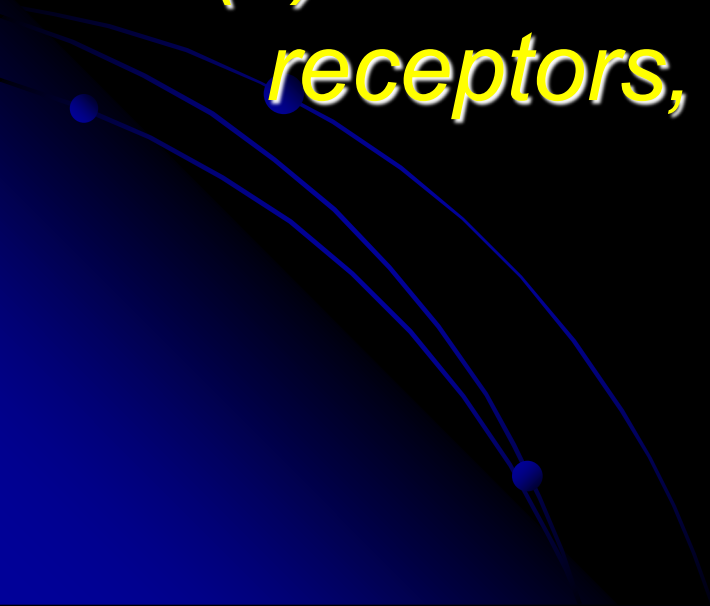


Neuroendocrinology & the Gastrointestinal System

(1) Hormones, chemical messages, receptors, food intake & exercise



Aims

- To review the basic principles by which cells communicate with each other via the endocrine and nervous systems.

Learning objective:

After this lecture you should recognise that:

- Hormones and hormone-like substances relay chemical signals around the body.
- Glands often exist along an axis
- Hormones and hormone-like substances communicate with cells in several different ways e.g. hemocrine, paracrine or autocrine manner.
- Food intake is affected by many different factors, including biological signals

Neuroendocrinology

- All physiological systems are controlled by the combined effects of the nervous and endocrine systems.
 - Endocrinology – concerned with glands and hormones.
 - Neurophysiology – concerned with the nervous system and the effects of the nervous system
 - Neuroendocrinology – the combined effects of these systems – *the neuroendocrine system*

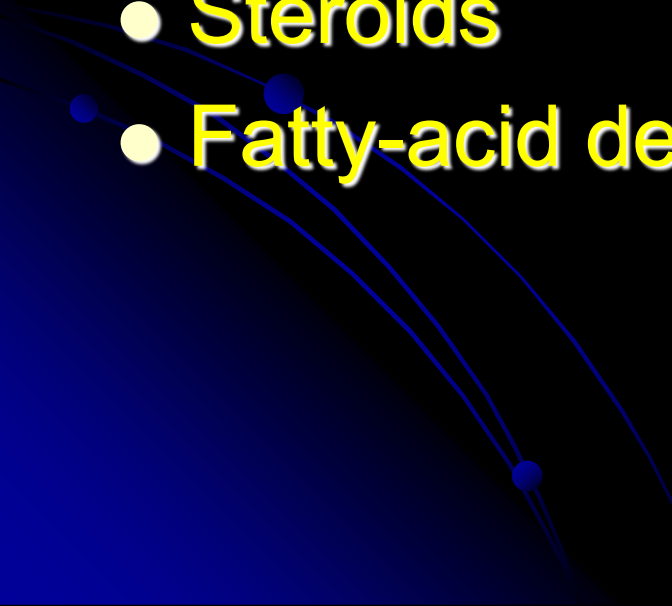
Hormones

- From the Greek *hormaein* – to arouse or excite.
- **Basically and classically!** – hormones are substances secreted into the extracellular fluid, blood and lymph from glands or specialised cells that interact with specific receptors to produce a particular biological effect (endocrine).
- **Glands** can also be exocrine – they secrete their hormone through their cell surface e.g. sweat, sebaceous and salivary glands
- ‘Recent’ discoveries are changing the way people think about this definition of hormones.
 - **What are the functions of adipose tissue, skeletal muscle, the heart for example?**

Hormone function

- Hormones participate in all physiologic functions:
 - Muscular activity
 - Cellular Respiration
 - Digestion, metabolism and food intake
 - Sense organ function, thought, mood, and behaviour
 - Thermoregulation
 - etc
- The overall purpose of the coordinating, regulating, integrating, stimulating, suppressing, and modulating effects of the many components of the endocrine system is **homeostasis**. “The tendency towards a relatively stable equilibrium between interdependent elements, especially as maintained by physiological processes”.

