ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 6, Issue 4, 2013

ISSN - 0974-2441

Review Article

GHRELIN –A REVIEW

HEMAMALINI BALAJI

Saveetha Dental College and Hospitals, 162,Poonamalle High Road, Chennai,Tamil Nadu,India. Email: b.hemamalini27@gmail.com

Received: 22 August 2013, Revised and Accepted: 22 September 2013

ABSTRACT

Ghrelin is a neuroendocrine hormone which is an octanoylated 28-residue peptide that exerts numerous physiological functions. It is produced primarily by the P/D1 cells of the gastric fundus. Ghrelin targets highly conserved G protein-coupled receptor known as the growth hormone secretagagogue receptor subtype 1a (GHS-R1a). Ghrelin plays a central role in energy balance and metabolism.[1]
Purpose of this Review: The Purpose of this review is to Compile the up –to date studies on the Functional effects of Ghrelin on various systems of Human body thus establishing link between pharmaco therapeutic effects of Ghrelin on certain Metabolic Disorders like obesity,diabetes and Neuro endocrine disorders.

Keywords: Ghrelin, Hormonal Secretion, GastricRegulation, Growth Hormone

Introduction:

Ghrelin and GHS-R1a are known to have important biological actions in many physiological processes, such as the central regulation of food intake and energy homeostasis [2], regulation of cardiovascular functions [3,4], stimulation of gastric acid secretion and motility [5], modulation of cell proliferation and survival [6], and inhibition of inflammation and regulation of immune function [7,8].

Each of its role will be described in detail below with evidences. The main goal of this review is not to provide an integral overview of previous research, but to indicate the importance of ghrelin in the regulation of blood glucose,energy balance, and implications for the treatment of disorders like diabetes and obesity .

Physiological Functions of Ghrelin

S.no	System Involved	Effect of Ghrelin		References
1.	Anabolic effects	Appetite	Increased	12,25
		Adipocity	Increased	50-52
		Blood Glucose	Increased	26,27
2.	Hormone secretion	Release of Growth Hormone	Increased	13,17,18
		Release of ACTH	Weakly Increased	11,24
		Release of Cortisol	Weakly Increased	11,24
		Release of Prolactin	Increased	11,24
		Insulin	Increased /Decreased	10,14,19,23
3.	Gastric Functions	Gastric Acid Secretion	Increased	15
		Gastric Motility	Increased	20
		Turn over of gastric and intestinal mucosa	Increased	9
4.	Cardio vascular System	Cardiac Output	Increased	21
		Blood Pressure	Decreased	16,22

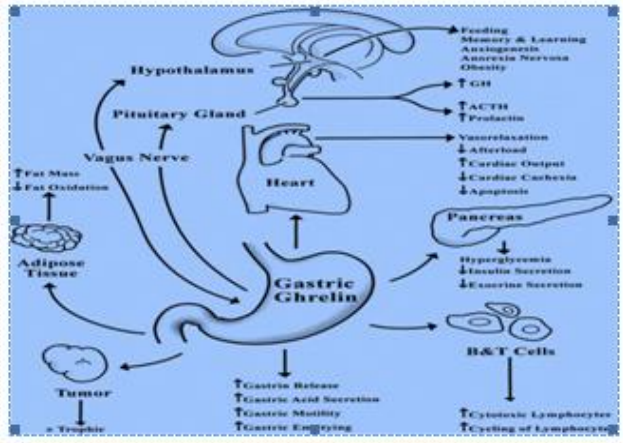

Fig.1: Functions of Ghrelin on various systems has been represented diagrammatically

Ghrelin and its effect on Hormonal Secretion:

Ghrelin has shown maximal stimulation of growth hormone by 2 to 3 folds greater than that of GHRH [28] . Ghrelin can be injected in two ways.

- Intravenous injection
- Intra cerebroventricular administration

Intravenous injection of Ghrelin in anasthetized rats may produce an increase in plasma GH concentration from 12.0 +/- 5.4 ng/ml to 129.7+/- 11.3ng/ml[18]. A single intracerebroventricular administration of ghrelin also increased rat plasma GH concentration in a dose- dependent manner, with a minimum dose of only 10pmol.[13]. Thus the latter appears to be a more potent route . In addition, high doses of ghrelin in humans increase ACTH, prolactin, and cortisol levels .[11,24].

