

Motility Conference Ghrelin

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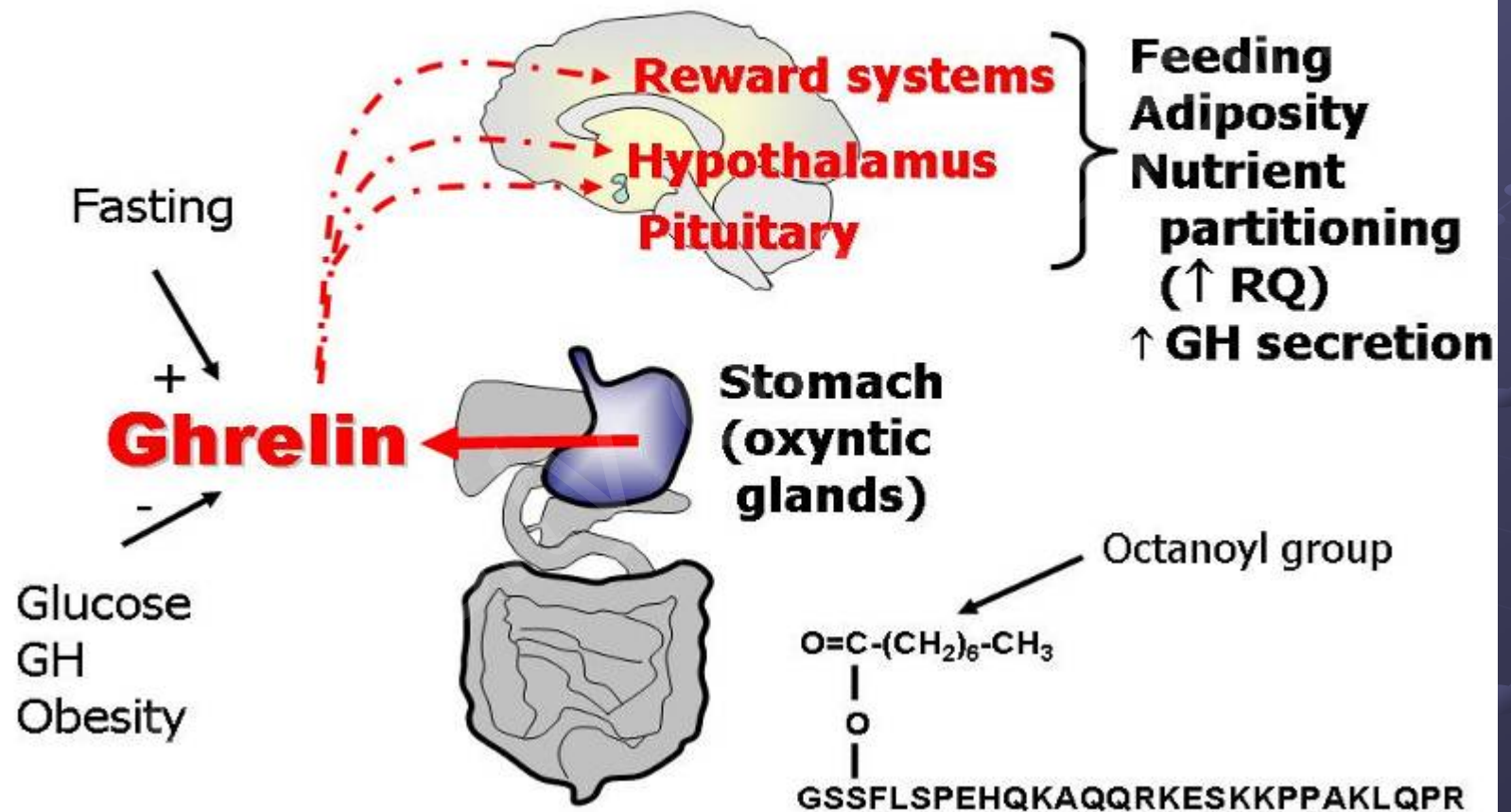
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Ghrelin: Basics

