

Can the gut fight obesity? The role of the gastrointestinal tract in controlling what we eat

Physiology conference

By: Amy Tiu, MD

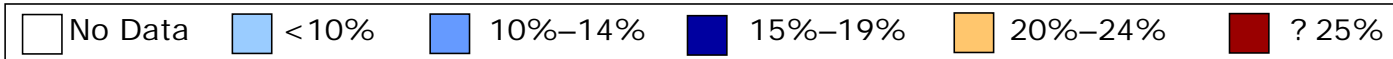
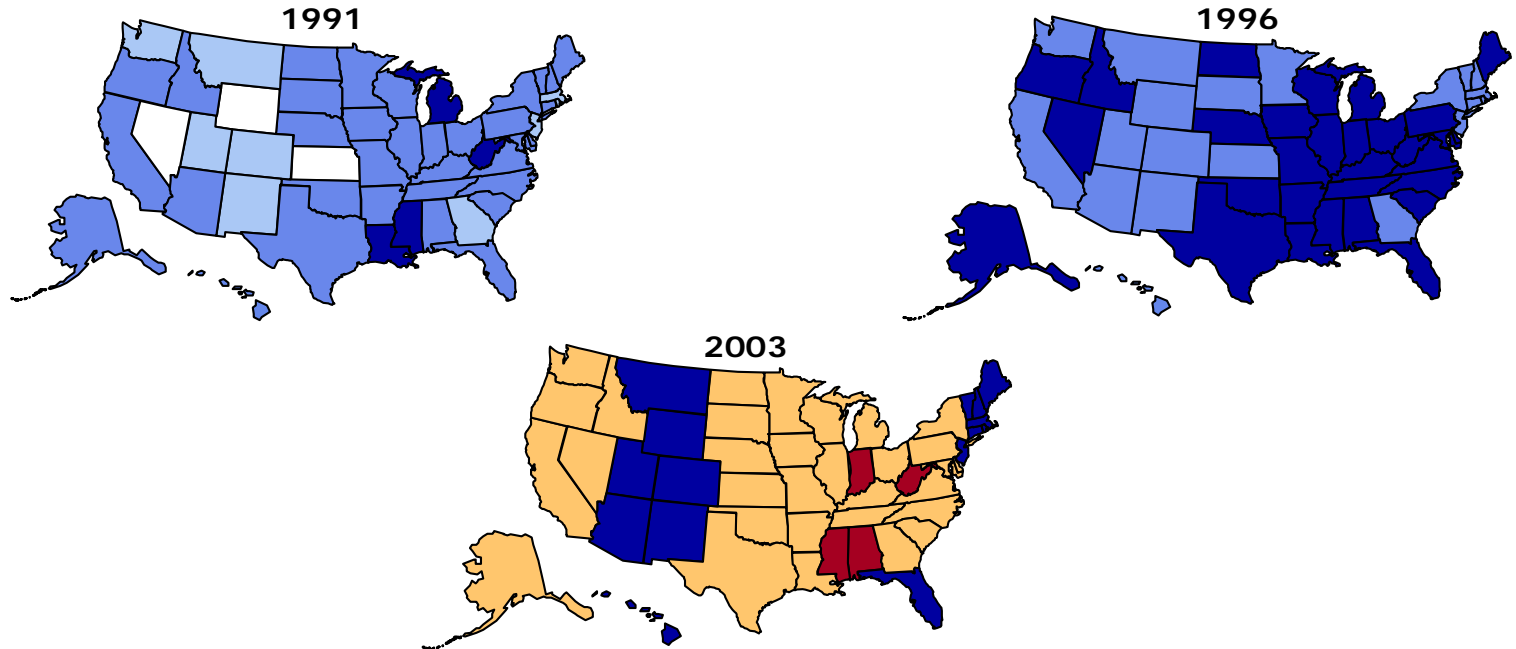
The problem of obesity

- Responsible for about 300,000 preventable deaths per year in the United States (second only to cigarette as the leading cause of preventable death)

Obesity Trends* Among U.S. Adults

BRFSS, 1991, 1996, 2003

(*BMI ≥ 30 , or about 30 lbs overweight for 5'4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Objectives

- Understand the role, interactions, and clinical implications of the following gut peptides
 - Ghrelin
 - PP-fold peptides (PYY, PP, and NPY)
 - Proglucagon products (OXM and GLP 1)
 - CCK
- Briefly comment on the effect of gastric bypass and the peptides

Appetite control: Basic Structure

- Central and Peripheral
- Needs signals for long-term nutritional status and acute changes in nutrition
- Involves brainstem and reward pathways
- Brain receives signals from the gut and adipose tissue

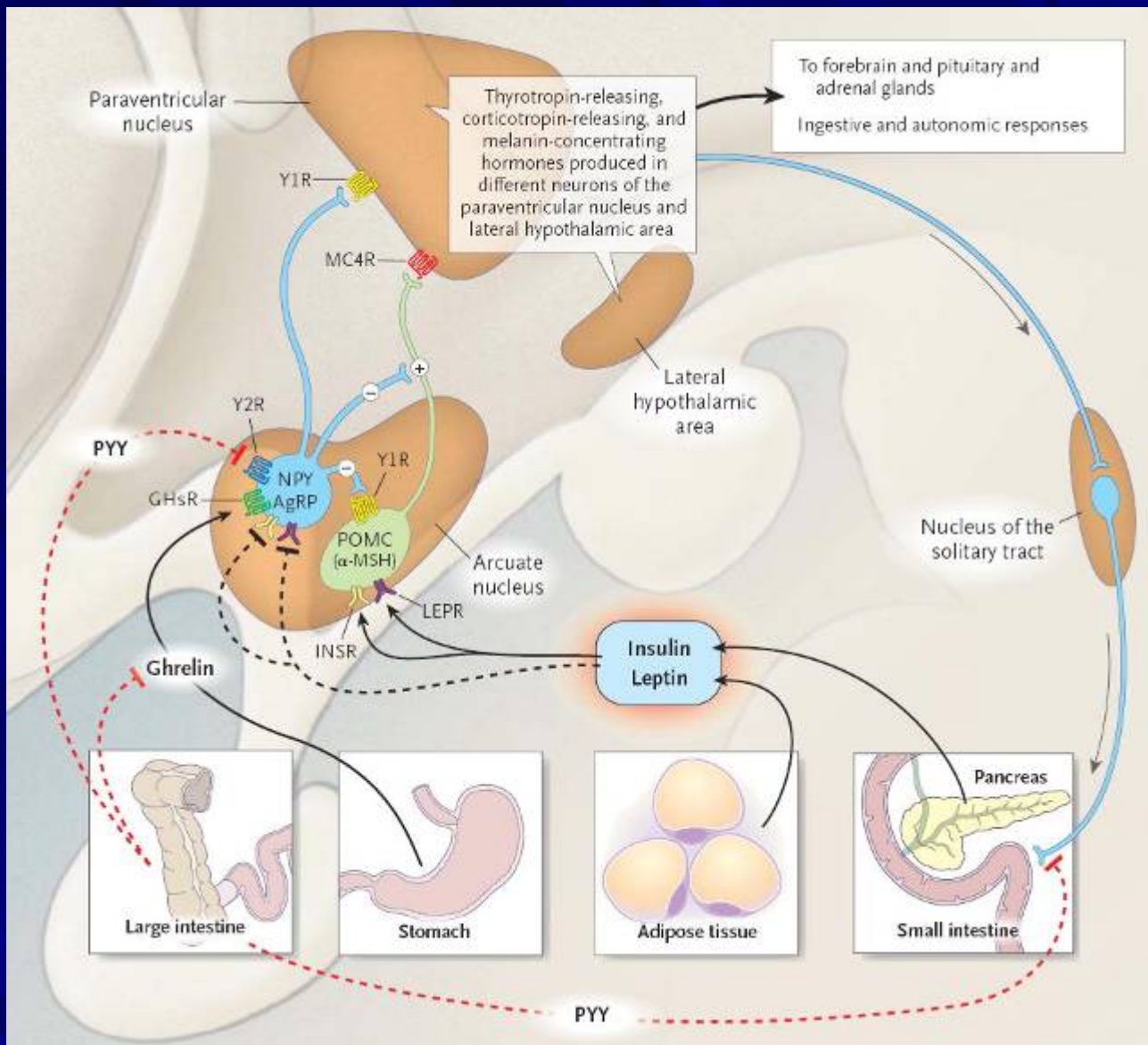
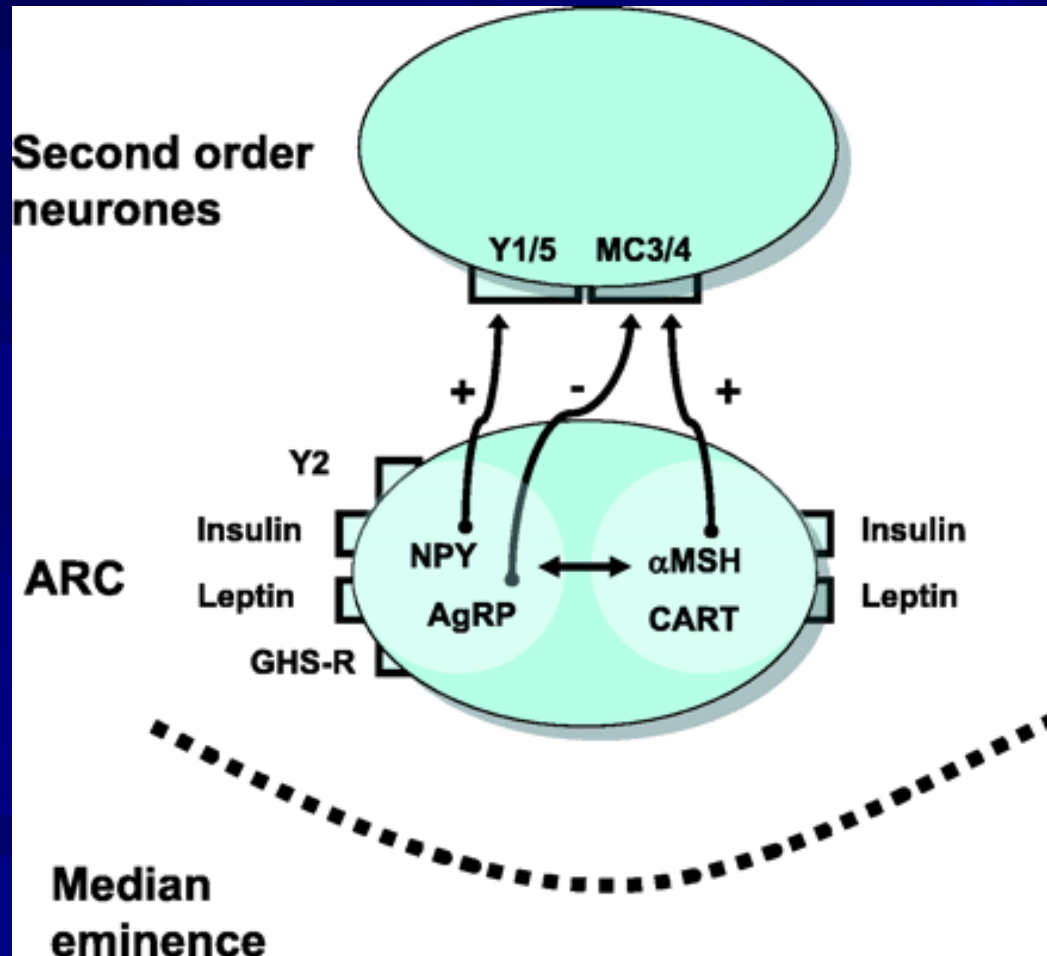


Figure 1. Interactions among Hormonal and Neural Pathways That Regulate Food Intake and Body-Fat Mass. In this schematic diagram of the brain, the dashed lines indicate hormonal inhibitory effects, and the solid lines stimulatory effects. The paraventricular and arcuate nuclei each contain neurons that are capable of stimulating or inhibiting food intake. Y1R and Y2R denote the Y1 and Y2 subtypes of the neuropeptide Y (NPY) receptor, MC4R melanocortin 4 receptor, PYY peptide YY_(3,36), GHsR growth hormone secretagogue receptor, AgRP agouti-related protein, POMC proopiomelanocortin, (α)-MSH (alpha)-melanocyte-stimulating protein, LEPR leptin receptor, and INSR insulin receptor.

