3573-8.