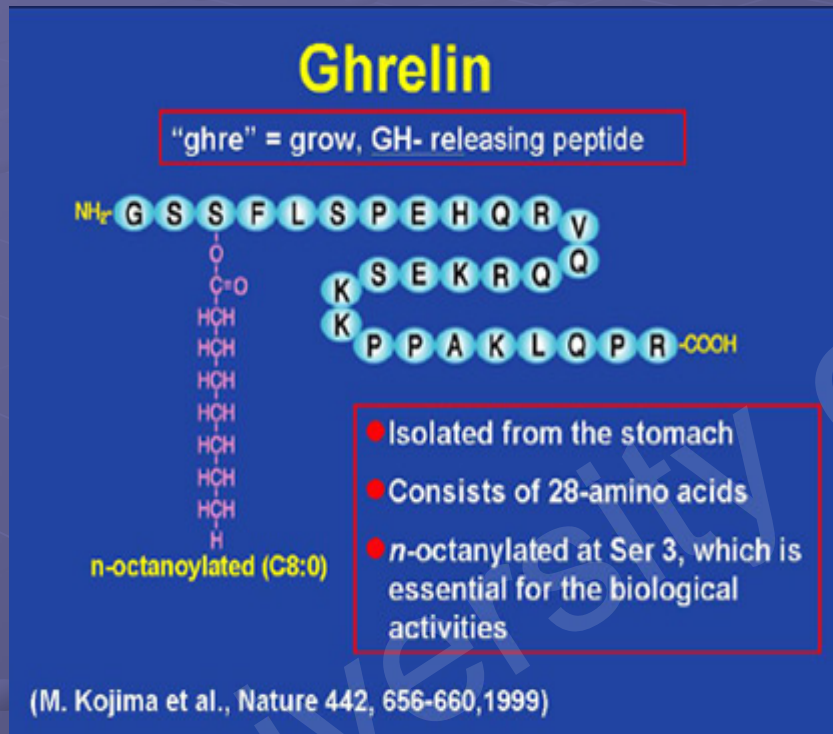
- Hormone produced by the A-like endocrine cells in the oxyntic mucosa (stomach body and fundus)
- Many functions
- Role in motility of the gut



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

Factors Affecting Ghrelin Release

INCREASE GHRELIN

● **FASTING**

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

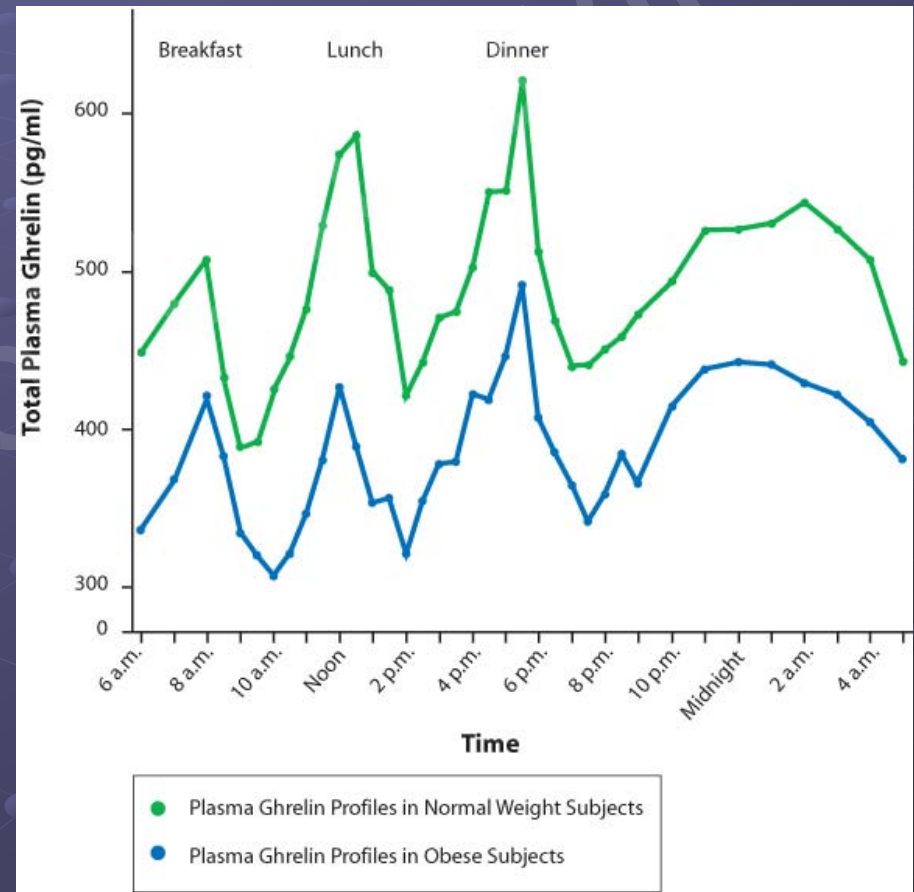
DECREASE GHRELIN

● **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 (5pmol/kg/min) increased appetite and increased food intake → human volunteers ate 28% additional calories at a buffet after ghrelin