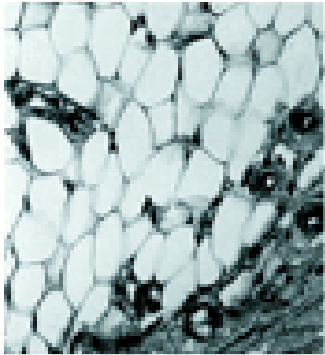
From: Korner: N Engl J Med, Volume 349(10).September 4, 2003.926-928

Central Control: The arcuate nucleus (ARC)



What is in the ARC?

- Neuropeptide Y (NPY) and the agouti-related peptide (AgRP)
- NPY and AgRP are populations of neurons that stimulate food intake (orexigenic)
- Pro-opiomelanocortin (POMC) and alpha melanocyte-stimulating hormone and cocaine and amphetamine regulated transcript (CART) decrease food intake (anorexigenic)

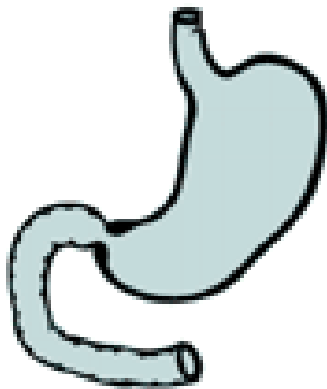


Adiposity signals

Insulin

Adiponectin

Leptin



Gut hormones

Ghrelin

CCK

GLP-1

OXM

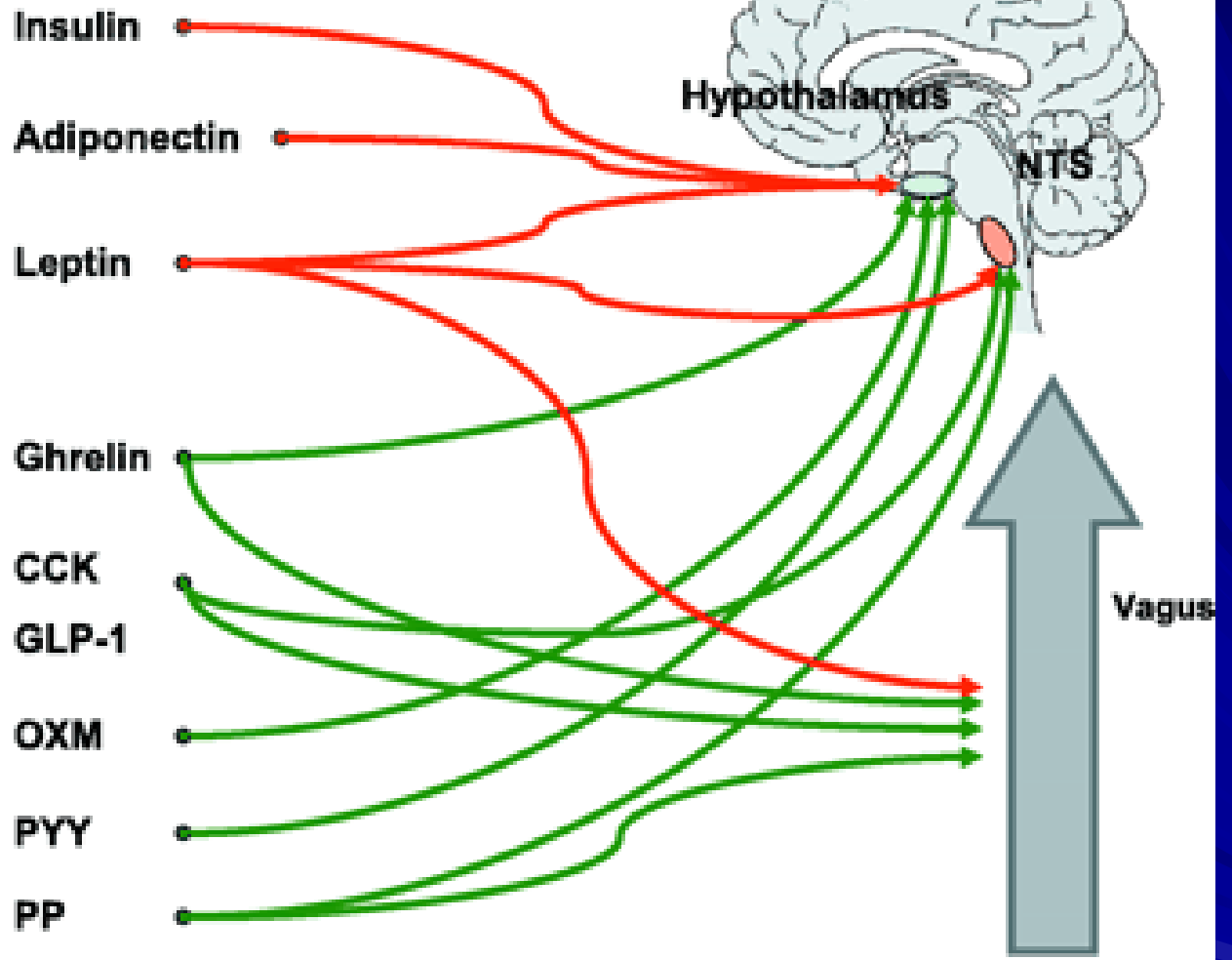
PYY

PP

Hypothalamus

NTS

Vagus



Prader-Willi Syndrome

- Chromosomal deletion of 15q11-13
- **High ghrelin levels**
- No cure; treatment mainly by exercise and diet control

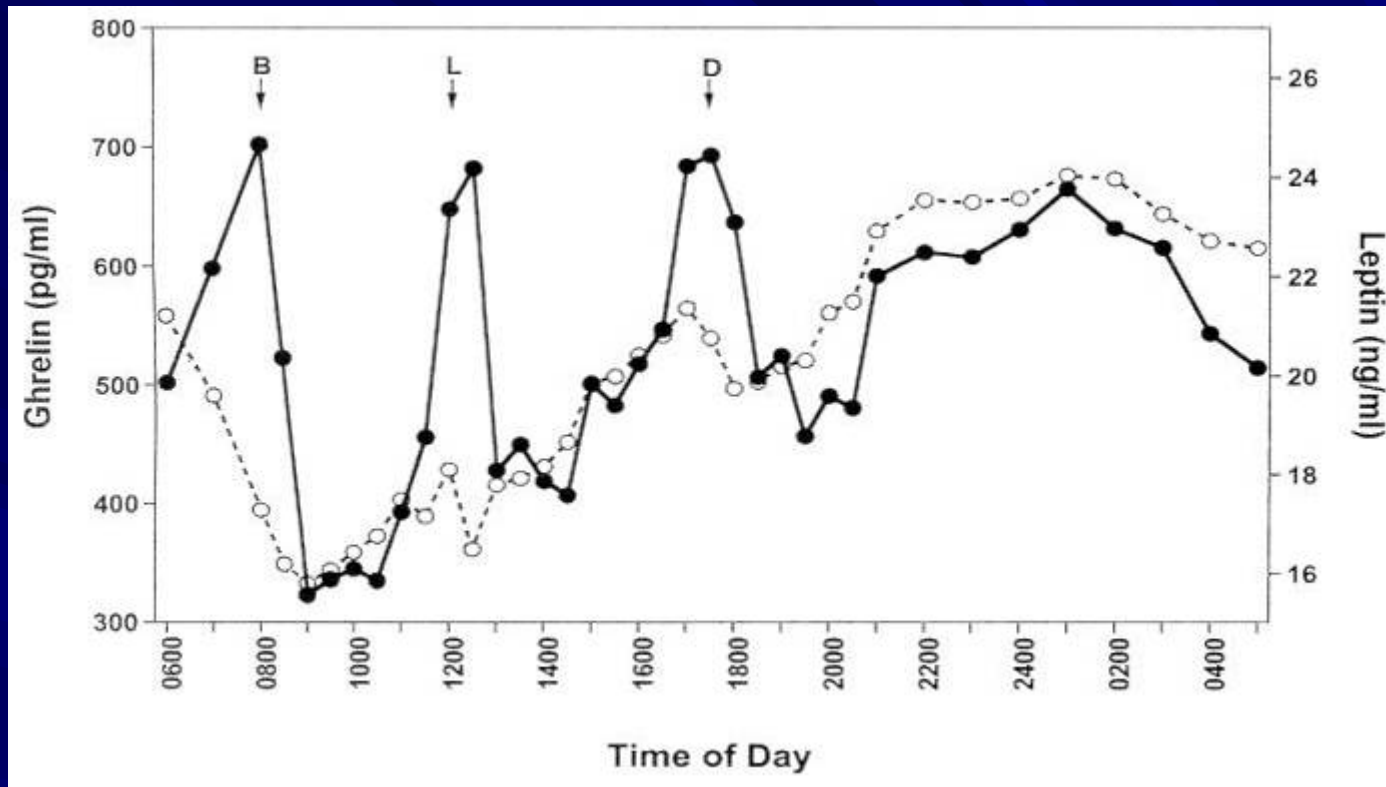


Ghrelin

- Discovered in 1999
- Released in a pulsatile manner from the oxyntic cells of the stomach, also from the duodenum, ileum, cecum, and colon
- Endogenous ligand for growth hormone secretagogue receptor (GHS-R)
- **Stimulates food intake**

Ghrelin

- Up-regulated by fasting
- Decreased by eating
- Prokinetic
- Inverse relationship with BMI



Overlaid average plasma ghrelin (●) and leptin ([white circle]) concentrations during a 24-h period in 10 human subjects consuming breakfast (B), lunch (L), and dinner (D) at the times indicated.

