Motility Conference
Ghrelin

Emori Bizer, M.D.
University of Louisville
Division of Gastroenterology/Hepatology
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Ghrelin: Basics

- Hormone produced by the A-like endocrine cells in the oxyntic mucosa (stomach body and fundus)
- Many functions
- Role in motility of the gut
Physiology/Endocrinology, dept. of Physiology, institute of Neuroscience and Physiology, the Sahlgrenska Academy at Göteborg University
Ghrelin: Discovery

- Discovered in 1999 as a natural ligand to the Growth Hormone Secretagogue Receptor (GHS-R)

- Kojima et al. found that the highest concentration of ghrelin is in the stomach and that ghrelin stimulates growth hormone (GH) secretion

- Also found in intestines, brain, lung, heart, kidney

- Tomasetto et al. named peptide motilin-related peptide but it didn’t have Ser-3
Ghrelin: Structure

- The n-octanoylation of Ser-3 residue is required for biologic activity of ghrelin.
- Human ghrelin differs from rat ghrelin by only 2 amino acids.

(M. Kojima et al., Nature 442, 656-660, 1999)
Factors Affecting Ghrelin Release

**INCREASE GHRELIN**
- FASTING
- Age (in rats)
- Diurnal rhythm – highest levels at midnight to 2am and before meals
- H.Pylori eradication

**DECREASE GHRELIN**
- FED STATE
- Obesity
- High GH levels
- Somatostatin
- ?Insulin
- S/p Gastrectomy, levels decrease by 65%
- H.Pylori gastritis
Ghrelin plasma levels:

- Ghrelin levels fluctuate throughout the day.
- Levels are high before a meal and also peak between midnight and 2am.
- Ghrelin plasma levels increase to nearly 2-fold shortly before meals and decrease to trough levels within one hour of eating (Cummings et al.)
Ghrelin

Factors that do not affect secretion:
- No difference in sex in rats

Not affected by gastrin levels (or PPI)
Ghrelin and GH Secretion

- Dose-dependent effect of Ghrelin and GH release.
  - Mechanism: May increase a “u-factor” in hypothalamus
- Ghrelin is a more potent stimulus for GH secretion than GHRH, but they work differently
  - Ghrelin leads to GH peak, then returns to baseline
  - GHRH leads to longer duration GH release
  - Controversial whether or not Ghrelin and GHRH have synergistic effect on GH release
  - Somatostatin inhibits GH release by either Ghrelin or GHRH
Ghrelin and Other Hormones

Increases other hormone secretion:
- Prolactin
- ACTH
- Cortisol

Of note, studies on humans have not found any adverse effects of ghrelin when given at 5pmol/kg/min infusions.
Ghrelin and Feeding

- Orexigenic effect = stimulates appetite
- Early studies - rats increased appetite and had weight gain with ghrelin
- Wern et al. showed that IV ghrelin infusion (5 pmol/kg/min) increased appetite and increased food intake → human volunteers ate 28% additional calories at a buffet after ghrelin
Ghrelin and Feeding

- Orexigenic effect similar to Neuropeptide Y (NPY), a neurotransmitter also secreted by the stomach with action in the arcuate nucleus of the hypothalamus.
  - Leptin effects likely mediated by NPY
- IV ghrelin leads to increase levels NPY.
Eating Disorders and Ghrelin

- Ghrelin levels inversely correlate with BMI
- High ghrelin levels in Anorexia Nervosa and Bulimia pts and in cancer cachexia (negative energy balance)
- Lower ghrelin levels in obese pts (positive energy balance)
  - Food fails to suppress ghrelin levels as well in obese pts as it does in lean pts
Weight Loss and Ghrelin

- Diet-induced weight loss of 17% was associated with 24% increased levels of Ghrelin
  - These people are hungry!

- Gastric bypass pts with 36% weight loss had 77% lower levels of ghrelin than matched obese controls
  - These people are not hungry
  - ?Mechanism – more satiety because smaller stomach or less ghrelin because oxyntic mucosa resected?
  - This degree of ghrelin decrease is not found in other antiobesity surgery pts
Tschop et al. showed ghrelin increases fat mass in rats without hyperphagia.

- Weight gain not due to GH levels; different mechanism
- Gastric distention alone does not affect ghrelin secretion
- Twin studies failed to show an association between Ghrelin and common obesity
- Prader-Willi pts have hyperghrelinemia
# Ghrelin vs. Leptin

Leptin is a hormone/cytokine released by adipocytes. It has many roles in satiety, energy metabolism, cardiovascular effects, and fertility.