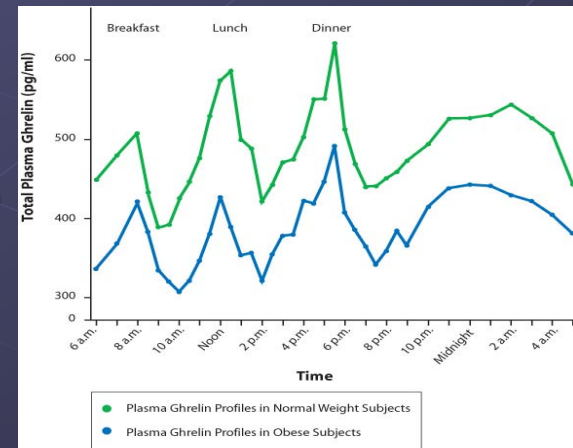


Ghrelin and Feeding

- 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



Weight Gain and Ghrelin

- 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.

SIMILARITIES

- Both released in pulsatile manner in fasted and fed states
- Both act on hypothalamus via Neuropeptide Y

DIFFERENCES

- Leptin inhibits appetite; ghrelin stimulates appetite
- Levels are inversely correlated

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

Ghrelin and Gastric Motility

- 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
 - Measured GET with USN and assessed symptoms of nausea, bloating and hunger. Checked plasma ghrelin, GH, PP. Maintained euglycemia throughout study period.
 - 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

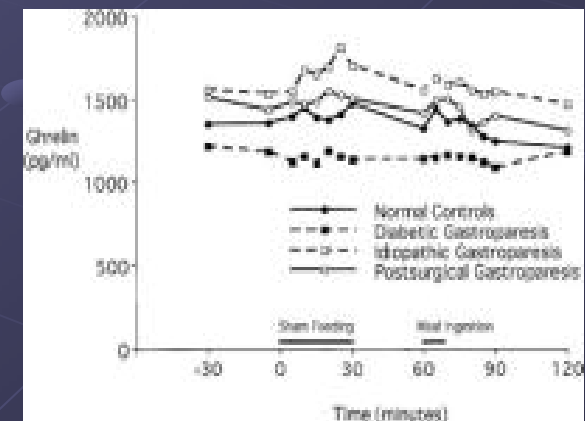
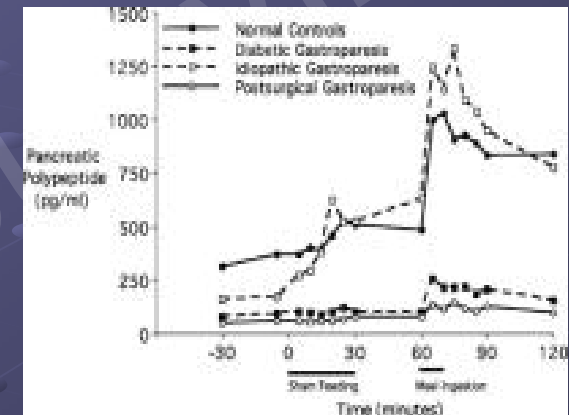
- Ghrelin's signals for starvation and GH secretion travels via vagal afferents to the brain
- Asakawa et al. showed that the orexigenic activity of ghrelin was lost after vagotomy
- Similarly, Date et al. showed that vagotomy abolished the ghrelin-induced feeding and activation of NPY neurons.