From: Cummings: Diabetes, Volume 50(8).August 2001.1714-1719

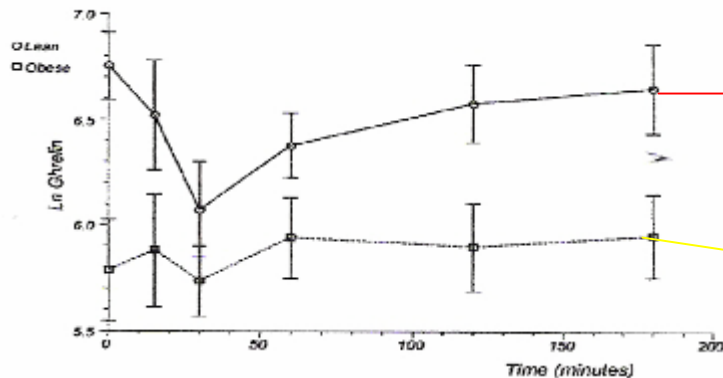
Ghrelin in obese subjects

- Ghrelin levels are low in obesity
- Do obese subjects have a normal post-prandial ghrelin level? NO, unlike lean subjects, obese subjects do not have the same rapid post-prandial drop in ghrelin levels
- Food fails to decrease levels in obese patients

Ghrelin in obese subjects after a meal

- Obese subjects do not exhibit the decline in ghrelin after a meal

English et al. Food Fails To Suppress Ghrelin Levels in Obese Humans. JCEM. 2002;87(6):2984-2987



Lean subjects

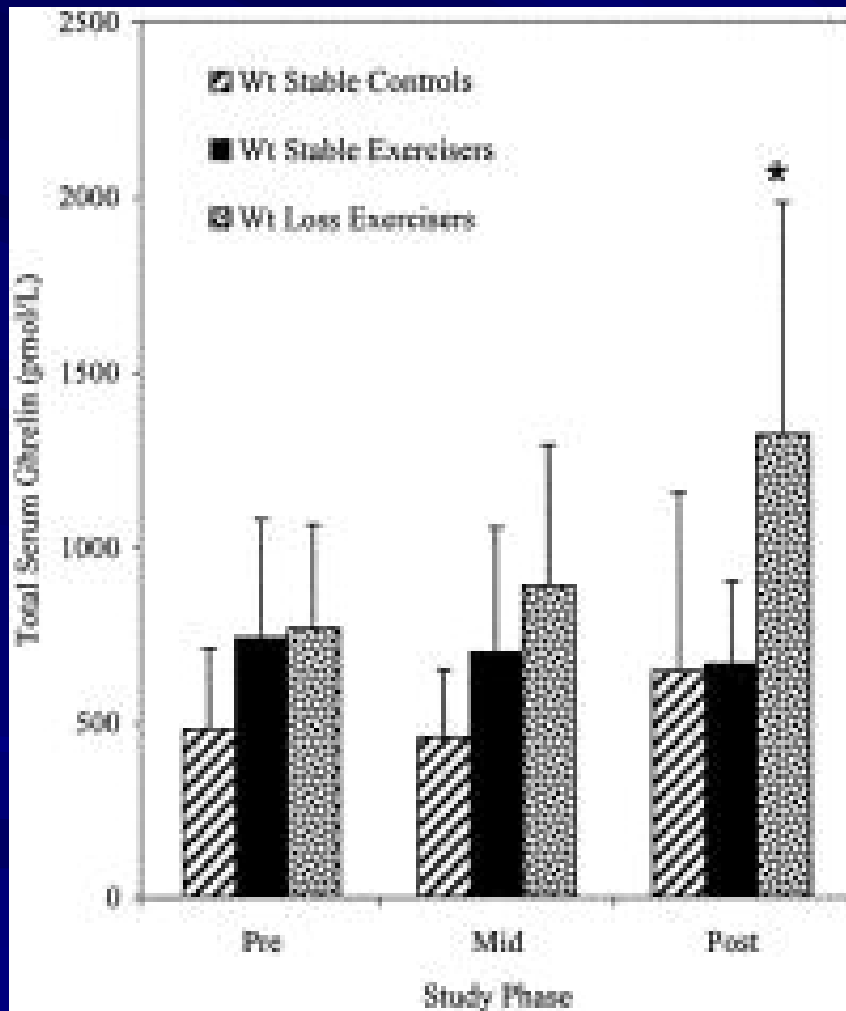
Obese subjects

Figure 1. Mean (\pm SEM) ln(ghrelin) response in lean and obese subjects following a test meal. There is a significant fall in ln(ghrelin) at 30 minutes following the meal in lean subjects ($p=0.003$, ANOVA for multiple comparisons with baseline), but no fall in obese subjects.

Ghrelin in anorexia and bulimia

- Patients with anorexia have a very high level, which return to reference range after treatment and weight gain
- Patients with bulimia show higher circulating levels of ghrelin when compared with controls. Frequent vomiting may be the cause of increased ghrelin levels.

What Happens to Ghrelin with change in body weight



- Ghrelin increased over time in the weight loss group ($p < 0.05$)
- Ghrelin responds in a compensatory manner to changes in energy homeostasis in healthy young women
- Leidy et al. Circulating Ghrelin Is Sensitive to Changes in Body Weight during a Diet and Exercise Program in Normal Weight Young Women. 2004 J Clin Endocrinol Metab 89(6):2659-2664

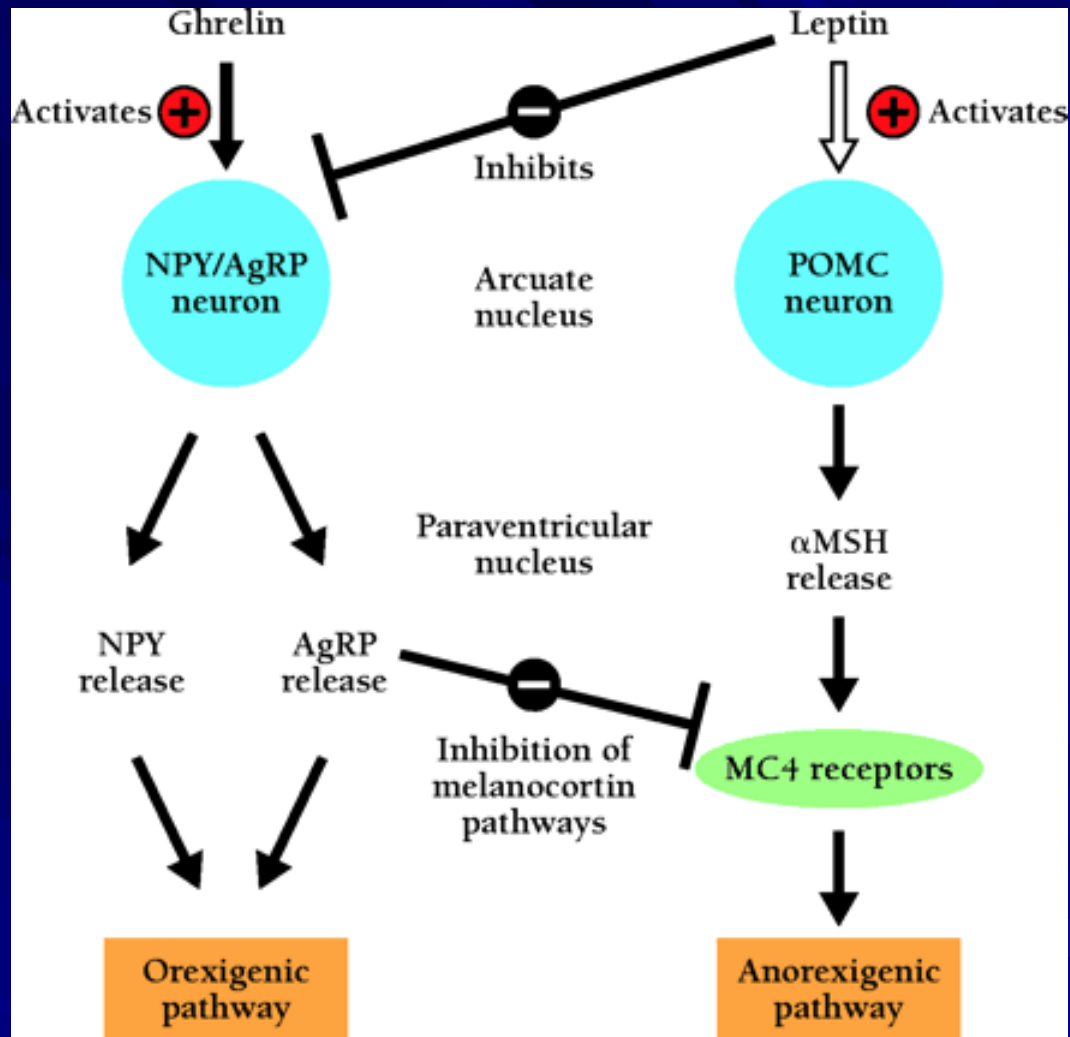
What happens with exogenous infusion of ghrelin in humans?

- Increased appetite
- Increased food intake
- Wren et al. showed subjects consumed a mean 28% additional calories from an unlimited buffet after administration



Leptin and Ghrelin

- Leptin is an adipocyte
- Analogous but reciprocal to ghrelin
- Both released in pulsatile manner
- Counter regulatory roles in energy homeostasis



A simplified model of the feeding-regulatory signaling of ghrelin and leptin. Leptin stimulates the POMC anorexigenic pathway and inhibits the NPY–AGRP orexigenic pathway, resulting in reduced food intake. The effect of ghrelin in the hypothalamus is opposite to that of leptin. The orexigenic effect of ghrelin is mediated by activating on the output of the NPY–AGRP neurons. Fasting increases ghrelin and decreases leptin production, leading to the activation of the orexigenic pathway. This response might be important for the adaptation to fasting. *Molecular Interventions* 2002;2: 495-503

Ghrelin and Leptin: Is there an association with obesity?

Example

Spiegel et al. Sleep Curtailment in Healthy Young Men is Associated with Decreased Leptin levels, Elevated Ghrelin Levels, and Increased Hunger and Appetite. *Annals of Internal Medicine* 2004;141(11):846-850

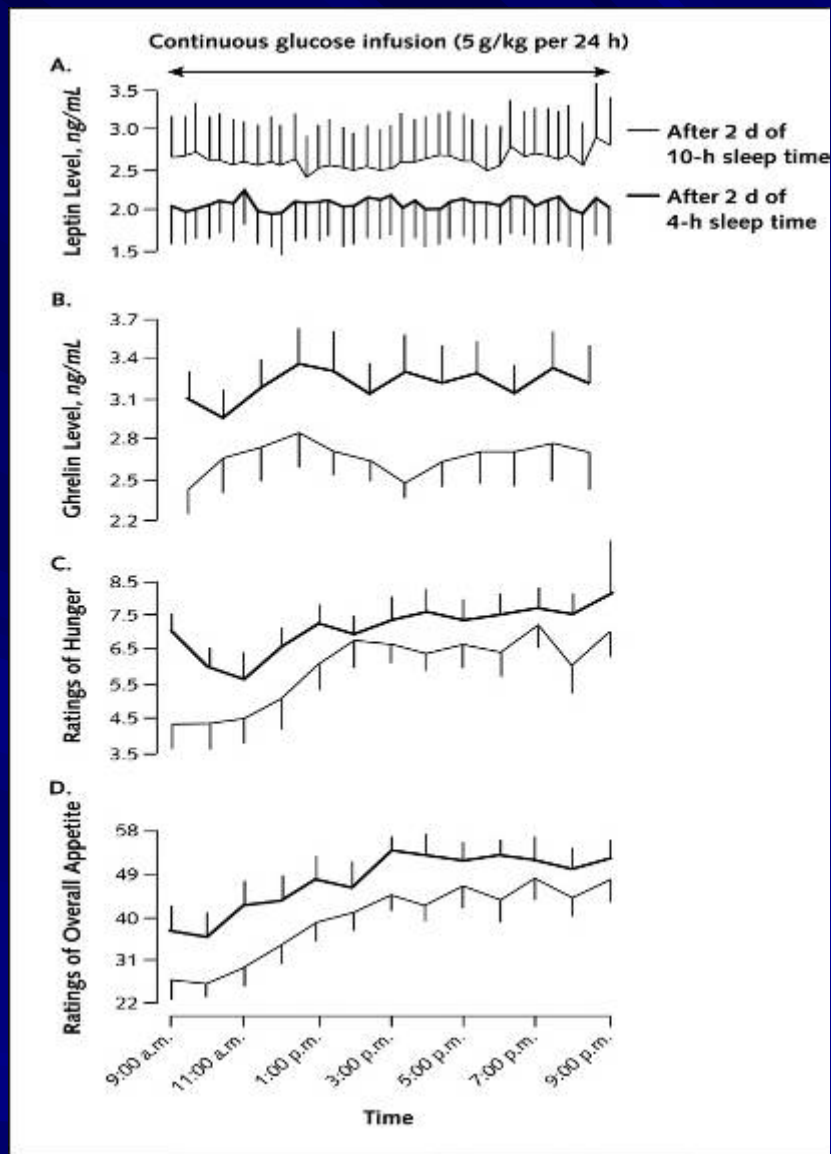


Figure 1. Effect of sleep duration on daytime leptin levels, ghrelin levels, hunger, and appetite. A. Mean (\pm SE) daytime (9:00 a.m. to 9:00 p.m.) profiles of leptin after 2 days with 4 hours in bed or 2 days with 10 hours in bed. Mean leptin levels were 18% lower when sleep was restricted. B. Mean (\pm SE) daytime (9:00 a.m. to 9:00 p.m.) profiles of ghrelin from 9 of the 12 participants after 2 days with 4 hours in bed or 2 days with 10 hours in bed. Mean ghrelin levels were 28% higher in the afternoon and early evening (12:00 noon to 9:00 p.m.) when sleep was restricted. C and D. Ratings of hunger (C) (0- to 10-cm visual analogue scale) and overall appetite (D) (0- to 70-cm visual analogue scale) after 2 days with 4 hours in bed or 2 days with 10 hours in bed. When sleep was restricted, ratings of hunger and overall appetite increased by 24% and 23%, respectively.