Chemical classification of hormones

- Peptides and proteins
 - Amines
 - Steroids
 - Fatty-acid derivatives
- 

Chemical classification of hormones

- **Peptides and proteins (e.g. insulin)**
 - Major form of hormone
 - Amino acid sequences of varying lengths
 - Hypothalamic, pituitary, pineal, pancreatic, parathyroid, gastrointestinal, kidney, liver, thyroid C cells, heart and thymus gland secretions
 - Preprohormones → prohormones → active hormone (e.g. preproinsulin → proinsulin → insulin)

● Amines

- Derived from the amino acid tyrosine
- Hormones secreted by thyroid and adrenal medulla
- e.g. catecholamines (adrenaline and noradrenaline and thyroid hormones (T3 and T4)

● Steroids

- Derived from cholesterol
- Secreted by adrenal cortex and gonads
- e.g. sex hormones, corticosteroids, mineralocorticoids

● Fatty-acid derivatives

- Derived from fatty acids
- e.g. prostaglandins, thromboxanes, leukotrienes

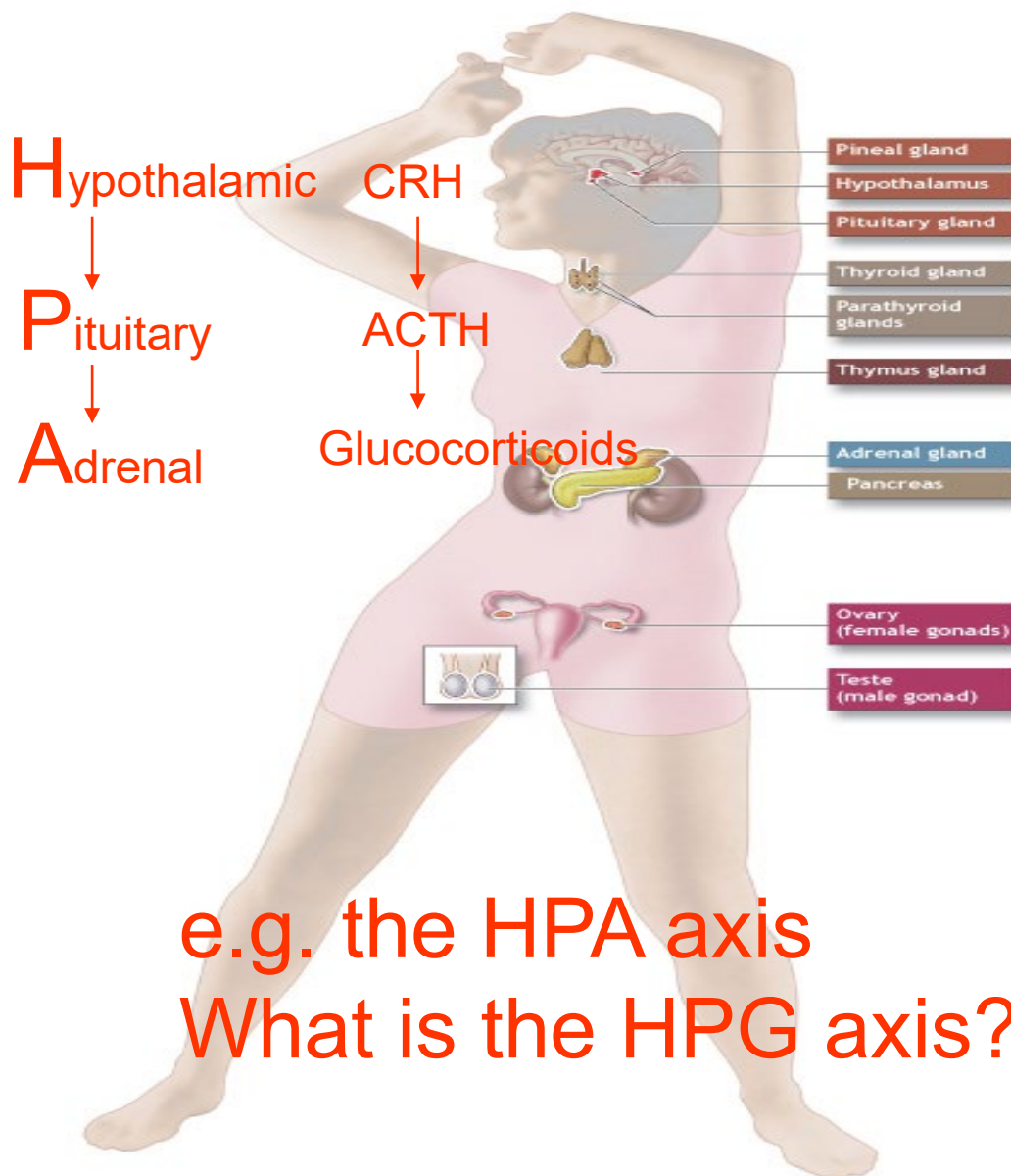


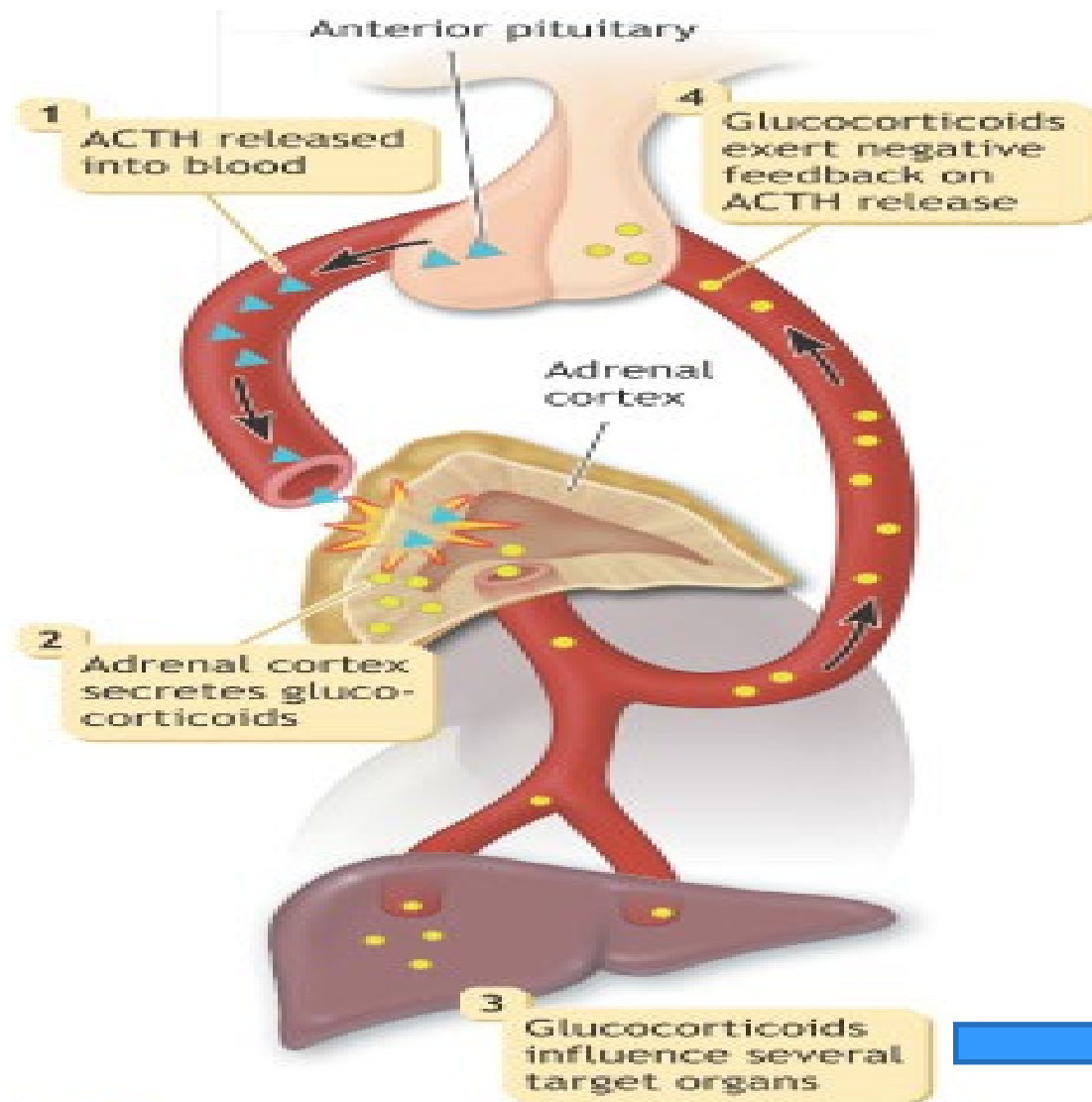
Figure 20.1. Location of the hormone-producing endocrine organs.

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Anatomical location of major glands – these often exist along an axis

Other major 'hormone' secreting organs include adipose tissue, liver, kidney, skin, heart and skeletal muscle, stomach

Feedback loops +ve and -ve



Hormonal
stimulation
of
hormone
secretion

e.g. Cortisol

A Hormonal

Figure 20.4A. Endocrine gland stimulation. **A.** Hormonal. Adrenocorticotropic hormone (ACTH) stimulates release of glucocorticoid hormones by the adrenal cortex.

