RESEARCH ARTICLE

ROLE OF GHRELIN IN REGULATION OF GROWTH HORMONE SECRETION BY GHRELIN-PITUITARY-GH AXIS LINKAGE

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ABSTRACT

Background: Ghrelin is the endogenous ligand of the growth hormone (GH) secretagogue receptor and is the first hormone linking gastrointestinal-pituitary axis. Actions of ghrelin on GH secretion provide a strong force for envisioning that one of the major role of ghrelin could be the regulation of secretion of GH.

Aims & Objective: To explore the intriguing dimensions on the possible physiological role of the Ghrelin /GHRP system.

Materials and Methods: The search was performed in electronic databases (Medline, Embase, Cochrane, Google scholar) and by hand searching by 2 reviewers. Clinical trials (Randomised and non-randomised trials), review articles, systematic reviews, conference proceedings and meta-analysis were included in the study.

Results: Ghrelin stimulates strong increase in circulating GH levels both in vitro and in vivo in a dose-dependent manner. Human or animal ghrelin was found to be significantly more potent than a synthetic GHS, hexarelin. The regulation of GH by Ghrelin is influenced by various other factors like autonomic nervous system, GHRH, IGF-1, anterior pituitary hormones, obesity, etc.

Conclusion: Ghrelin is a specific endogenous ligand for the GHS receptor and suggests the existence of a GHS–GHS receptor signaling system in the regulation of GH secretion. Stomach-ghrelin - pituitary-GH axis links nutritional intake to regulation of GH secretion. However, the mechanism underlying the feedback actions of GH on the regulation of ghrelin remains unanswered. Under physiological conditions, ghrelin administered either centrally or peripherally, exerts a potent, time-dependent stimulation of pulsatile secretion of GH by ghrelin-pituitary-GH axis.

Key Words: Ghrelin; Growth Hormone; Ghrelin-Pituitary-GH Axis Linkage

Introduction

Ghrelin is the endogenous ligand of the growth hormone secretagogue receptor (GHSR) and is the first hormone linking gastrointestinal-pituitary axis.[1-4] In collaboration with GHRH and somatostatin, ghrelin may well be the third peptidergic factor involved in GH regulation.[5] Ghrelin exerts pleiotropic actions, consistent with the widespread distribution of ghrelin and GHS-R expression in central and peripheral tissues.[6] In mammals, ghrelin has been shown to exhibit a range of actions on cardiovascular, gastrointestinal, and pancreatic functions, as well as lipogenic and glucogenic actions.[7-9] In mammals, it is suggested that the main physiological function of ghrelin is to stimulate growth hormone release from the pituitary and increase food intake.[10] Actions of ghrelin on GH secretion provide a strong force for envisioning that one of the major role of ghrelin could be the regulation of secretion of GH. This review addresses the timely topic on a gut hormone ghrelin and its role in the regulation of growth hormone secretion and we intend to explore the intriguing dimensions on the possible physiological role of the Ghrelin /GH system. The review has put forth the findings of the effect of human ghrelin as well as Growth Hormone Releasing Hormone (GHRH) and synthetic Ghrelin on GH secretion. This study is to comprehensively review the existing literature on the effects of ghrelin on secretion of growth hormone.

Materials and Methods

Criteria for considering studies for this review:

- *Types of studies:* Randomised controlled trials or non-randomised trials were included in the review that evaluated one or both the outcome measures.
- *Types of participants:* Participants were healthy adult male volunteers.
- *Types of interventions:* The active intervention was Ghrelin, marketed under any brand name. The review included trials comparing the effect of Ghrelin in different doses and different types. Also trials comparing the effect of ghrelin vs GHRH on the release of growth hormone were included in the review.
- *Types of outcome measures:* (i) Primary outcomes: Secretion of growth hormone; (ii) Secondary outcomes: Change in body weight.

Search methods for identification of studies: Searches were not conducted for trials before 1999 because ghrelin was discovered in 1999. We searched the following electronic databases: The Cochrane Library; MEDLINE; Pub Med; Science Citation Index; BIOSIS, EMBASE, CINAHL. The references of all identified studies were inspected for further randomized controlled trials. No language restrictions were applied. A manual search was performed for medical journals. Experts, authors and manufacturers were contacted to seek clarifications and asked to contribute published and unpublished material.