Conclusions from Study

- Less sleep: decreased Leptin and increased Ghrelin
- Less sleep: Increased hunger (24%) and increase appetite (23%) especially for calorie dense foods
- No change in weight loss or energy supply
- Further studies are needed to clarify if sleep deprivation, leptin, and ghrelin are associated with obesity

Ghrelin has other associations

- Leptin may not be the only peptide associated with Ghrelin
- Orexin from the lateral hypothalamus may also be involved in a balance with ghrelin. Of note, disruption of this system is a major cause of narcolepsy
- Also associated with PYY, OXM

State	Ghrelin level
Obese	Low
Gastric bypass	Low
Prader-Willi	Extremely high
Lean	High
Diet induced weight loss	High

It may not be the level that contributes to the obesity, but the antagonism on ghrelin that will contribute to application to weight loss.

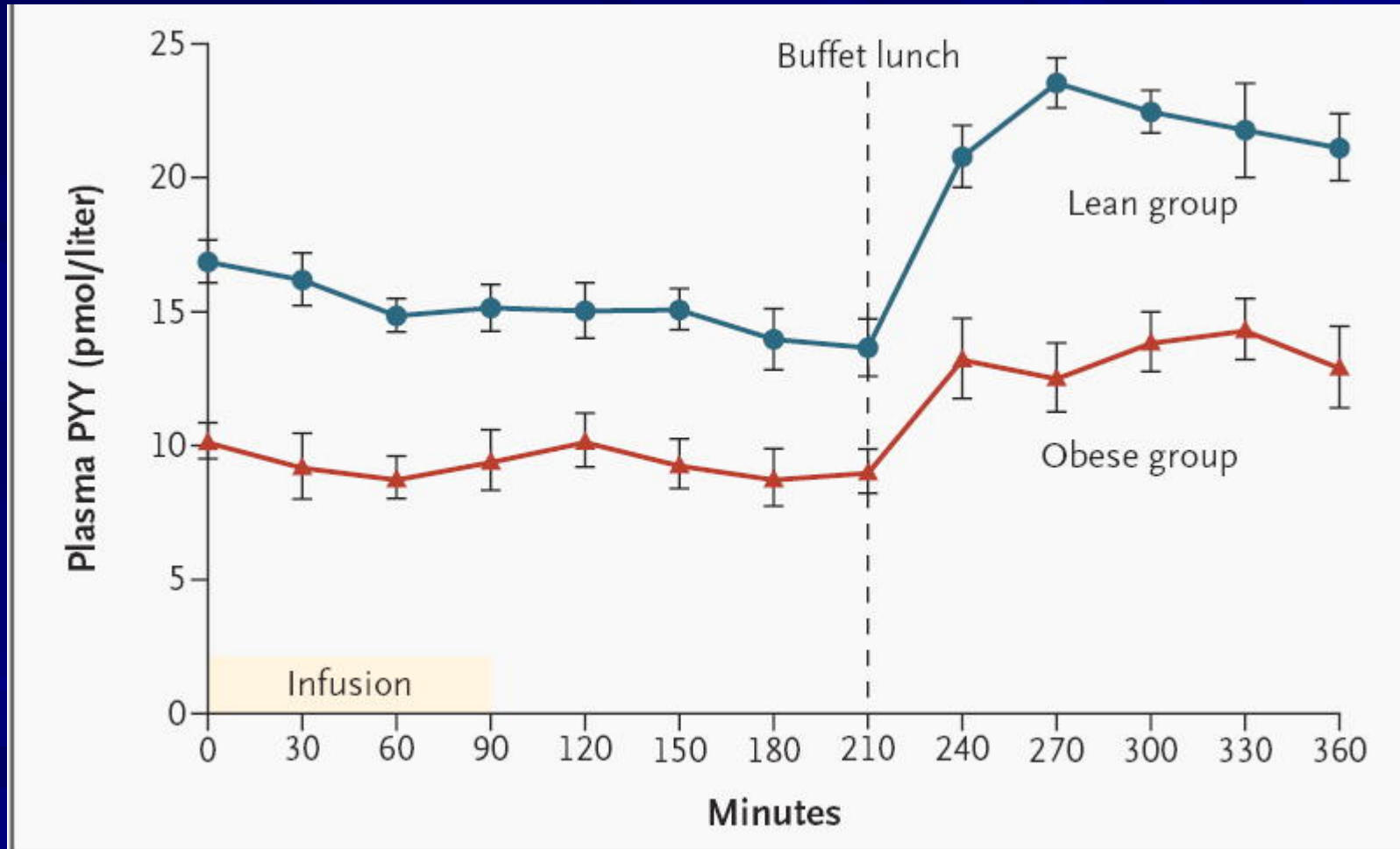
The PP-fold peptides

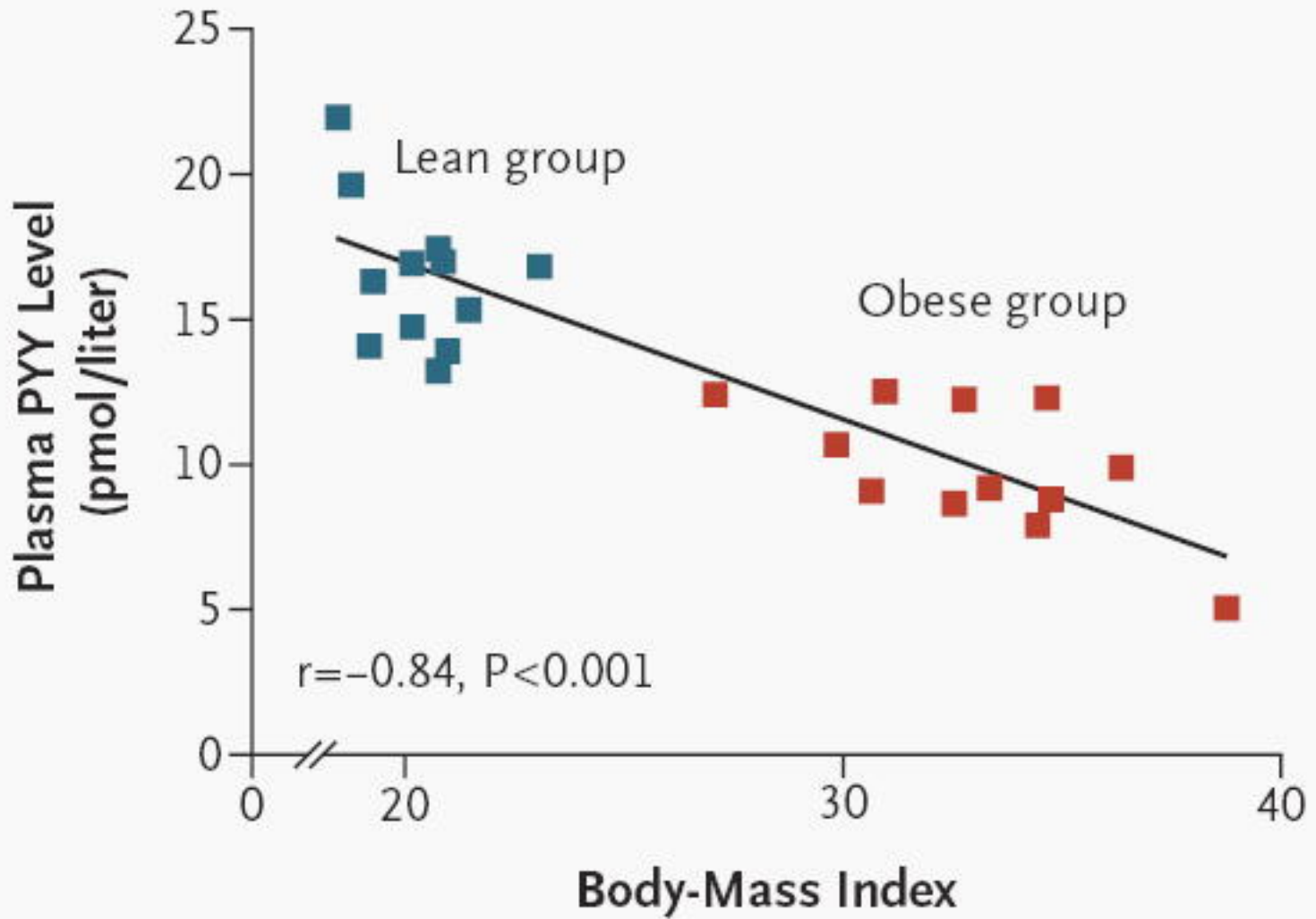
- Peptide YY (PYY): Gut peptide
- Pancreatic polypeptide (PP): Gut peptide
- Neuropeptide Y (NPY) (in neurons)
- Characteristic U shaped fold known as a PP fold
- PYY and PP are peripheral gut peptides that help to **reduce food intake**

PYY

- Secreted from the entire gastrointestinal tract
- Common in the ileum, colon, and very high levels in the rectum
- Lower basal fasting level in obese patients
- **Reduces food intake**

Fasting PYY levels were significantly lower in obese than lean subjects





Effects of exogenous infusion of PYY

- Reduction in food intake in humans by 30% in obese subjects and by 31% in lean group
- Reduction in plasma levels of ghrelin
- Obese subjects were not resistant to anorectic effects of PYY