Ghrelin and its effect on cardiovascular Functions

Evidence for cardiovascular function of ghrelin has been found: expression of mRNA encoding both ghrelin and its receptor has been observed in the heart and aortas [16,22] and intravenous injection

of ghrelin into human volunteers induces a decrease in blood pressure[22].

An intravenous bolus of human ghrelin decreased mean arterial pressure without changing the heart rete [22,29]. Ghrelin also increased the cardiac index and stroke volume indices. Rats with chronic heart failure (CHF) that were treated with ghrelin showed higher cardiac output, stroke volume, and left ventricular dP/dt-[max] compared with afflicted, but placebo-treated controls [21].

Ghrelin and its effect on Gastric Functions

Ghrelin is a gastric peptide released from oxyntic cells in the stomach [30].Plasma levels of ghrelin rise prior to meals and rapidly decline when food is consumed .[31].Exogenous ghrelin administration increases food intake [32]and ghrelin is thought to play a role in meal initiation. Examinations of meal patterns in response to ghrelin administration have demonstrated major effects on meal number with smaller effects on the size of spontaneous meals[33]. Central and peripheral ghrelin administration results in increased expression of the orexigenic peptides NPY and AgRP within the hypothalamic arcuate nucleus suggesting a common final pathway for the feeding stimulatory effects[34,35]. Ghrelin transport across the blood brain barrier has been demonstrated suggesting that such hypothalamic sites may be directly sensing alterations in plasma ghrelin levels[36]. These sites do contain ghrelin receptors [37].

In addition to a hypothalamic mode of action for ghrelin, the brainstem also has been suggested to play a role. Ghrelin receptors are also expressed by extra-hypothalamic cells including those of the dorsal vagal complex [38].Central and peripheral administration of ghrelin activates cells in the nucleus of the solitary tract and area postrema as indicated by an increase in the number of c-fos positive cells[39]. Administration of ghrelin in the fourth ventricle or directly in the dorsal vagal complex results in a hyperphagic response with a magnitude similar to the one obtained after injection into the third ventricle [33].The ability of peripheral and central injections of ghrelin into the forebrain or brainstem to stimulate food intake and increase arcuate NPY mRNA expression suggests a distributed ghrelin system that mediates changes in food intake through a final common output involving the arcuate nucleus [35].

Intravenous administration of ghrelin dose-dependently increases gastric acid secretion and stimulates gastric motility[15,20]. The maximum response to ghrelin in terms of gastric acid secretion is almost as high as that elicited 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 og ghrelin also increases gastric acid secretion in a dose-dependent manner[40].

Ghrelin and its effect on Glucose Regulation

Immunohistochemical analyses have demonstrated that ghrelin is endogenously expressed in pancreatic islets in theα-, β-, and δ-cells, while the GSH-R1a is expressed primarily on pancreatic α- and β-cells [41]. These findings indicate that the regulation of ghrelin and insulin is tightly linked. In addition to obesity, low plasma ghrelin levels have been associated with major hallmarks of metabolic syndrome, such as hyperinsulinemia and insulin resistance [42]. Ghrelin's ability to regulate glucose metabolism via insulin is another essential mechanism through which it mediates energy homeostasis. In both humans and rodents, acute ghrelin administration has been shown to induce hyperglycemia and reduce insulin secretion [43]. In rodents, this effect was shown to be completely lost with the administration of a GHS-R antagonist, demonstrating the importance of the ghrelin receptor in mediating this effect [44]. It is thought that stomach derived ghrelin acts distally in the brain to regulate food intake, while pancreatic ghrelin acts locally to influence insulin release as a paracrine hormone.