Data collection and analysis: Selection of studies: Two reviewers independently screened the title and abstracts from searches on electronic databases to identify those articles relevant to this review. Full articles were retrieved for further assessment. All full text articles were read independently by two reviewers to make a decision on inclusion. Disagreements were resolved by discussion and by seeking the opinion of the third reviewer.

Data extraction and management: A data extraction form was designed to include: design, details of the participants (age, BMI), Intervention (intervention groups, dosage, duration and mode of administration of the intervention), outcome measures as detailed above and adverse events. Data were extracted by two reviewers independently. Additional unpublished data were also obtained by contacting the authors of the paper

Analysis issues: As the trials were not carried out according to a common protocol and there were variations in clinical settings, dosage; etc. Meta-analysis could not be performed.

Results

The literature searches identified 15 references that described 10 potentially relevant trials. Eight publications were excluded because they varied in participant characteristics and intervention strategy. Seven trials (Table 1) involving 83 participants met the inclusion criteria and were included in this review. These trials are described in the characteristics of included studies table. Three trials were done in Japan and one each in Italy, USA, Austria and Yugoslavia. All the trials were randomized. Trial size ranged from 6 to 32 participants. Six trials administered ghrelin and one trial administered anamorelin. The daily dose used in these trials ranged between 0.08 to 5 μg/kg. Reported outcomes included amount of/ change in release of growth hormone, change in body weight and adverse effects of ghrelin. Mean age of the included patients in each trial ranged from 25 to 40 years.

Effects of interventions: Three studies (Peino et al, Maier et al, Tokoyo et al) studied the effect of different doses of ghrelin on secretion of growth hormone. Ghrelin at the dose of 0.08, 0.25, 0.5 and 1.0 μg/kg elicited a peak GH secretion that was not significantly different than placebo group. The trials found that Ghrelin is a potent releaser of GH in normal individuals, with a dose-response pattern of operation. Takaya et al studied the time course of serum GH levels after various doses of ghrelin. All doses (0.2 μg/kg, 1.0 μg/kg and 5.0 μg/kg) produced monophasic responses and reached the peak values at 30 min. After administration of 0.2 μg/kg and 1.0 μg/kg of ghrelin, GH levels returned to basal values by 180 min while 5.0 μg/kg dose of ghrelin, the value was still higher than the basal level.

Two trials (Avat et al and Micic et al) compared the potencies of ghrelin with GHRH, GHRP and synthetic ghrelin like Hexarelin (HEX) for secretion of GH and also the effect of co-administration of these peptides. They found that the GH response to ghrelin was higher ($P < 0.01$) than GHRH and even significantly higher ($P < 0.05$) than that after HEX. In Arvat's trial; GH response to ghrelin plus HEX was similar to that recorded after ghrelin alone ; i.e the endocrine responses to ghrelin were not modified by the co-administration with HEX while in Hataya's trial, mean GH response of two peptide combinations were more than the summed mean GH response values of each peptide alone ($P < 0.05$). Micic's study found that on clinical grounds, GHRP-6 is less potent but more efficacious at releasing GH and that on molar basis the order of potency is ghrelin > GHRH> GHRP- 6. Also, the study showed that a previous injection of saturating doses of GHRP-6 partially, but not totally, desensitized the ghrelin-mediated GH secretion.

Garcia studied the effect of different doses of Anamorelin on GH levels and body weight and found that Anamorelin significantly increases GH levels in dose-related pattern and also increases body weight with good tolerability and selectivity. Maier studied the effect of autonomic system on the ghrelin and found that atropine alone significantly reduced fasting ghrelin levels, whereas under pyridostigmine alone did not alter ghrelin levels. Ghrelin in combination with atropine induced significantly reduced GH concentrations compared with ghrelin administration alone for both ghrelin doses, whereas ghrelin-induced GH peak concentrations were not enhanced by pyridostigmine treatment.