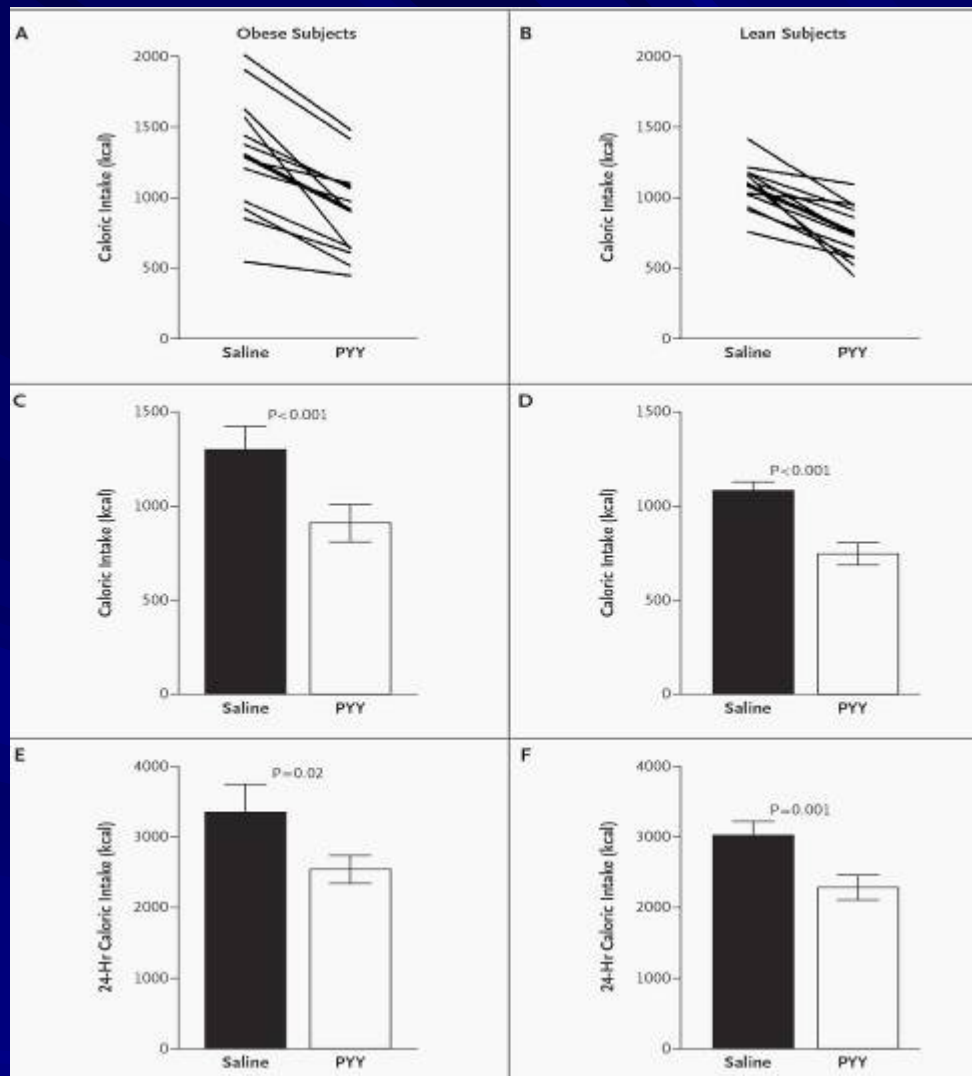
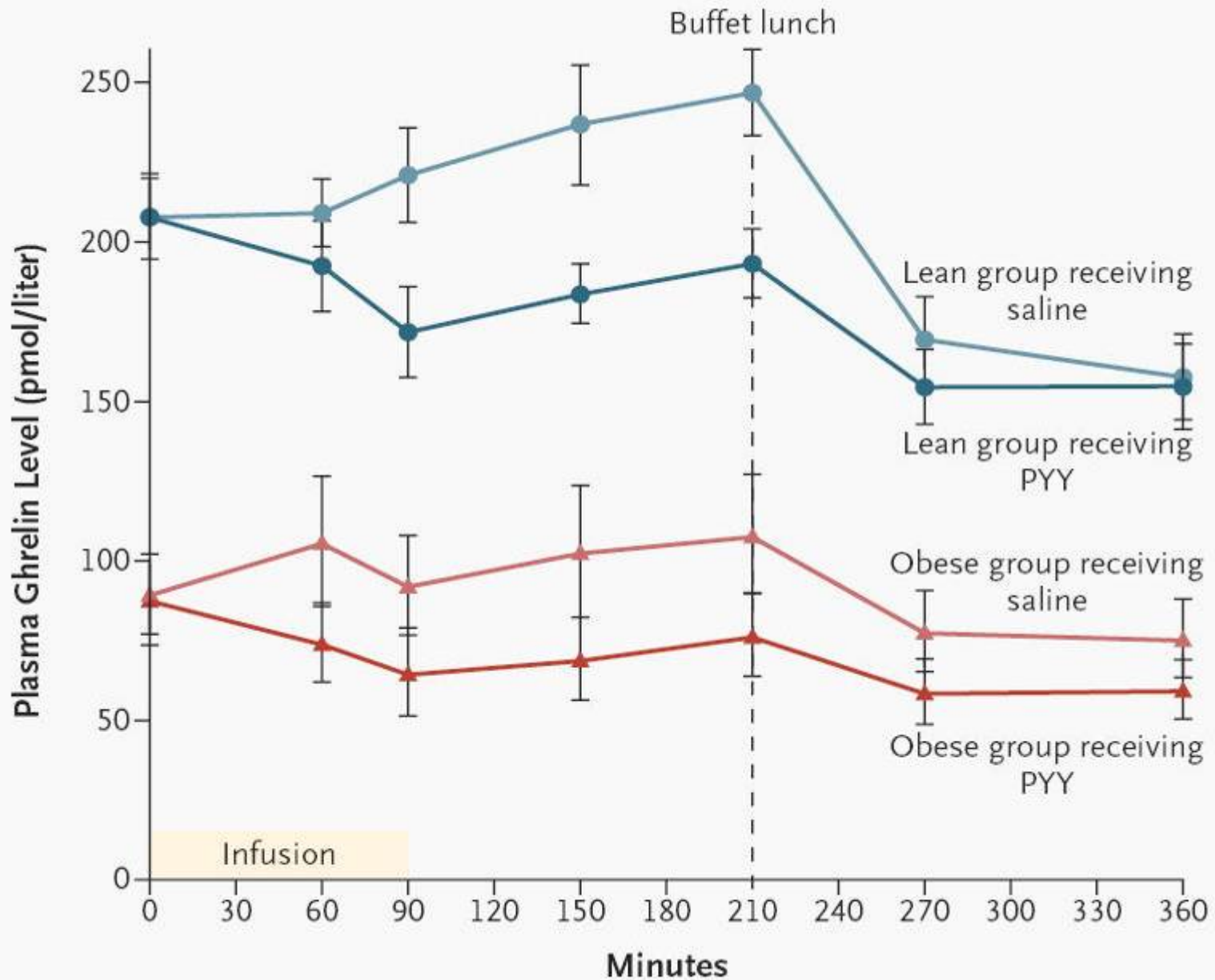


Figure 1. Caloric Intake by Obese and Lean Subjects after Infusion of Peptide YY₍₃₋₃₆₎ (PYY) or Saline. Panel A shows the caloric intake by individual obese subjects, and Panel B shows the intake by individual lean subjects, during a buffet lunch two hours after the infusion of PYY or saline. Panel C shows the mean (+/-SE) caloric intake by obese subjects, and Panel D shows the intake by lean subjects, during a buffet lunch two hours after infusion of saline or PYY. Panel E shows the mean (+/-SE) cumulative 24-hour caloric intake by obese subjects, and Panel F shows the intake by lean subjects, after infusion of saline or PYY. In all panels, the lean and obese groups each consisted of 12 subjects: 6 women and 6 men.

Batterham R et al. Inhibition of Food Intake in Obese Subjects by Peptide YY. 2003 NEJM 349(10): 941-948



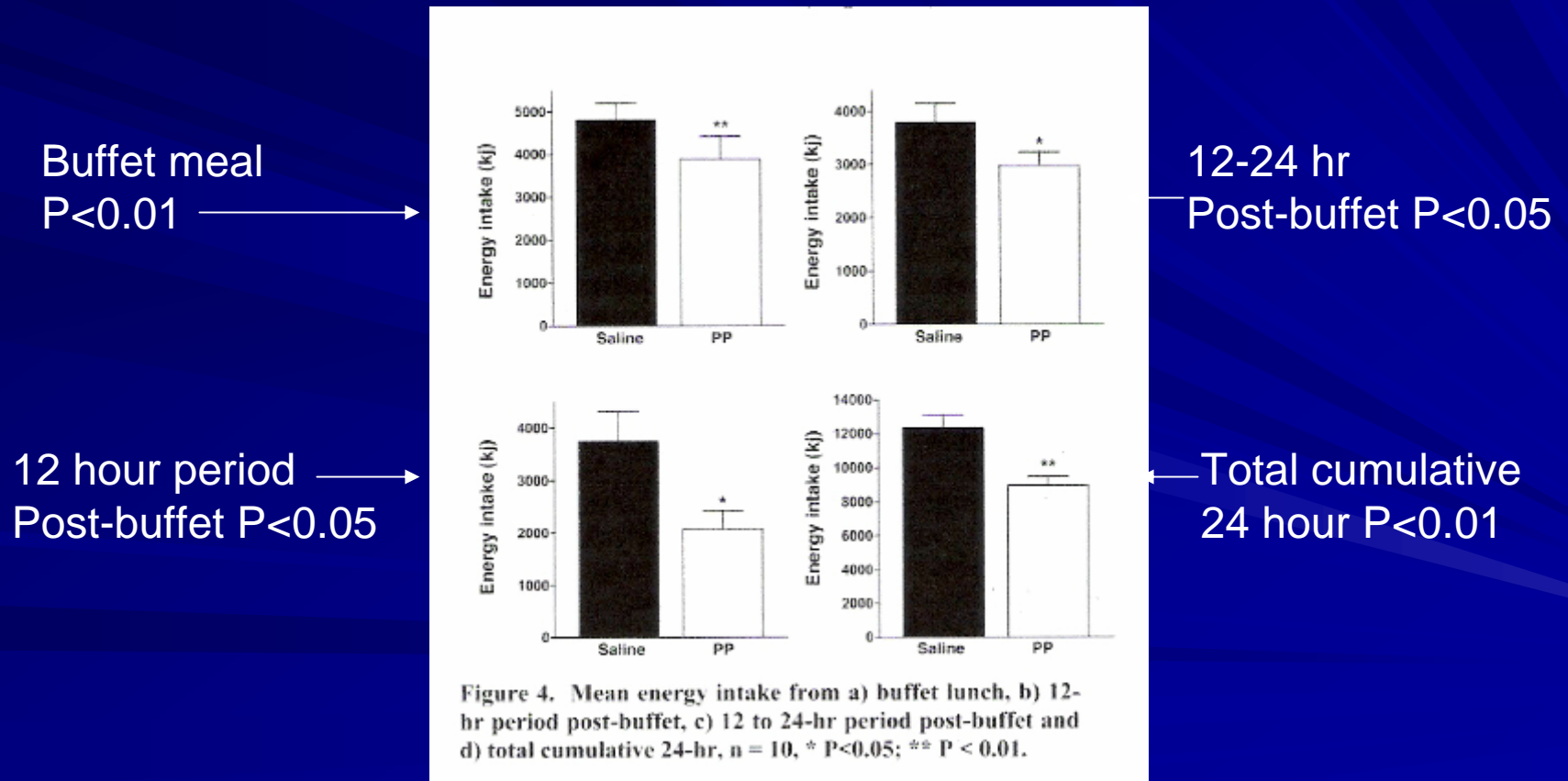
PYY

- Influenced by both the number of calories and the composition of food (higher if more fat)
- Release occurs BEFORE nutrients reach distal GI tract
- Gastric acid, CCK, and luminal bile salts stimulate
- Gastric distention has not been found to stimulate PYY
- Can cross the blood brain barrier

Pancreatic Polypeptide (PP)