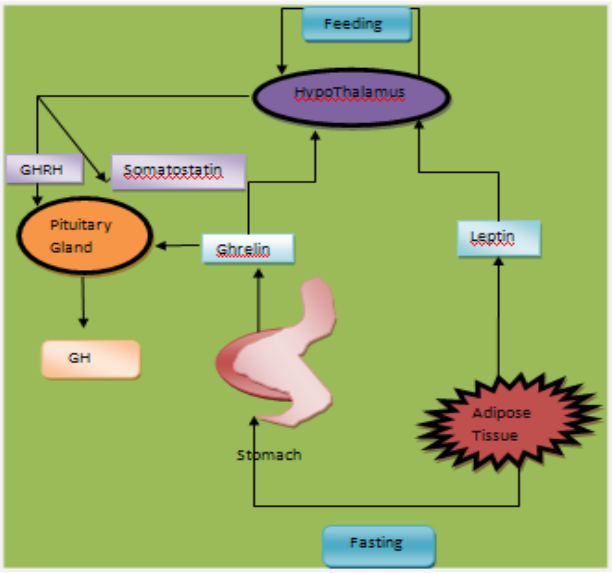

Fig1: Effects of Ghrelin on Gastric Functions in fasting and Feeding conditions

Ghrelin and its effect on Obesity

Obesity

Obesity is a widespread health issue caused by chronic impaired balance between energy supply and its expenditure. It leads to gathering of excessive fat tissue and numerous co-morbidities.As ghrelin is functionally associated with energy balance,it is intimately related to obesity.

Data –Rise in Obesity

. Obesity adversely affects health by increasing the risk for various associated conditions including metabolic syndrome, type 2 diabetes, coronary artery disease, and hypertension, all of which are associated with increased mortality [45].

The economic ramifications of this consistent rise in obesity were estimated to be $75 billion in 2003, of which roughly half was subsidized by Medicare and Medicaid [46]. Within the United States, the percentage of the population aged 20–74 considered to be overweight or obese (BMI >25) has increased from 45.8% in the early 1960s to over 72% in the year 2006, and this number continues to rise rapidly [47]

A recent research highlighted above known points towards ghrelin as a key modulator of energy metabolism during negative energy balance and starvation. Most notably, knockout models show that ghrelin is indispensable for blood glucose control during starvation. Whether or not ghrelin plays a role in the pathogenesis of diabetes, by promoting hyperglycemia, remains to be determined. In DIO, the actions of ghrelin to increase food intake in the brain are suppressed at the level of the hypothalamic ARC nucleus. Furthermore, ghrelin peptide in the circulation, as well as ghrelin and mRNA in the stomach and GHSR in the hypothalamus are all reduced.These observations further support the important role of ghrelin in negative energy balance, rather than positive energy balance, i.e. obesity. [48].

Appetite and feeding behavior are regulated by a complex balance of stimulatory and inhibitory signals in the central nervous system, particularly in the hypothalamus.

[49] Essential elements of this control system are ghrelin and leptin, both of which signal nutritional status and energy storage levels to the hypothalamic feeding centers. Ghrelin is orexigenic when

administered both centrally and peripherally, and it is one of several appetite-regulating humoral signals to the central nervous system.

GHRELIN IN OBESITY

The discovery of ghrelin and its influence on appetite, fuel utilization, and body weight added complexity to centrally regulated energy balance. In general, human plasma ghrelin levels are inversely correlated with positive energy balance, body mass index, body fat mass, adipocyte size, and leptin levels,[50-51] while they are lower in obese subjects than in controls.

A Study states that[52] Indians, known for their propensity to develop type II diabetes and obesity, also have lower circulating ghrelin levels, independent of body mass index, compared with matched controls.

Patients with anorexia nervosa exhibit high plasma ghrelin levels when compared with age- and sex-matched controls, and weight gain decreases their elevated ghrelin concentrations.[52]

Thus,there are fluctuations of plasma ghrelin levels with respect to physiological adaptation of long-term alterations in energy balance.[53]

Plasma leptin correlates with body fat content despite its anorectic effects, suggesting that human obesity is associated with a state of leptin resistance. However, 5%–10% of obese people have relatively low levels of leptin, indicative of a reduced rate of leptin production.[54-55]

A recent study by Barazzoni et al reported that hyperleptinemia blunted the increase of serum ghrelin during caloric restriction, suggesting that the anorectic effects of leptin act both via direct central actions, and via peripheral inhibition of orexigenic effects of ghrelin.[56]