<table>
<thead>
<tr>
<th>SIMILARITIES</th>
<th>DIFFERENCES</th>
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<tbody>
<tr>
<td>Both released in pulsatile manner in fasted and fed states</td>
<td>Leptin inhibits appetite; ghrelin stimulates appetite</td>
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<tr>
<td>Both act on hypothalamus via Neuropeptide Y</td>
<td>Levels are inversely correlated</td>
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Nutrients and Ghrelin

- Erdmann, et al. demonstrated different affects of nutrients on ghrelin release in healthy pts

- Carbohydrates, glucose, and fats decrease ghrelin release post-prandially
  - Fats decreased ghrelin at later time post-prandial than carbohydrate-rich meal

- Proteins may increase ghrelin post-prandially
Ghrelin and Gastric Motility

- Ghrelin increases gastric motility
  - Ghrelin is structurally similar to motilin peptide
- Mechanism unclear – vagal pathway and intrinsic neural pathway
- Ariga, et al. showed increased antro-pyloric coordination in rats with ghrelin vs. saline intraperitoneal infusion
Tack et al. studied 6 pts (5 women) with idiopathic gastroparesis.

- Measured GET with breath testing and assessed GI GP symptoms after ghrelin infusion.
- Ghrelin increased liquid emptying, trended to increase solid emptying, and improved symptoms of fullness and pain.

Murray et al. - DM GP pts saline vs. ghrelin infusion

- Increase in GER in 7/10. No change in symptoms with ghrelin
Ghrelin and Intestinal Motility

- Ghrelin also increases small bowel transit
- Reverses post-op ileus
Ghrelin and Vagus Nerve

- Ghrelin receptors are synthesized in the vagal afferent cell bodies in the nodose ganglia and transported to the periphery.

Initially there were conflicting reports regarding the relationship between ghrelin and the Vagus nerve:

- Vagus nerve inhibit ghrelin release?
  - Lee et al. showed increased ghrelin levels in rats after vagotomy.
  - Some human studies failed to show changes in ghrelin levels with sham feedings (Vagal Stimulation).
- **Vagus nerve stimulate ghrelin release?**
  - Electrical vagal stimulation can increase ghrelin levels.
Ghrelin and Vagus Nerve

- Ghrelin’s signals for starvation and GH secretion travels via vagal afferents to the brain
- Asakawa et al. showed that the orexigenic activity of ghrelin was lost after vagotomy
- Similarly, Date et al. showed that vagotomy abolished the ghrelin-induced feeding and activation of NPY neurons.
Ghrelin and Vagus Nerve

Simonian, et al. studied 15 healthy pts after sham feedings and meals, checked serial ghrelin and PP levels q 5 min x 30min & 60 min.

- Sham (bacon & cheese): increased PP, ghrelin levels significantly from baseline
- Meal: increased PP, decreased ghrelin levels
- Showed a clear association between vagal efferents and ghrelin release
- Post-prandial decrease in ghrelin levels: Must be a gastric phase component which inhibits ghrelin release
Ghrelin, Vagus, and Gastroparesis

Gaddipati, et al. (same as previous) did similar study with gastroparesis pts

Assessed ghrelin, PP, insulin, glucose levels and GI symptom scores in healthy controls compared with GP pts (DM vs idiopathic vs post-surg)

Sham:
- PP: normal increase in PP in healthy and idiopathic GP pts, but not in diabetic and post-surgical GP’s
- Ghrelin: normal increase in ghrelin in healthy and idiopathic GP pts. Decrease levels non-significantly in post-surgical GP and minimal change in DM pts

Meal: no change in ghrelin levels in all groups

Glucose: higher in DM GP’s which could have influenced Vagal input
Ghrelin and Vagus Nerve

VAGAL AFFERENTS

VAGAL AFFERENTS

GHRELIN

SHAM FEEDING

ACID AND GASTRIN

PANCREATIC POLYPEPTIDE

ACh
Ghrelin and Insulin

- Conflicting data on this relationship
- Insulin may suppress ghrelin release
- Inverse relationship between these two hormones
Ghrelin: Cardiovascular Effects

Ghrelin decreases Mean Arterial Pressure and increases Cardiac Output

- It antagonizes endothelin-1, a potent vasoconstrictor
Ghrelin: Summary of Functions

- Also increases vasopressin
- May also increase aldosterone
- Role in thyroid metabolism
- Reciprocal negative feedback mechanism with insulin
Ghrelin: Research at UL

- Gastric Electrical Stimulation for Severe Gastroparesis: A Long-Term Follow-Up
  - Will also assess ghrelin levels before and after gastric stimulator implantation
- Tranzyme pharmaceuticals
  - IV ghrelin for gastroparesis patients.
References