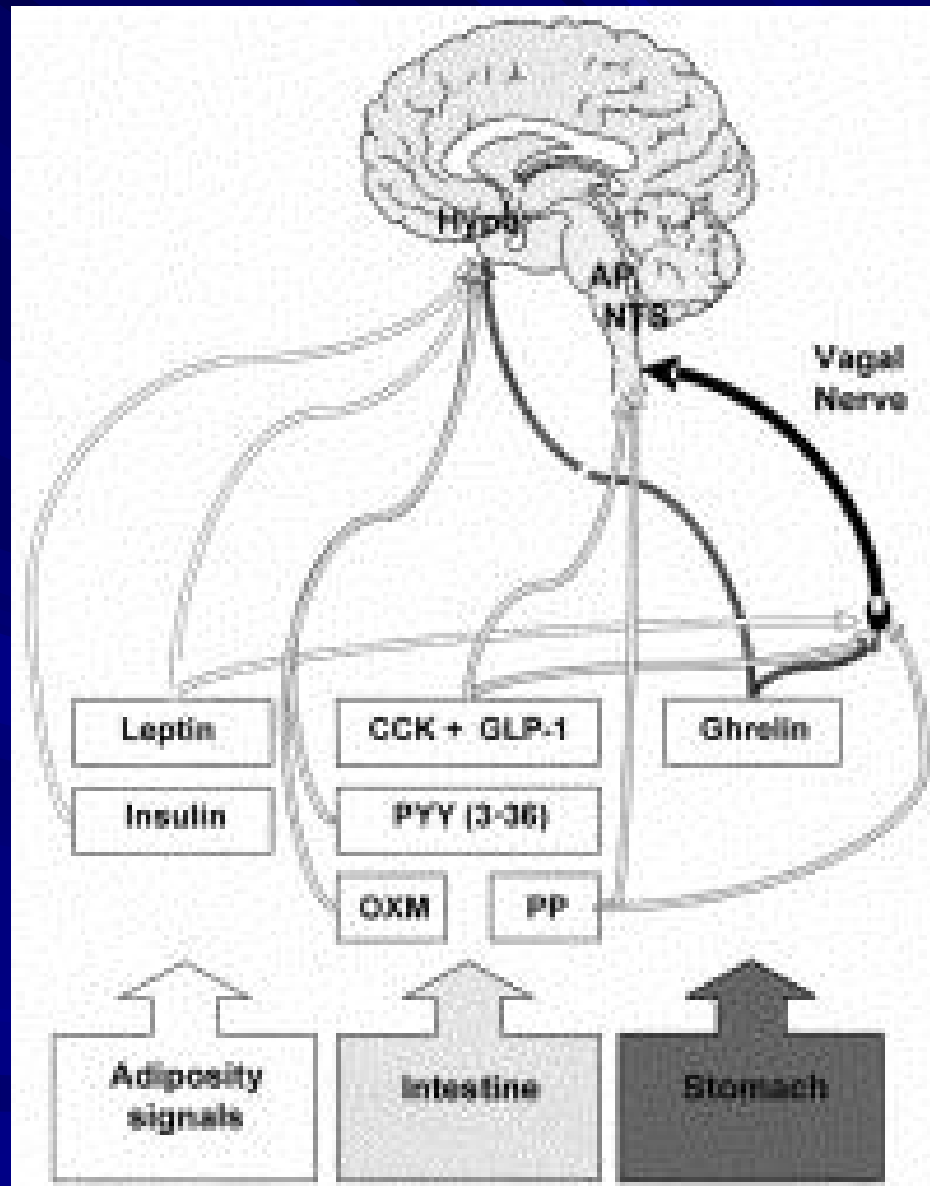
- Largely produced by pancreas, but also found in the colon and rectum
- Main stimulus is food intake
- Proportional to caloric load
- Biphasic release
- Can be influenced by gastric distention, vagal tone, adrenergic stimulation

Effects of exogenous infusion PP: Energy intake saline vs PP



Effects of exogenous infusion PP

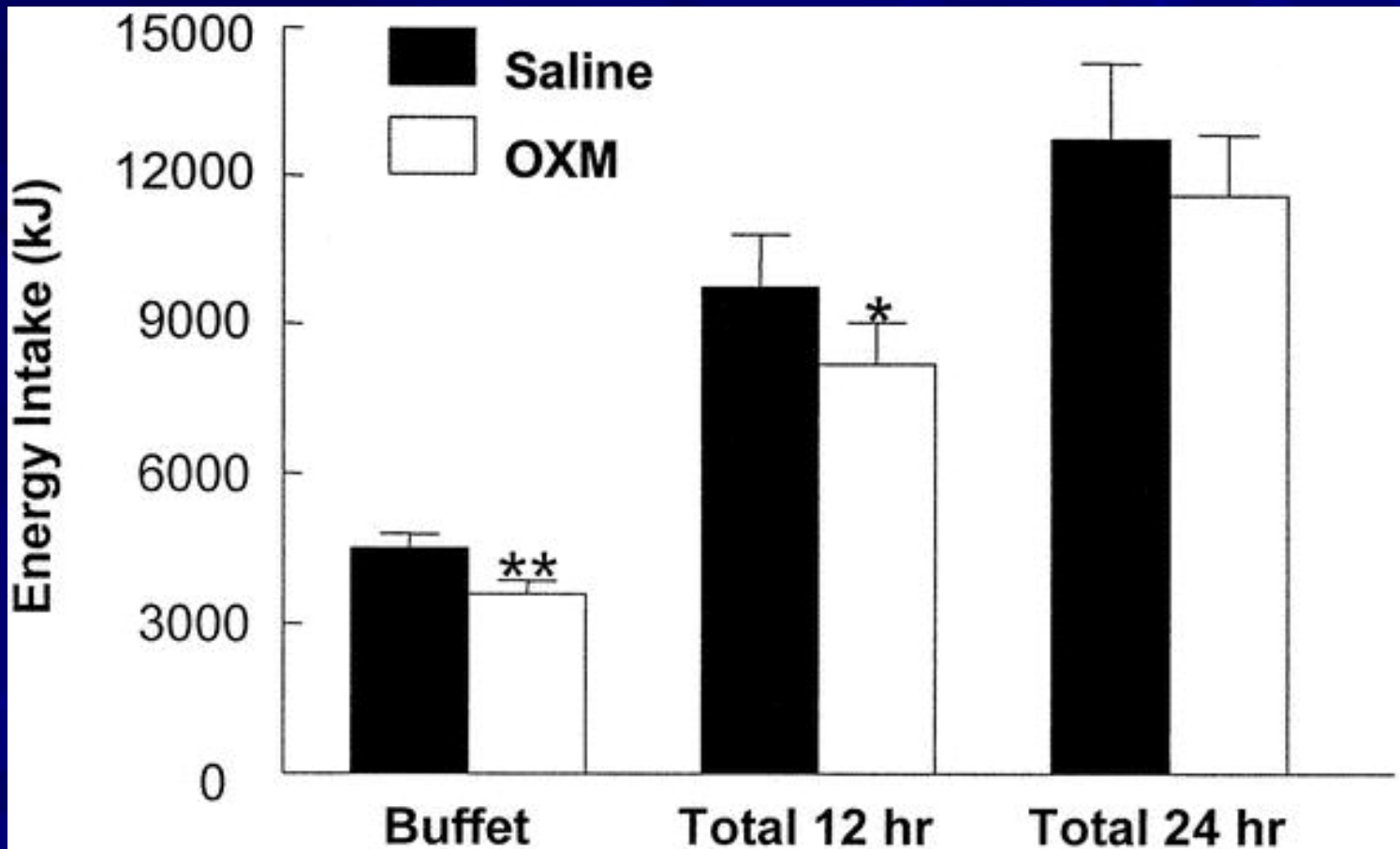
- Normal-weight human volunteers given an infusion of PP demonstrate decreased appetite and a 25% reduction in food intake over the following 24 hours
- No studies on obese humans
- Appears to be efficacious treatment for Prader Willi
- Able to reduce ghrelin



Products of Preproglucagon gene

- OXM (oxyntomodulin)
- Glucagon-like peptide 1 (GLP 1)
- Released in proportion to calorie intake
- Satiety signals from the L cells of the small intestine

What happens when OXM is given IV to normal subjects?

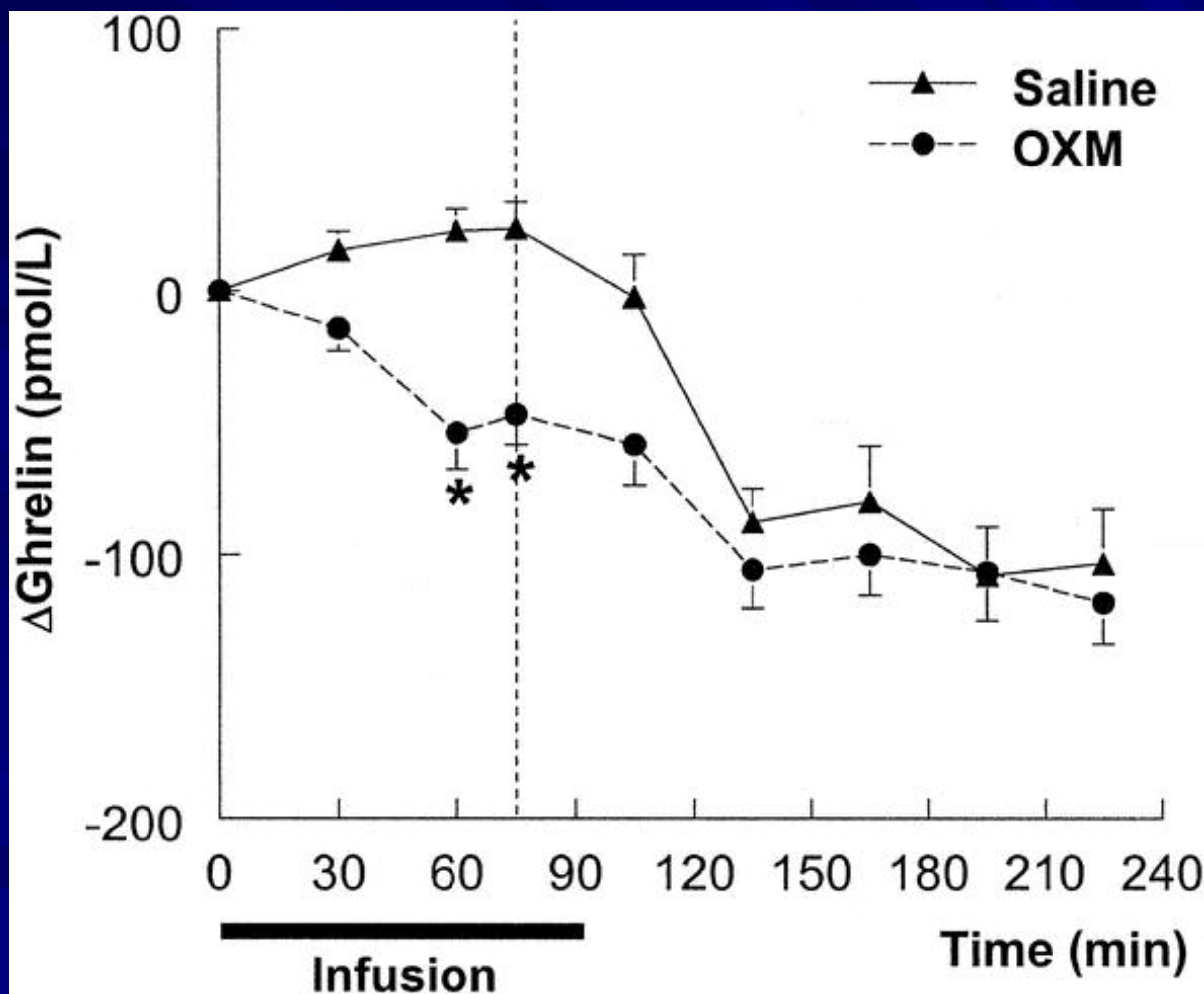


Cohen et al. Oxyntomodulin Suppresses Appetite and Reduces Food Intake in Humans
2003. J of Clinical Endocrinol & Metab 88(10): 4696-4701

Oxyntomodulin (OXM)

- From posttranslational processing of proglucagon in intestinal cells
- An infusion in humans was shown to immediately reduce calorie intake by 19.3% and was effective in reducing food intake for up to 12 hours post infusion
- Part of its effect may be via suppression of plasma ghrelin

Effects of OXM infusion on plasma Ghrelin



Cohen et al. Oxyntomodulin Suppresses Appetite and Reduces Food Intake in Humans. 2003. J of Clinical Endocrinol & Metab 88(10): 4696-4701

OXM

- No effects on PYY or leptin
- Inhibit gastric emptying in humans
- May augment postprandial insulin
- Reduces gastric motility
- Exact receptor for which OXM uses and long term effects are unknown

The second proglucagon product: GLP-1

- Glucagon-Like Peptide 1
- Released in proportion to calorie intake
- Regulator of satiety
- Also able to act on the pancreas to cause insulin release (incretin)

What happens with IV GLP-1 in both lean and obese individuals?