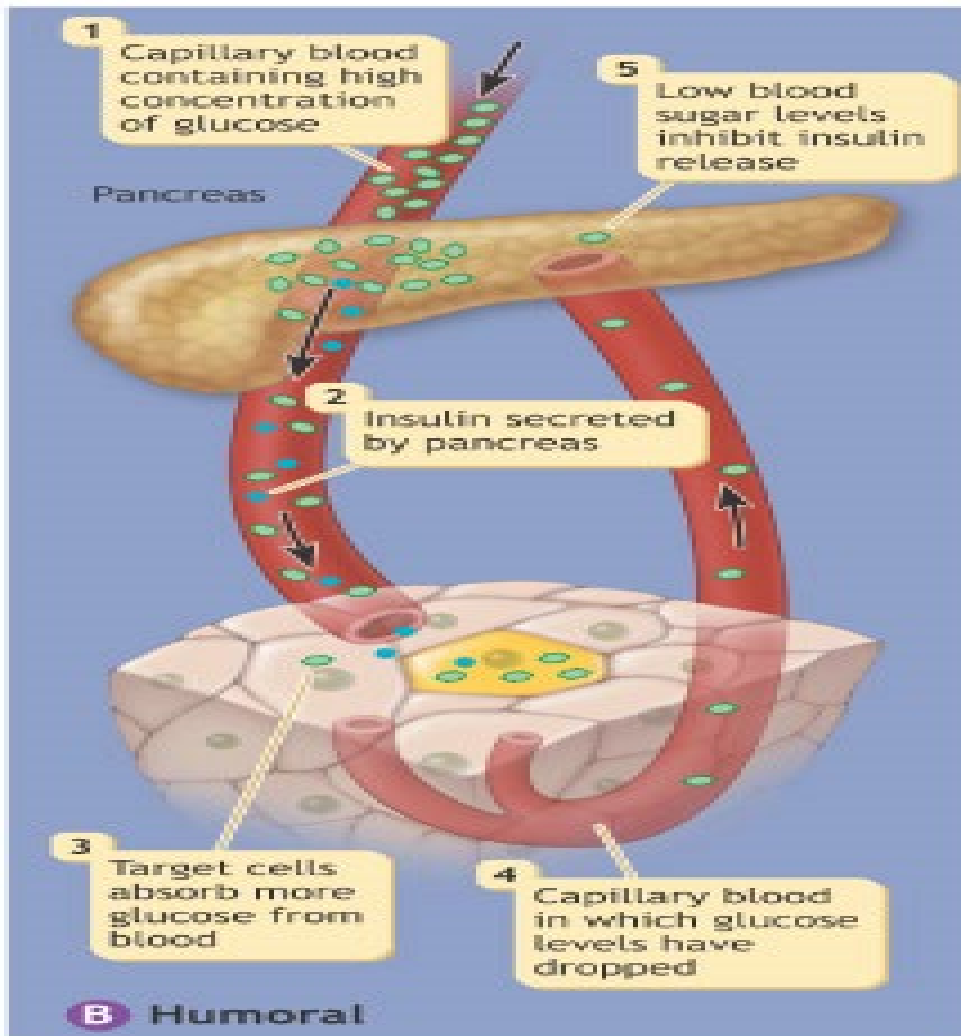


Figure 20.4B. Endocrine gland stimulation. **B.** Humoral. High blood glucose concentrations trigger insulin release, causing rapid cellular glucose uptake. The subsequent decrease in blood glucose removes the stimulus for insulin release.

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Humoral
stimulation
of hormone
secretion