Given the orexigenic and adipogenic properties of ghrelin, treatment with an antagonist would seem logical in obesity. In animal studies, the biologic actions of the ghrelin antagonist ([D-Lys-3]-GHRP-6) appear to be mediated through GHSR antagonism.[57]

This antagonist has been shown to inhibit ghrelin-induced GH release[58-59] and to reduce food intake and body weight gain in mice.[57]

Korbonits et al further substantiated this observation noting that obese children carrying the single nucleotide polymorphism (a nonconservative amino acid change in the protein sequence in the C-terminal tail of the preproghrelin protein) have higher body mass index, and reduced insulin secretion. [50] .Recent evidence indicated that elevated serum ghrelin may be responsible, at least in part, for the hyperphagia observed in patients with PWS.[60]

The mechanism underlying elevated ghrelin levels in PWS is unknown, but is not likely to reflect a mutation of the genes encoding ghrelin or GHRS, but rather genetic alteration(s) on chromosome 15 indirectly affecting ghrelin expression. High ghrelin levels in PWS are also unlikely to arise from a decreased negative feedback from GH; Janssen et al have shown that ghrelin concentrations are not elevated in adults with GH deficiency, and GH therapy in these same individuals does not alter their ghrelin levels.[61-63]

Similar findings were also observed in obese subjects and children with PWS.[64].Regardless of the etiology of elevated ghrelin in PWS, additional studies will be required to validate the functional activity of ghrelin by demonstrating whether ghrelin antagonists effectively reduce food intake in PWS.[65,66]

CONCLUSION

This Review serve to provide a compiled Version of many of the recent Literature on Ghrelin and its Functions. Existing literature supports the short-term safety of ghrelin administration and its efficacy as an appetite stimulant in diverse patient populations. There is some evidence to suggest that ghrelin has wider ranging therapeutic effects, although these areas require further investigation. Hope this Review provides windows for New Possibilities in Therapeutic Research and Development.

Abbreviations: GH-Growth Hormone,GHRH-Growth Hormone Releasing Hormone. NPY-neuropeptide Y; AGRP-agouti-related peptide; POMC- proopiomelanocortin

REFERENCES

1. 1.Wei-na Cong, Erin Golden, Nick Pantaleo, Caitlin M. White, Stuart Maudsley, and Bronwen Martin»Ghrelin receptor signaling: a promising therapeutic target for metabolic syndrome and cognitive dysfunctionCNS Neurol Disord Drug Targets. 2010 November 1; 9(5): 557–563. PMCID: PMC2967656-NIHMSID: NIHMS231921
2. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, Matsukura S. A role for ghrelin in the central regulation of feeding. Nature. 2001;409(6817):194–198. [PubMed]
3. Shimizu Y, Nagaya N, Teranishi Y, Imazu M, Yamamoto H, Shokawa T, Kangawa K, Kohno N, Yoshizumi M. Ghrelin improves endothelial dysfunction through growth hormone-independent mechanisms in rats. Biochem Biophys Res Commun. 2003;310(3):830–835. [PubMed]
4. Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, Shimizu W, Ueno K, Kitakaze M, Miyatake K, Kangawa K. Effects of Ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation. 2004;110(24):3674–3679. [PubMed]
5. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, Hosoda H, Kojima M, Kangawa K. Ghrelin stimulates gastric acid secretion and motility in rats. Biochem Biophys Res Commun. 2000;276(3):905–908. [PubMed]
6. Baldanzi G, Filigheddu N, Cutrupi S, Catapano F, Bonissoni S, Fubini A, Malan D, Baj G, Granata R, Broglio F, Papotti M, Surico N, Bussolino F, Isgaard J, Deghenghi R, Sinigaglia F, Prat M, Muccioli G, Ghigo E, Graziani A. Ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI 3-kinase/AKT. J Cell Biol. 2002;159(6):1029–1037. [PMC free article] [PubMed]
7. Li WG, Gavrila D, Liu X, Wang L, Gunnlaugsson S, Stoll LL, McCormick ML, Sigmund CD, Tang C, Weintraub NL. Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. Circulation. 2004;109(18):2221–2226. [PubMed]
8. Xia Q, Pang W, Pan H, Zheng Y, Kang JS, Zhu SG. Effects of ghrelin on the proliferation and secretion of splenic T lymphocytes in mice. Regul Pept. 2004;122(3):173–178. [PubMed]
9. 9.Adami GF, Cordera R, Andraghetti G, Camerini GB, Marinari GM, and Scopinaro N. Changes in serum ghrelin concentration following biliopancreatic diversion for obesity. Obesity Res 12: 684–687, 2004.
10. 10.Adeghate E and Ponery AS. Ghrelin stimulates insulin secretion from the pancreas of normal and diabetic rats. J Neuroendocrinol 14: 555–560, 2002.
11. Arvat E, Maccario M, Di Vito L, Broglio F, Benso A, GotteroC, Papotti M, Muccioli G, Dieguez C, Casanueva FF, Deghenghi R, Camanni F, and Ghigo E. Endocrine activities of ghrelin, a natural growth hormone secretagogue (GHS), in humans:comparison and interactions with hexarelin, a nonnatural peptidyl GHS, and GH-releasing hormone. J Clin Endocrinol Metab 86: 1169–1174, 2001.
12. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, and Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 50: 1714–1719,2001.
13. Date Y, Murakami N, Kojima M, Kuroiwa T, Matsukura S,Kangawa K, and Nakazato M. Central effects of a novel acylated peptide, ghrelin, on growth hormone release in rats. Biochem Biophys Res Commun 275: 477–480, 2000.
14. Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H, Kojima M, Kangawa K, Arima T, Matsuo H, Yada T,and Matsukura S. Ghrelin is present in pancreatic alpha-