- Decreased food intake in both groups in a dose dependent manner
- **HOWEVER**, when infusions achieve levels comparable to those seen in the physiological state after meals, the effect small



GLP-1 in obese subjects

- Unclear as to whether levels are reduced in obese subjects
- Obese subjects given subcutaneous GLP-1 prior to meals reduced their calorie intake by 15% and lost 0.5kg in weight over 5 days

Can GLP-1 make a difference in diabetes? YES

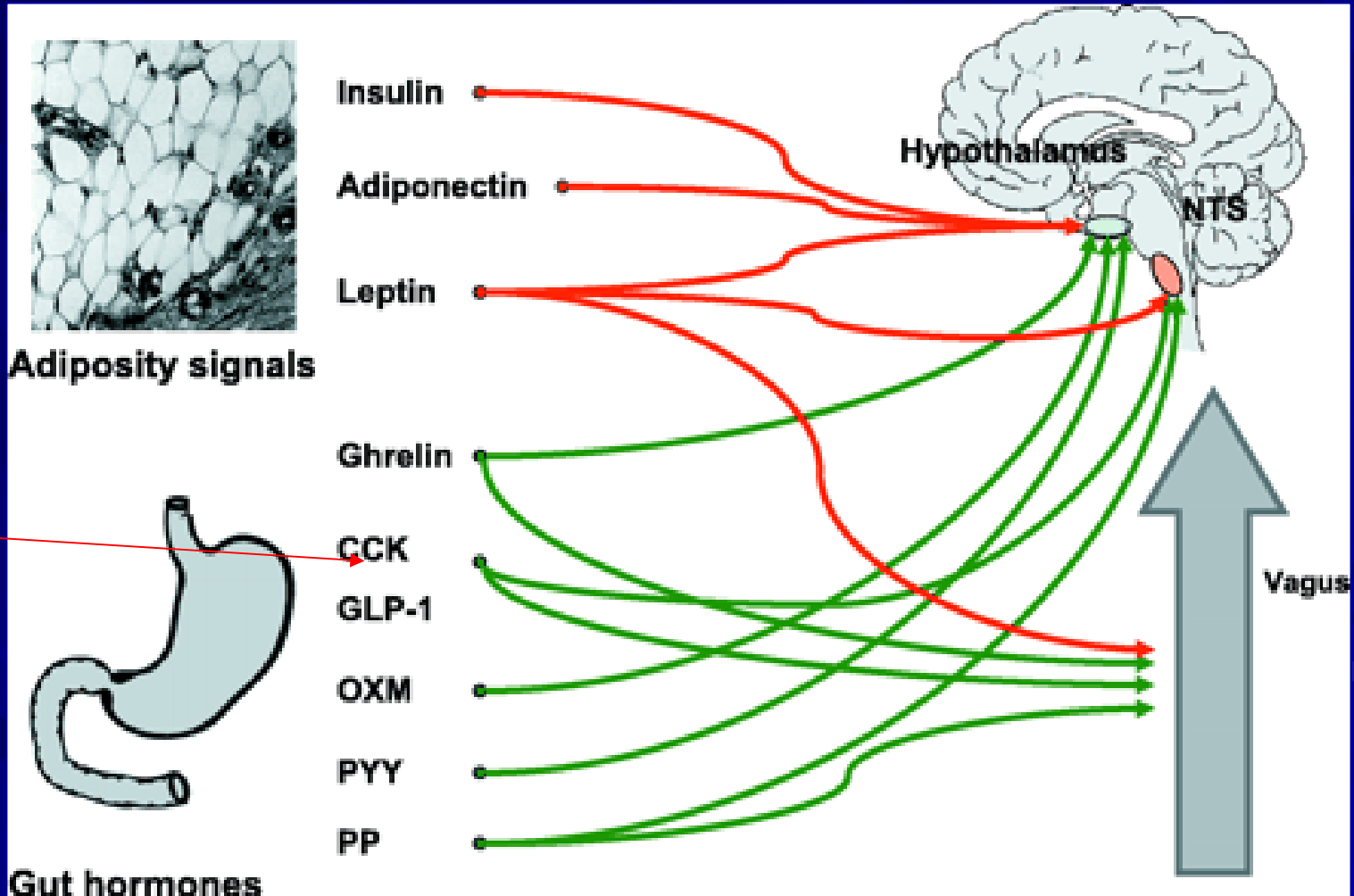
- GLP-1 has been found to normalize blood glucose levels in poorly controlled type 2 diabetes during both a short-term IV infusion and after a 6 week subcutaneous infusion

GLP-1

- May be implicated in the pathogenesis of obesity with replacement restoring satiety
- May play an important role diabetes treatment

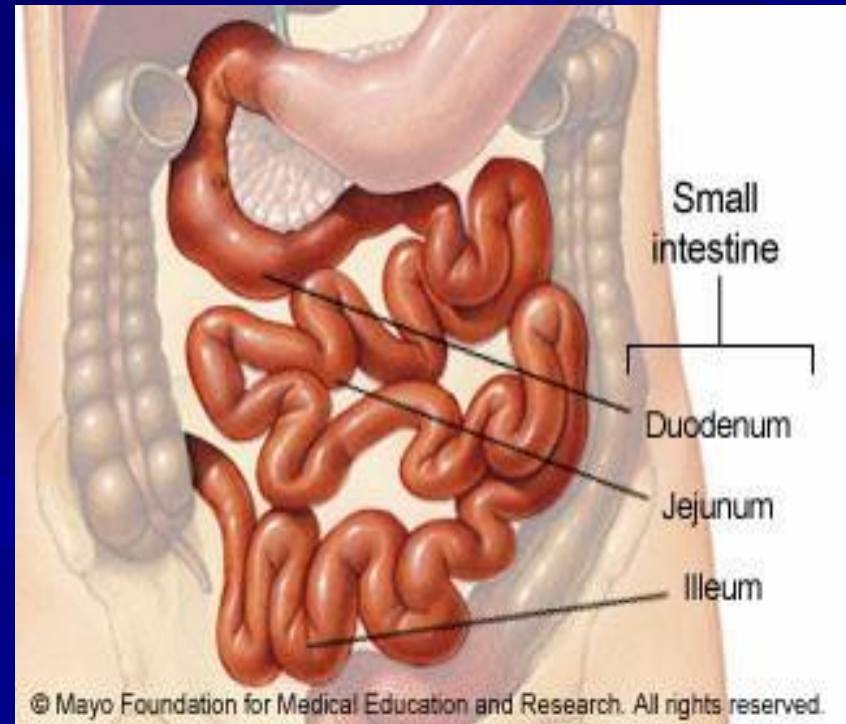


Cholecystokinin (CCK)



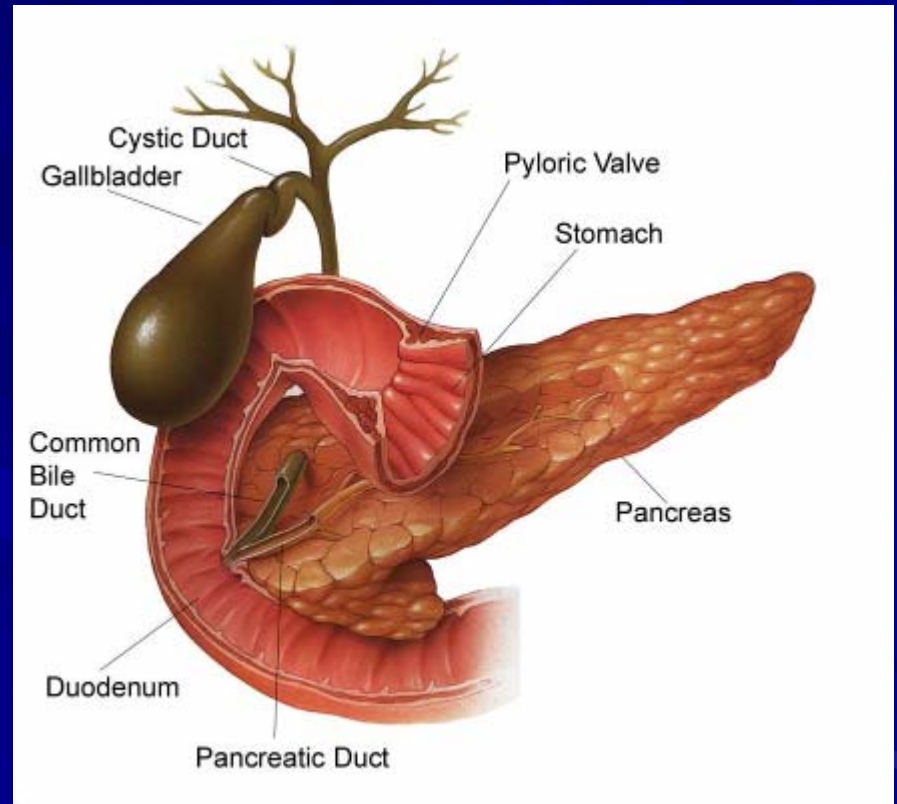
CCK

- Found predominantly in duodenum and jejunum
- Released immediately and remains elevated for 5 hours
- Involved in reward behavior, memory and anxiety, as well as satiety



CCK

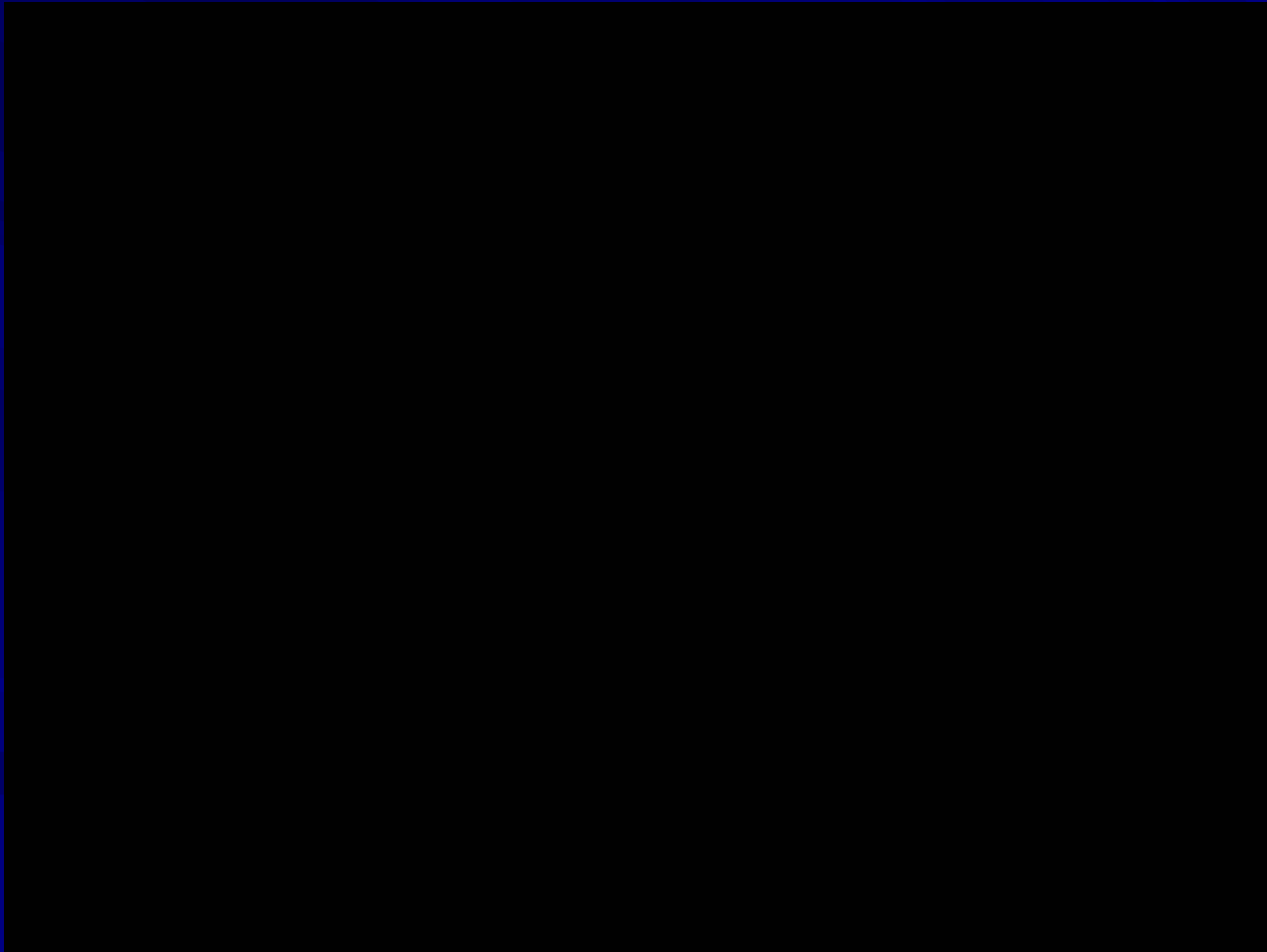
- Stimulates the release of enzymes from the pancreas and gallbladder
- Increase motility and inhibiting gastric emptying



What happens when CCK given?