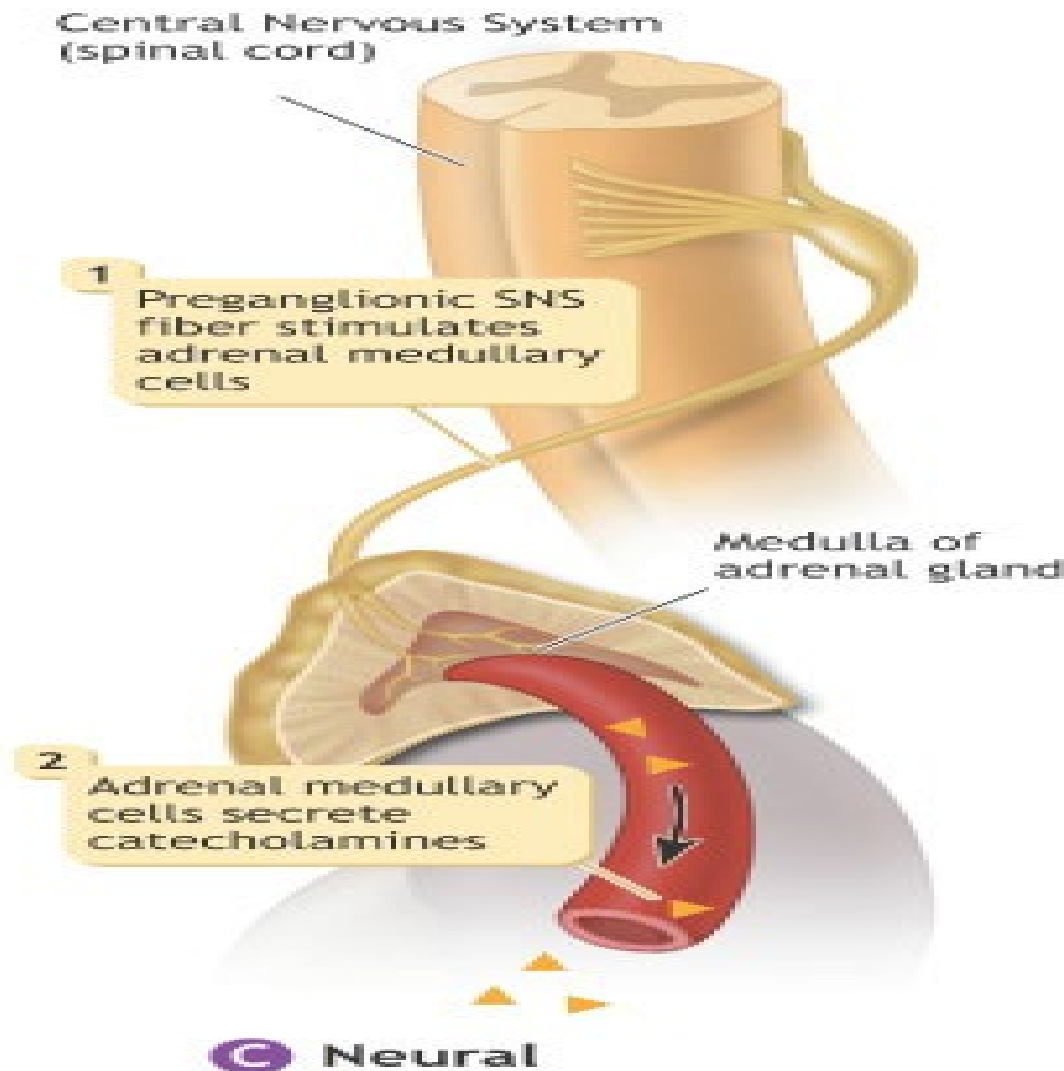


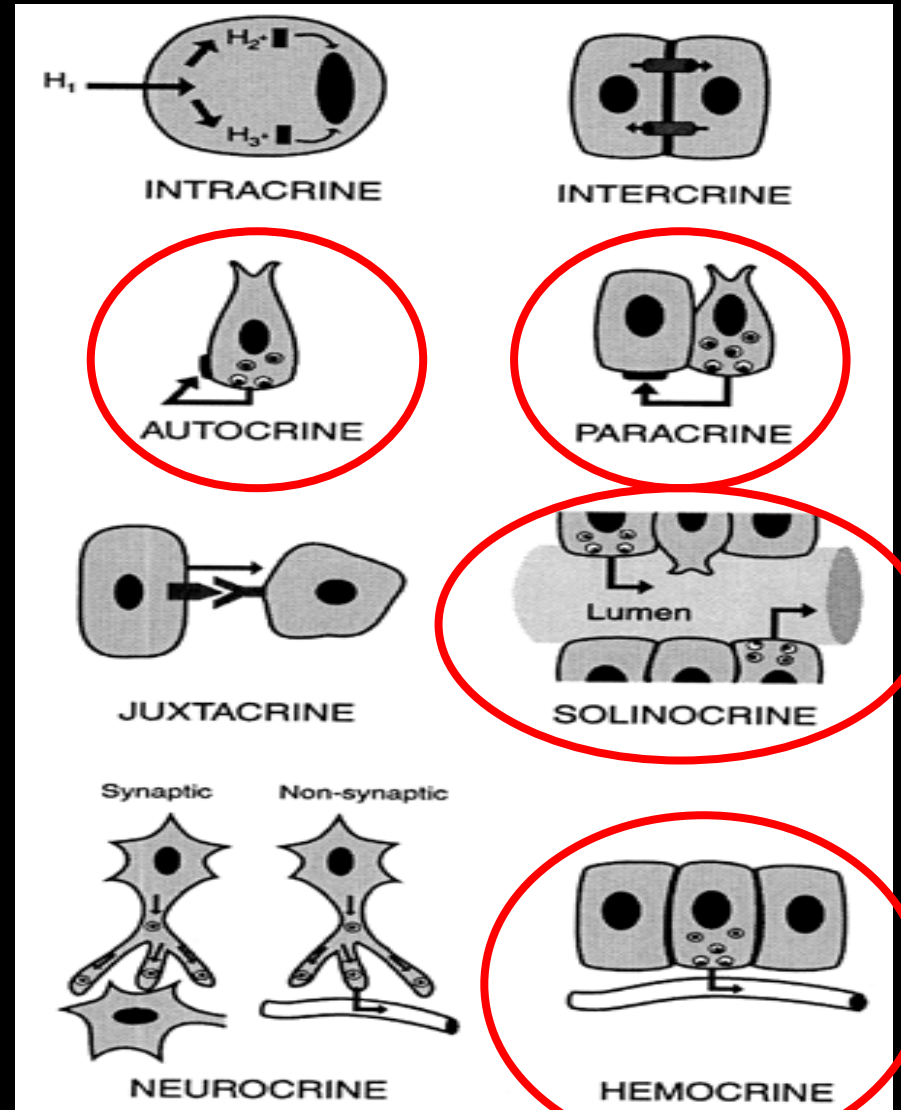
Figure 20.4C. Endocrine gland stimulation. C. Neural. Sympathetic nervous system (SNS) fibers trigger catecholamine release to blood. (From Marieb E. Anatomy and physiology. Redwood City, CA: The Benjamin/Cummings Company, 1989.)