Ghrelin and Vagus Nerve

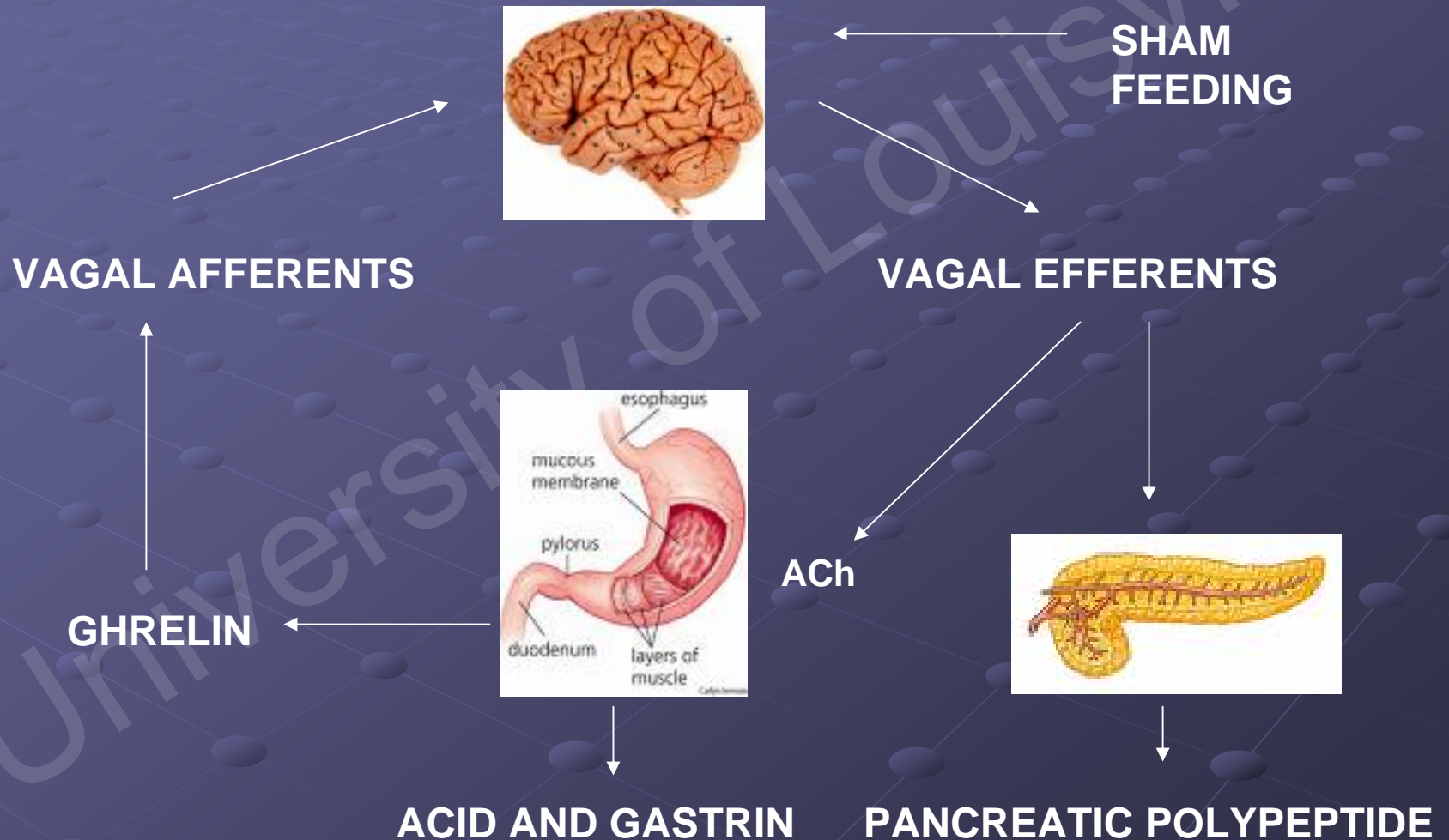
- Simonian, et al. studied 15 healthy pts after sham feedings and meals, checked serial ghrelin and PP levels q 5 min x 30min & 60 min.
- Sham (bacon & cheese): increased PP, ghrelin levels significantly from baseline
- Meal: increased PP, decreased ghrelin levels
- Showed a clear association between 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



Ghrelin and Insulin

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

Ghreltin: Cardiovascular Effects

- Ghreltin decreases Mean Arterial Pressure and increases Cardiac Output
 - It antagonizes endothelin-1, a potent vasoconstrictor

Ghrelin: Summary of Functions

Growth hormone release	↑
ACTH release	↑
Prolactin release	↑
Appetite	↑
Fat mass	↑
Gastric motility	↑ or (↓)
Gastric acid secretion	↑
Cardiac output	↑
Vasodilatation	↑
Glucose	↑ or (→)
Insulin secretion	↓ or (↑)
Proliferation	↑ or ↓

- 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.

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