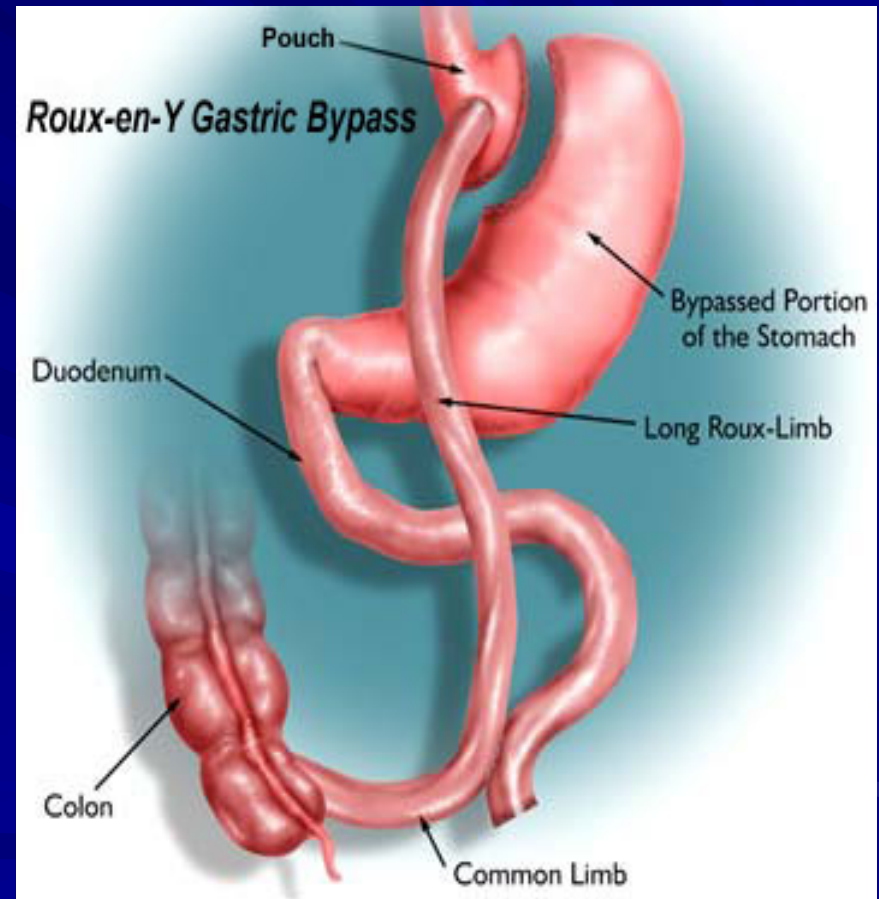
- Inhibit food intake by reducing meal size and duration
- At high dose, nausea and taste aversion
- Very short term modulator of appetite
- NOTE: while **repeated** preprandial administration of CCK **reduces** food intake, it **increases meal frequency**

Gut peptides and Gastric bypass

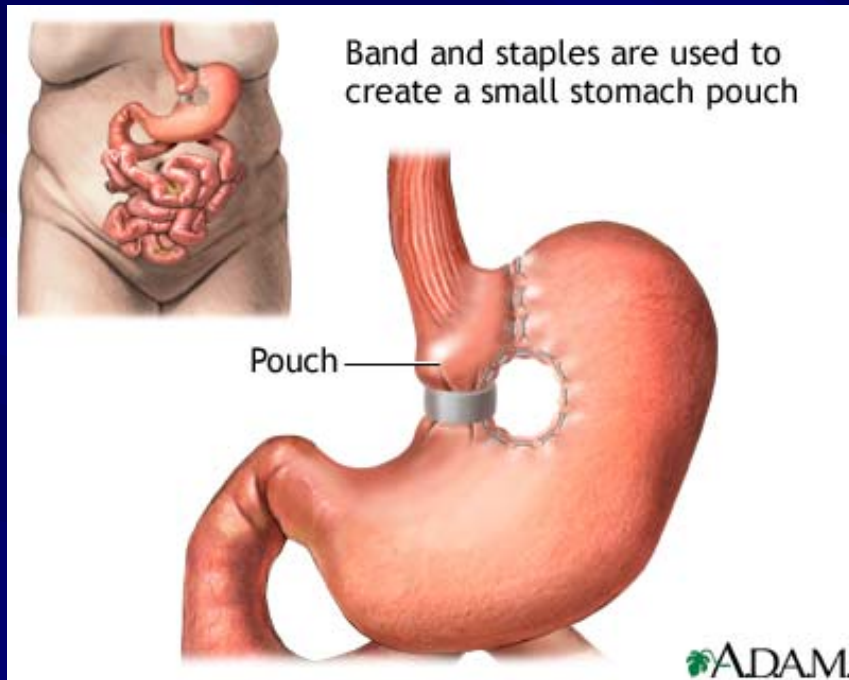


Roux-en-Y Gastric Bypass

- Patients typically lose 35-40% of total body weight and most of this effect is maintained for 15 years



Vertical banded gastroplasty

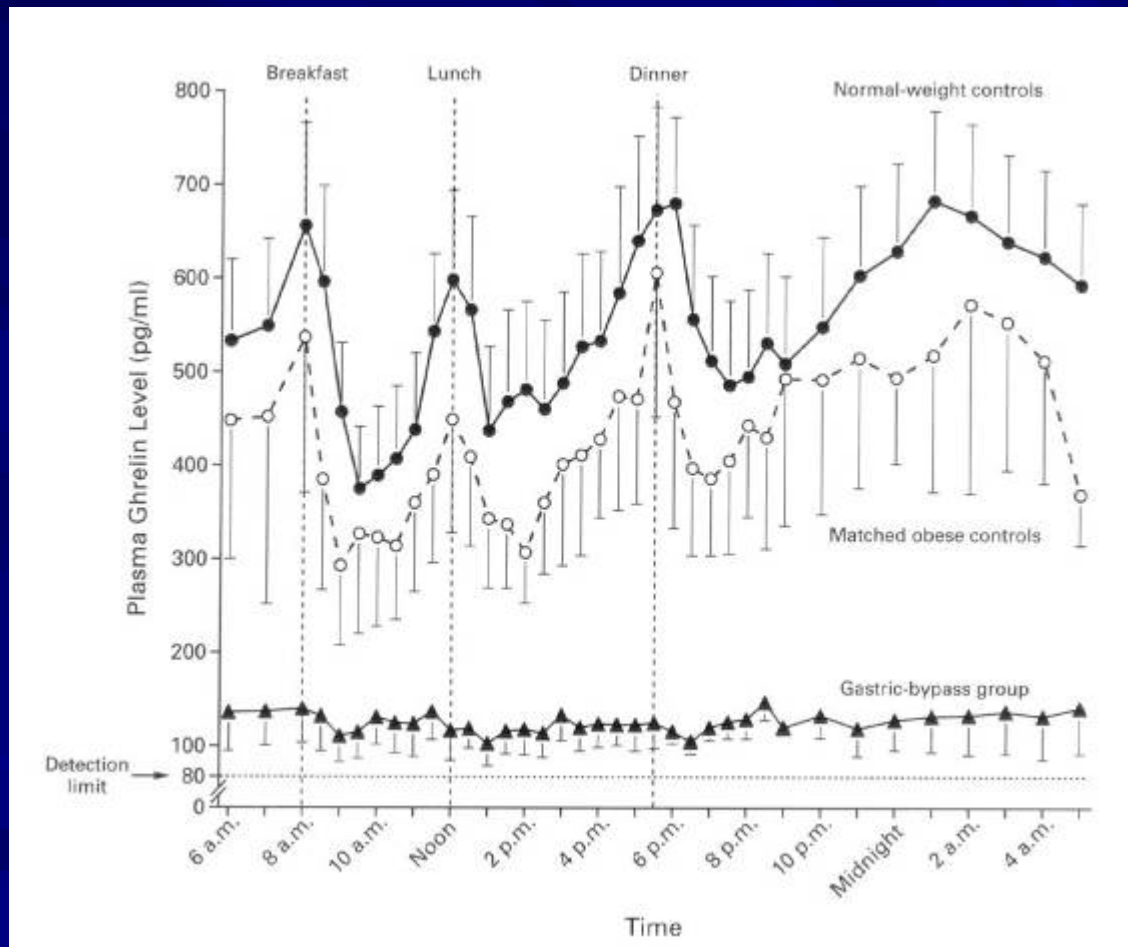


- Causes 30-50% reduction in excess body weight within the first 1-2 years
- Long term results disappointing
- Patient start to accommodate by eating frequent, small meals, and calorie dense foods

Why might RYGB be better than VBG?

- Patients who underwent RYGB typically eat fewer meals and snacks
- Perhaps, even if the degree of gastric restriction is the same, the physiologically changes that occur with RYGB may be the key to its success

After RYGB, ghrelin values were 77% lower



Ghrelin in RYGB

- Most studies have demonstrated that levels decrease
- Why? “override inhibition” because the stomach (fundus) no longer exposed to enteral nutrients the ghrelin producing cells are inhibited
- Note if the partition slightly includes the fundus, this might undermine this inhibition

Antidiabetic effects of gastric bypass

- In five published studies, a total of 3568 people undergoing RYGB, diabetic patients had complete remission of their disease at rates ranging from 82-98%



Antidiabetic effects of gastric bypass

- Starvation induced alleviation
- Decrease in ghrelin (ghrelin has diabetogenic effects)
- Larger postprandial bolus of nutrients into the hindgut after RYGB may lead to increase in GLP-1
- PYY levels increase after other surgeries that expedite nutrient delivery to the hindgut

Future in Obesity treatment

Target	Delivery	Trial
NPY antagonist	Intranasal (Pfizer)	Clinical trial
Hypothalamus (Rimonabant)	<i>PO Acomplia</i> (Sanofi-Aventis)	Phase III
PYY	Intranasal (Merck)	Phase I
GLP-1	IV (Amylin)	Phase III
CCK	Oral	Phase II

Summary

- The brain integrates peripheral signals from the gut via peptides to regulate energy homeostasis
- Ghrelin is an important gut peptide signalling hunger
- PYY, PP, OXM, CCK, and GLP-1 are thought to contribute more to satiety
- Understanding the contributions of the gut peptides may lead to better understanding of weight loss and weight maintenance
- These peptides may lead to further therapeutic options for obesity and a better understanding for the mechanisms of weight loss in gastric bypass