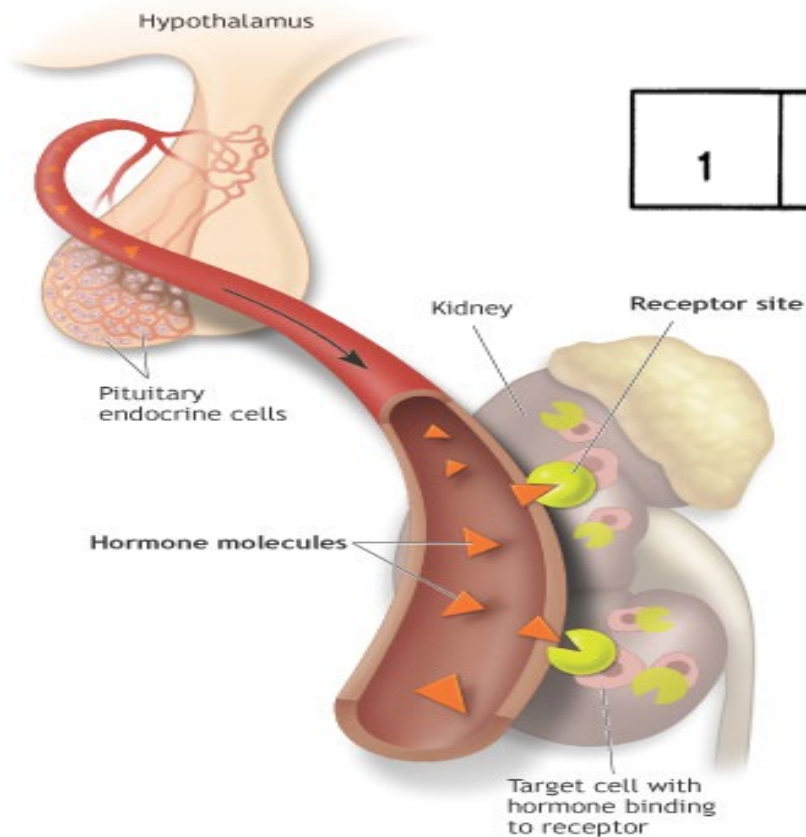
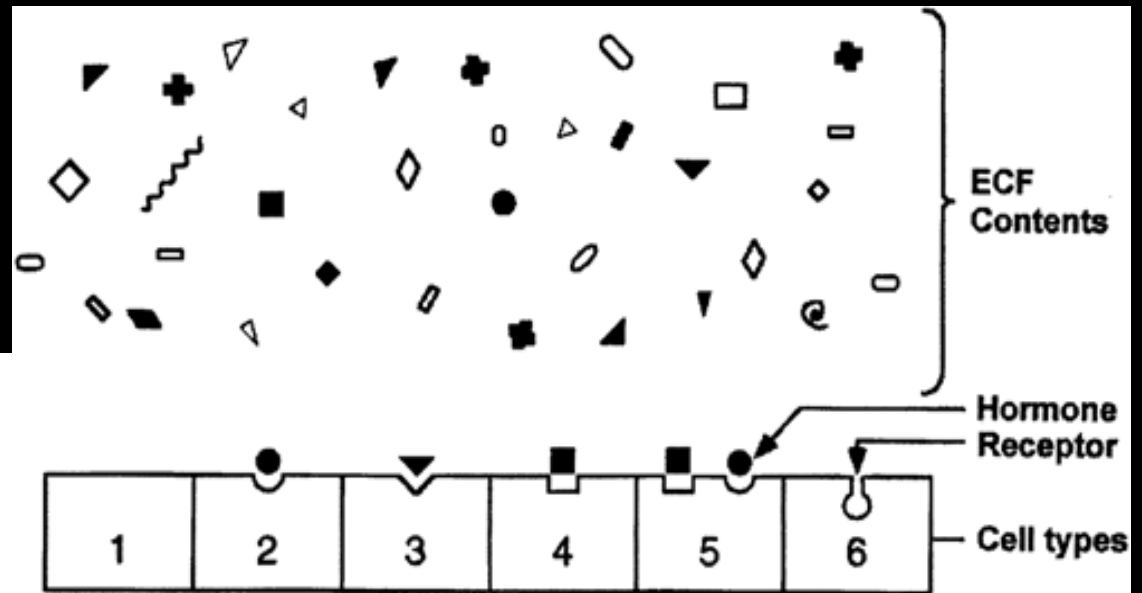
Neural
stimulation
of
hormone
secretion

Cell-to-cell communication

- Not all hormones and hormone-like substances are transported in the blood.