cells of humans and rats and stimulates insulin secretion. Diabetes 51:124–129, 2002.

15. Dornonville De La Cour C, Lindstrom E, Norlen P, and Hakanson R. Ghrelin stimulates gastric emptying but is without effect on acid secretion and gastric endocrine cells. Regul Pept 120:23–32, 2004.
16. Gnanapavan S, Kola B, Bustin SA, Morris DG, McGee P, Fairclough P, Bhattacharya S, Carpenter R, Grossman AB, and Korbonits M. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J Clin Endocrinol Metab 87: 2988, 2002.
17. Kaiya H, Kojima M, Hosoda H, Koda A, Yamamoto K, Kitajima Y, Matsumoto M, Minamitake Y, Kikuyama S, and Kangawa K. Bullfrog ghrelin is modified by n-octanoic acid at its third threonine residue. J Biol Chem 276: 40441–40448, 2001
18. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, and Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402: 656–660, 1999.
19. Lee HM, Wang G, Englander EW, Kojima M, and Greeley GH Jr. Ghrelin, a new gastrointestinal endocrine peptide that stimulates insulin secretion: enteric distribution, ontogeny, influence of endocrine, and dietary manipulations.Endocrinology 143: 185–190,2002.
20. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, Hosoda H, Kojima M, and Kangawa K. Ghrelin stimulates gastric acid secretion and motility in rats. Biochem Biophys Res Commun 276: 905–908, 2000.
21. Nagaya N and Kangawa K. Ghrelin improves left ventricular dysfunction and cardiac cachexia in heart failure.Curr Opin Pharmacol 3: 146–151, 2003.
22. Nagaya N, Kojima M, Uematsu M, Yamagishi M, Hosoda H, Oya H, Hayashi Y, and Kangawa K. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. Am J Physiol Regul Integr Comp Physiol 280: R1483–R1487, 2001.
23. Reimer MK, Pacini G, and Ahren B. Dose-dependent inhibition by ghrelin of insulin secretion in the mouse. Endocrinology 144: 916–921, 2003.
24. Takaya K, Ariyasu H, Kanamoto N, Iwakura H, Yoshimoto A,Harada M, Mori K, Komatsu Y, Usui T, Shimatsu A, Ogawa Y,Hosoda K, Akamizu T, Kojima M, Kangawa K, and Nakao K. Ghrelin strongly stimulates growth hormone release in humans.J Clin Endocrinol Metab 85: 4908–4911, 2000.
25. Tschop M, Wawarta R, Riepl RL, Friedrich S, Bidlingmaier M, Landgraf R, and Folwaczny C. Post-prandial decrease of circulating human ghrelin levels. J Endocrinol Invest 24: 19–21, 2001.
26. Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H, Kojima M, Kangawa K, Arima T, Matsuo H, et al. Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. Diabetes. 2002;51:124–129. [PubMed]
27. Tong J, Prigeon RL, Davis HW, Bidlingmaier M, Kahn SE, Cummings DE, Tschöp MH, D'Alessio D. Ghrelin suppresses glucose-stimulated insulin secretion and deteriorates glucose