Table-1: Characteristics and finding of the included studies

Country & Type of study	**Peino et al (2000)**	Japan. Randomized
	Arvat (2001)	Italy. Randomized, single blind
	Garcia (2009)	USA. Randomized, double-blind, placebo-controlled
	Maier (2004)	Austria. Randomized, double-blind, placebo-controlled, crossover study
	Hataya (2001)	Japan. Randomized
	Micic (2002)	Yugoslavia. Randomized
	Takaya (2000)	Japan. Randomized
Partici-pants	**Peino et al (2000)**	12 normal, healthy male volunteers; Age: 26.2±1:1 years; BMI: 24.0 ±0.4 kg/m^2
	Arvat (2001)	7 healthy male volunteers; Age: 28.6 ± 2.9 years (mean ±SEM); BMI: 22.1 ± 0.8 kg/m^2
	Garcia (2009)	32 healthy normal volunteers
	Maier (2004)	12 healthy male volunteers; Age: 27.6 ± 1.1 years (mean ±SEM); BMI: 24.0 ± 0.5 kg/m^2
	Hataya (2001)	8 healthy male volunteers; Age: 28-46 years; BMI: 22.8 ±2.3 kg/m^2
	Micic (2002)	6 healthy male volunteers; Age: 32±3 years
	Takaya (2000)	6 healthy male volunteers; Age: 28-37 years; BMI: 22.6± 2.8 kg/m^2
Interve-ntion	**Peino et al (2000)**	6 subjects: ghrelin at four different doses, 0 (placebo), 0.25, 0.5 and 1.0 mg/kg on four different days. 6 different subjects were tested with ghrelin at either 3.3 mg/kg or 6.6 mg/kg on two different occasions.
	Arvat (2001)	All subjects underwent 4 sessions,3 days apart: (1) Placebo (2 mL isotonic saline iv at 0 min); (2) Ghrelin (1.0 µg/kg iv at 0 min); (3) HEX (1.0 µg/kg iv at 0 min); and (4) GHRH-29 (1.0 µg/kg iv at 0 min). 6 subjects also underwent two further sessions in which they were administered: (1) Ghrelin and HEX or (2) Ghrelin and GHRH.
	Garcia (2009)	Administered escalating doses of anamorelin (25, 50, and 75 mg daily) vs. placebo.
	Maier (2004)	For all subjects, 6 study days (A-F) with 3-d intervals were scheduled in randomized order: Day A: PD at -60 and placebo (isotonic saline) iv at time point 0; Day B: ATR,1 mg iv at time point 0 and placebo iv at time point 0; Day C: PD at -60 and ghrelin 0.25 µg/ kg BW at 0; Day D: ATR at 0 and ghrelin 0.25 µg/ kg BW at 0; Day E: PD at −60 and ghrelin 1 µg/ kg BW at 0; Day F: ATR at 0 and ghrelin 1 µg/ kg BW at 0. 6 of the 12 subjects were also tested with the two doses (0.25 and 1 µg/ kg, respectively) of ghrelin alone
	Hataya (2001)	3 different doses of combinations of ghrelin (0.08, 0.2, 1.0 µg/kg + fixed doses of GHRH (1.0 µg/kg) were administered to 3 groups of 4 subjects
	Micic (2002)	On each day, subjects were challenged twice with different GH stimulants: each subject served as his own control. Day1: Saline at 0 min and at 120 min ghrelin iv 1.0µg/kg Day 2: GHRH at a dose of 1.0µg/kg at 0 min and at 120 min ghrelin at a dose of 1.0µg/kg Day 3: GHRP-6 at a dose of 1.0µg/kg at 0 min followed at 120 min by ghrelin at a dose of 1.0µg/kg
	Takaya (2000)	2-3 doses of ghrelin randomly allocated 7 days apart among 6 subjects Synthetic ghrelin administered 0.2, 1.0 or 5 µg/kg iv
Result	**Peino et al (2000)**	Ghrelin at the dose of 0.25, 0.5 and 1.0 µg/kg elicited a peak GH secretion of 0.5 ±0.007; 0.6 ± 0.09 and 6.5 ± 2.6 µg/l resp that was not significantly different than placebo group (0.6 ± 0.08 µg/kg). These higher ghrelin doses elicited a robust GH release significantly higher than the placebo (P<0.005) and then the 1µg/kg dose (P<0.005).