- Autocrine** – cell produces hormone that has effect on itself
- Paracrine** – cell produces hormone that has effect on neighbouring cells
- Solinocrine** – into a 'hollow tube' i.e. gut hormones
- Hemocrine (endocrine)** hormone enters blood





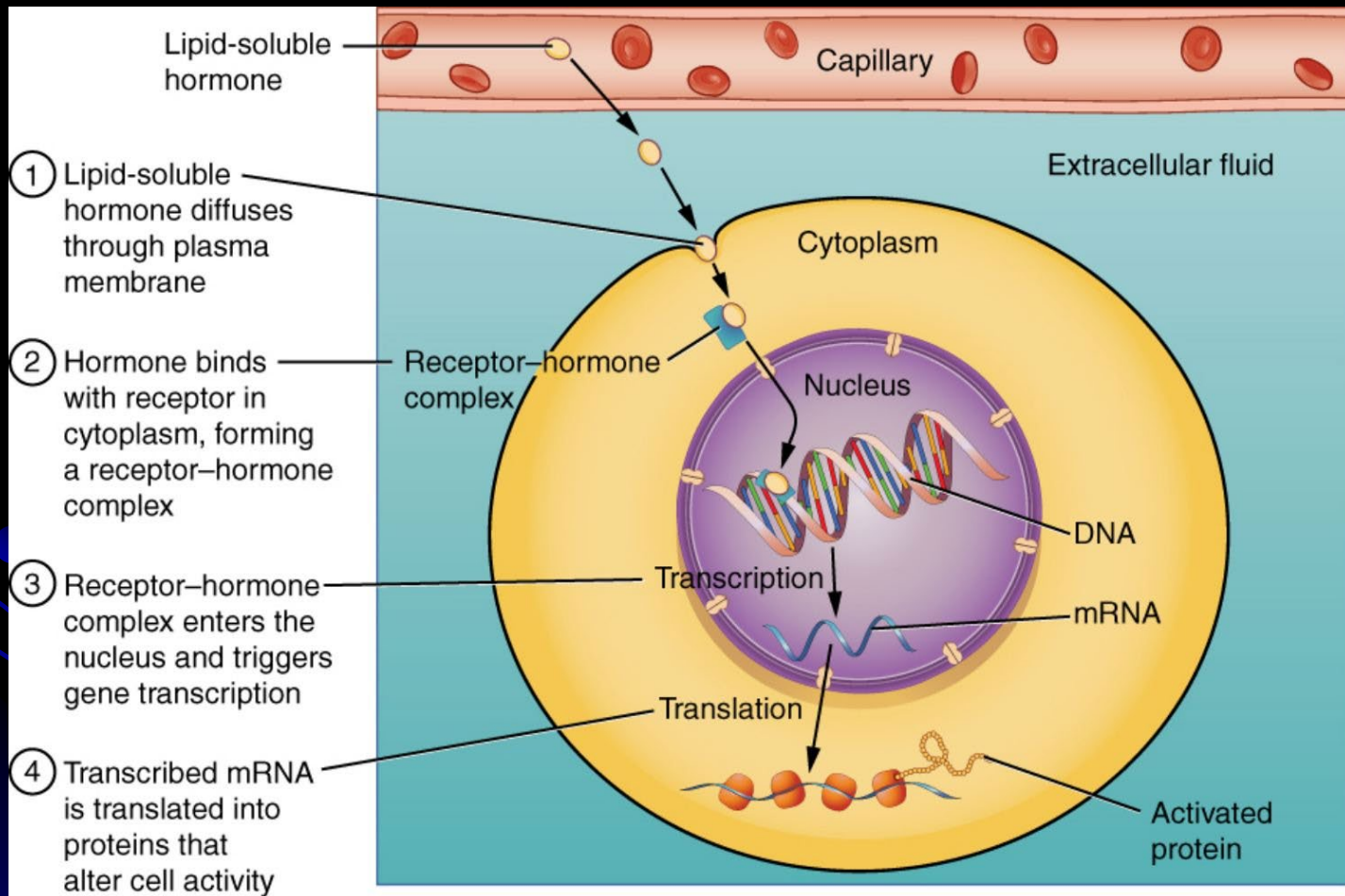
Receptor mechanisms.
Some receptors are on the cell surface, others are in the cytoplasm or in the nucleus of the cell – nuclear receptors

Figure 20.2. Hormones secreted from endocrine glands travel in the bloodstream to exert their influence on various tissues throughout the body.