28. 28.Arvat E , Di Vito L, Broglio F, Papotti M, Muccioli G, Dieguez C, Casanueva FF, Deghenghi R, Camanni F, and Ghigo E. Preliminary evidence that Ghrelin, the natural GH secretagogue (GHS)- receptor ligand, strongly stimulates Gh secretion in humans, J Endocrinal Invest 23: 493-495, 2000.
29. Nagaya N, Miyatake K, Uematsu M, Oya H, Shimizu W, Hosoda H, Kojima M, Nakanishi N, Mori H and Kanagawa K. Hemodynamic, renal and hormonal effects of ghrelin infusion in patients with chronic heart failure. J Clin Endocrinal Metab 86:5854-5859,2001.
30. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402:656–660. [PubMed]
31. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. 2001;50:1714–1719. [PubMed]
32. Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature. 2000;407:908–913. [PubMed]
33. Faulconbridge LF, Cummings DE, Kaplan JM, Grill HJ. Hyperphagic effects of brainstem ghrelin administration. Diabetes. 2003;52:2260–2265. [PubMed]
34. Seoane LM, Lopez M, Tovar S, Casanueva FF, Senaris R, Dieguez C. Agouti-related peptide, neuropeptide Y, and somatostatin-producing neurons are targets for ghrelin actions in the rat hypothalamus. Endocrinology. 2003;144:544–551. [PubMed]
35. Kinzig KP, Scott KA, Hyun J, Bi S, Moran TH. Lateral ventricular ghrelin and fourth ventricular ghrelin induce similar increases in food intake and patterns of hypothalamic gene expression. Am J Physiol Regul Integr Comp Physiol. 2006;290:R1565–1569. [PubMed]
36. Banks WA, Tschop M, Robinson SM, Heiman ML. Extent and direction of ghrelin transport across the blood-brain barrier is determined by its unique primary structure. J Pharmacol Exp Ther. 2002;302:822–827. [PubMed]
37. Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman M, Heiman ML, Garcia-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Cone RD, Horvath TL. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron. 2003;37:649–661. [PubMed]
38. Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, Sirinathsinghji DJ, Smith RG, Van der Ploeg LH, Howard AD. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Res Mol Brain Res. 1997;48:23–29. [PubMed]
39. Hashimoto H, Fujihara H, Kawasaki M, Saito T, Shibata M, Otsubo H, Takei Y, Ueta Y. Centrally and peripherally administered ghrelin potently inhibits water intake in rats. Endocrinology. 2007;148:1638–1647. [PubMed]
40. Date Y, Nakazato M, Murakami N, Kojima M, Kangawa K, and Matsukara s. Ghrelin acts in the central nervous system to stimulate gastric acid secretion. Biochem Biophys Res Commun 280: 904-907,2001.
41. Dezaki K, Sone H, Yada T. Ghrelin is a physiological regulator of insulin release in pancreatic islets and glucose homeostasis. Pharmacol Ther. 2008;118(2):239–249. [PubMed]
42. McLaughlin T, Abbasi F, Lamendola C, Frayo RS, Cummings DE. Plasma ghrelin concentrations are decreased in insulin-resistant obese adults relative to equally obese insulin-sensitive controls. J Clin Endocrinol Metab. 2004;89(4):1630–1635. [PubMed]
43. Broglio F, Arvat E, Benso A, Gottero C, Muccioli G, Papotti M, Lely AJvd, Deghenghi R, Ghigo E. Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. J Clin Endocrinol Metab. 2001;86(10):5083–5086. [PubMed]
44. Dezaki K, Hosoda H, Kakei M, Hashiguchi S, Watanabe M, Kangawa K, Yada T. Endogenous Ghrelin in pancreatic islets restricts insulin release by attenuating Ca2+ signaling in beta-cells. Diabetes. 2004;53(12):3142–3151. [PubMed]
45. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health. 2009;9:88. [PMC free article] [PubMed]
46. Finkelstein EA, Fiebelkorn IC, Wang G. State-level estimates of annual medical expenditures attributable to obesity. Obes Res. 2004;12(1):18–24. [PubMed]
47. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010;303(3):235–241. [PubMed]
48. 48.Dana I. Briggs Zane B. Andrews-Metabolic Status Regulates Ghrelin Function on Energy Homeostasis.- Neuroendocrinology 2011;93:48–57 DOI: 10.1159/000322589