	Arvat (2001)	Basal GH levels were similar in all sessions. Ghrelin induced a prompt and marked increase in circulating GH levels. The GH response to ghrelin was higher (P < 0.01) than GHRH (Cmax, 26.7 ± 8.7 µg/L; AUC, 619.6 ± 174.4 µg/L·h; Tmax, 25.7 ± 4.3 min) and even significantly higher (P < 0.05) than that after HEX (Cmax, 68.4 ± 14.7 µg/ L; AUC, 1546.9 ± 380.0µ g/L·h; Tmax, 30.0 ± 3.3 min). The endocrine responses to ghrelin were not modified by the co-administration with HEX. GH response to ghrelin plus HEX was similar to that recorded after ghrelin alone (Cmax, 99.7 ± 12.9 vs. 100.3 ± 17.3µ g/L; AUC, 2265.9 ± 201.8 vs. 2066.0 ± 358.3µ g/L·h
	Garcia (2009)	Anamorelin significantly increased GH levels at all doses (p<or=0.01). Significant dose-related increases in body weight were recorded. Changes in body weight directly correlated with changes in IGF-1 levels.
	Maier (2004)	ATR alone significantly reduced fasting ghrelin levels by 25%. PD alone did not alter ghrelin levels and did not enhance Ghrelin-induced GH peak concentrations. Ghrelin + ATR: Significantly reduced GH concentrations compared with ghrelin administration alone for both ghrelin doses. Ghrelin at 0.25 µg/ kg increased circulating ghrelin conc. with peak values of 634 ± 22.6 fmol/ml. Higher ghrelin dosage (1 µg/ kg) induced peak values of 1959.4 ± 163.5 fmol/ml.
	Hataya (2001)	At small doses of 0.08 and 0.2 µg/kg ghrelin, combined administration of the two peptides significantly stimulated GH release in a synergistic manner. Mean GH response of two peptide combinations were more than the summed mean GH response values of each peptide alone (P < 0.05). At 1.0 µg/kg ghrelin, the tendency of the synergistic effect was observed
	Micic (2002)	Saline –ghrelin test: Saline did not modify GH basal levels; mean GH peak: 1.5±0.6mg/l. Ghrelin at 120 min elicited a significant GH mean peak of 39:9± 2:8 mg/l . GHRH –ghrelin test: the GH secretion elicited by GHRH was rather erratic with a mean GH peak of 9.4±2.8mg/l; and when ghrelin was administered 120 min later the GH mean peak was 26.8±4.7mg/l. GHRP-6–ghrelin test: GHRP-6 induced a mean GH peak of 18:4±5:9mg/l; while ghrelin at 120 min induced a GH mean peak of 19:8±2:9mg/l.
Side effects	**Peino et al (2000)**	No relevant side effects were observed with ghrelin
	Arvat (2001)	No changes in heart rate and blood pressure were recorded after ghrelin administration. 3 out of seven subjects were hungry at the end of the ghrelin testing session. Transient facial flushing in 2 out of seven subjects after HEX administration. Co-administration of ghrelin and HEX or ghrelin and GHRH did not modify the side effects recorded after the administration of various peptides alone.
	Garcia (2009)	Anamorelin was well tolerated.
	Hataya (2001)	Ghrelin + GHRH produced bowel movement in 3 out of 4 subjects. GHRH-6 produced facial flushing in all the subjects for 1-3 min.
	Micic (2002)	No significant change in heart rate and blood pressure. No side-effects were reported in any stimulation test
	Takaya (2000)	2-4 sujects with 1.0 or 5.0 µg/kg reported warm sensation in upper trunk and/or bowel movements for few minutes. No other side effects.
Conclusion	**Peino et al (2000)**	Ghrelin is a potent releaser of GH in normal individuals, with a dose-response pattern of operation. No saturating dose