49. Schwartz MW, Woods SC, Porte D Jr, et al. Central nervous system control of food intake. *Nature*. 2000;404:661–671. [PubMed]
50. Ravussin E, Tschop M, Morales S, et al. Plasma ghrelin concentration and energy balance: overfeeding and negative energy balance studies in twins. *J Clin Endocrinol Metab*. 2001;86:4547–4551. [PubMed]
51. Tschop M, Wawarta R, Riepl RL, et al. Post-prandial decrease of circulating human ghrelin levels. *J Endocrinol Invest*. 2001;24:RC19–21. [PubMed]
52. Tschop M, Weyer C, Tataranni PA, et al. Circulating ghrelin levels are decreased in human obesity.*Diabetes*. 2001;50:707–709. [PubMed]
53. Otto B, Cuntz U, Fruehauf E, et al. Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. *Eur J Endocrinol*. 2001;145:669–673. [PubMed]
54. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med*. 1995;1:1155–1161. [PubMed]
55. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996;334:292–295. [PubMed]
56. Ikezaki A, Hosoda H, Ito K, et al. Fasting plasma ghrelin levels are negatively correlated with insulin resistance and PAI-1, but not with leptin, in obese children and adolescents. *Diabetes*. 2002;51:3408–3411. [PubMed]
57. Barazzoni R, Zanetti M, Stebel M, et al. Hyperleptinemia prevents increased plasma ghrelin concentration during short-term moderate caloric restriction in rats. *Gastroenterology*. 2003;124:1188–1192. [PubMed]
58. Pinilla L, Barreiro ML, Tena-Sempere M, et al. Role of ghrelin in the control of growth hormone secretion in prepubertal rats: interactions with excitatory amino acids. *Neuroendocrinology*. 2003;77:83–90. [PubMed]
59. Asakawa A, Inui A, Kaga T, et al. Antagonism of ghrelin receptor reduces food intake and body weight gain in mice. *Gut*. 2003;52:947–952. [PMC free article] [PubMed]
60. Burman P, Ritzen EM, Lindgren AC. Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev*. 2001;22:787–799. [PubMed]
61. DelParigi A, Tschop M, Heiman ML, et al. High circulating ghrelin: a potential cause for hyperphagia and obesity in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2002;87:5461–5464.[PubMed]
62. Cummings DE, Clement K, Purnell JQ, et al. Elevated plasma ghrelin levels in Prader Willi syndrome. *Nat Med*. 2002;8:643–644. [PubMed]
63. Haqq AM, Farooqi IS, O'Rahilly S, et al. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2003;88:174–178. [PubMed]
64. Janssen JA, van der Toorn FM, Hofland LJ, et al. Systemic ghrelin levels in subjects with growth hormone deficiency are not modified by one year of growth hormone replacement therapy. *Eur J Endocrinol*. 2001;145:711–716. [PubMed]
65. Murdolo G, Lucidi P, Di Loreto C, et al. Circulating ghrelin levels of visceral obese men are not modified by a short-term treatment with very low doses of GH replacement. *J Endocrinol Invest*. 2003;26:244–249. [PubMed]
66. Haqq AM, Stadler DD, Jackson RH, et al. Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2003;88:2206–2212. [PubMed]