Table-1: Characteristics and finding of the included studies

	was observed.
Arvat (2001)	Ghrelin is important in the control of somatotroph function in humans. Non-natural GHSs imitate its GH-releasing effect.
Garcia (2009)	Anamorelin increases GH, IGF-1, IGFBP-3 and body weight with good tolerability and selectivity
Maier (2004)	In humans, fasting ghrelin concentrations might be under cholinergic control and that the cholinergic system appears to modulate ghrelin-induced GH release.
Hataya (2001)	Ghrelin acts synergistically with GHRH in humans
Micic (2002)	Ghrelin is a more potent releaser of GH. On molar basis the order of potency is ghrelin > GHRH> GHRP- 6 On clinical grounds, GHRP-6 is less potent but more efficacious at releasing GH.

BW: Body weight; PD: Pyridostigmine, ATR: Atropinum sulfuricum

No side effects were reported in three studies while three studies noted adverse effects of transient facial flushing, warm sensation in upper trunk and/or bowel movements for few minutes.

Discussion

Ghrelin appears to be highly potent, probably being the strongest GH secretagogue when administered alone.[18] The results of the studies show that, in humans, ghrelin releases more GH than GHRH, GHRP-6 and even than a non-natural GHS, such as HEX.[19] It is not yet established if this is due to a higher affinity for the GHS-receptor or to prolonged plasma half-life. The endocrine responses to ghrelin are not modified by its co-administration with HEX which indicates the reproducibility of somatotroph responsiveness to ghrelin. Along with GHRH, ghrelin has a synergistically effect on GH secretion which agrees with the synergism between non-natural GHS and GHRH[20] and indicates that these peptides act, at least partially, via different mechanisms. In normal individuals, ghrelin is partially resistant to a previous administration of GHRP-6 and to the ensuing GH rise for which two types of cellular responses have been proposed: the homologous desensitization effects and the cross-talk observed between the GHRH receptor and the GHS receptor. Homologous desensitization has been described in vivo for GHRH-mediated GH secretion, wherein; a first administration of GHRH leads to a reduced or absent GH response to a second GHRH dose, provided that the two challenges are separated by few hours.[21] The basis of the homologous desensitization phenomenon is most probably a down-regulation of the cell membrane receptor, internalized after activation, and requires more than 2 h before being recycled towards the membrane again. Previous administration of GHSs such as hexarelin or GHRP-6 leads, 2 h later, to a near complete blockade of GHRH-mediated GH secretion, a finding called heterologous desensitization.[22]

Growth hormone secretagogues (GHSs) are synthetic peptidyl and nonpeptidyl compounds that are believed to stimulate the release of GH by a direct effect on the pituitary somatotroph and by stimulation of growth hormone-releasing hormone (GHRH) release and/or via functional antagonism of somatostatin (SRIH) tone.[24] They also binds and activate hypothalamic GHS-R. Maier's study shows that cholinergic blockade with ATR suppresses ghrelin plasma concentrations and modulation of the cholinergic system with ATR, but not PD, influences the ability of different ghrelin dosages to induce GH release. The main influence of PD on GH release is via lowering somatostatinergic tone in the median eminence of the hypothalamus.[24] The non-additive effect of ghrelin and PD could be attributed to the fact that both substances act on the same pathway. The study provides evidence that interplay exists between ghrelin and the cholinergic system in humans. The adverse effects reported in the trials were mild, infrequent, and transient thereby indicating that ghrelin is well tolerated and can be used therapeutically. Limitations of our review pertain to the potential incompleteness of the reviewed evidence. We aimed to identify all RCTs on the topic. However, only a few studies provided data on our primary outcome variable and we could not find trials after 2009. We did not restrict our searches by publication language, and are therefore confident that our strategy minimised bias. We only included data from clinical trials that were randomised. Nevertheless, the extent of methodological rigor varied among trials.

Conclusion

The best evidence that is available suggests that ghrelin significantly increases GH, compared with placebo, GHRH and HEX and can be used as an adjunctive treatment. Reported adverse events were infrequent, mild, and transient. Future trials should report clinical as well as physiological outcomes. The role of ghrelin in the regulation of GH and its clinical implication needs further assessment.

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