Hormonal communication

- Hormones influence the biological activity of their target cells through three mechanisms:
 1. Changing the cell's permeability by opening or closing channels in the membrane (e.g. insulin and glucose transport across the cell membrane)
 2. Activation of a second-messenger system that alters the activity of pre-existing proteins (enzymes) that produce the effect (peptide hormones and catecholamines) [e.g. the breakdown of muscle glycogen or glycogenolysis, the breakdown of fat in fat cells or lipolysis]
- Direct effect on specific genes to make new proteins that produce the effect (thyroid hormones and steroids)

3. Direct effect on specific genes to make new proteins that produce the effect (thyroid hormones and steroids) [e.g. muscle protein synthesis]



Some major 'hormones' involved in metabolism – where do they come from?

- Growth hormone
- Thyroid hormones – TSH, T3 and T4
- Insulin, glucagon and somatostatin
- Cortisol
- Adrenaline and noradrenaline
- Gastrin, secretin, GLP, cholecystokinin, ghrelin, PYY3-36
- Leptin, adiponectin, resistin, interleukin-6 (IL-6)

Mouth

Breaks up food particles
Assists in producing
spoken language

Salivary glands

Saliva moistens and
lubricates food
Amylase digests
polysaccharides

Pharynx

Swallows

Esophagus

Transports food

Liver

Breaks down and builds up
many biological molecules
Stores vitamins and iron
Destroys old blood cells
Destroys poisons
Bile aids in digestion

Stomach

Stores and churns food
Pepsin digest protein
HCl activates enzymes, breaks
up food, kills germs
Mucus protects stomach wall
Limited absorption

Gallbladder

Stores and concentrates bile

Pancreas

Hormones regulate blood glucose levels
Bicarbonates neutralize stomach acid
Trypsin and chymotrypsin digest proteins
Amylase digests polysaccharides
Lipase digests lipids

Small intestine

Completes digestion
Mucus protects gut wall
Absorbs nutrients, most water
Peptidase digests proteins
Sucrases digest sugars
Amylase digests polysaccharides

Large intestine

Reabsorbs some water
and ions
Forms and stores feces

Anus

Opening for elimination
of feces

Rectum

Stores and expels feces

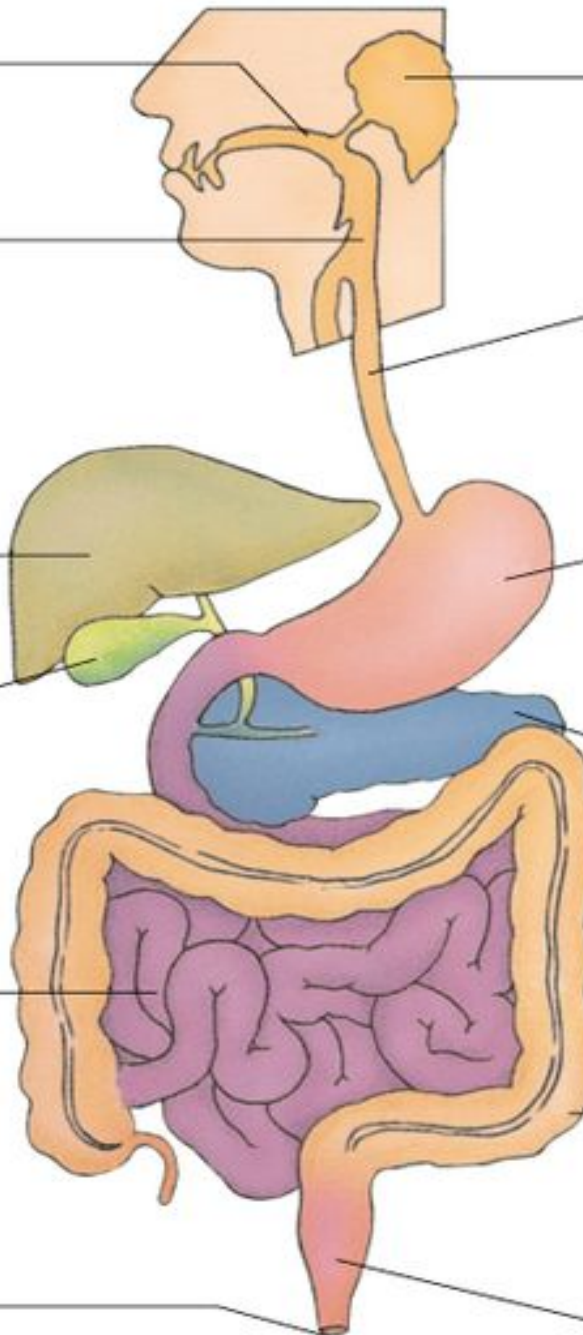
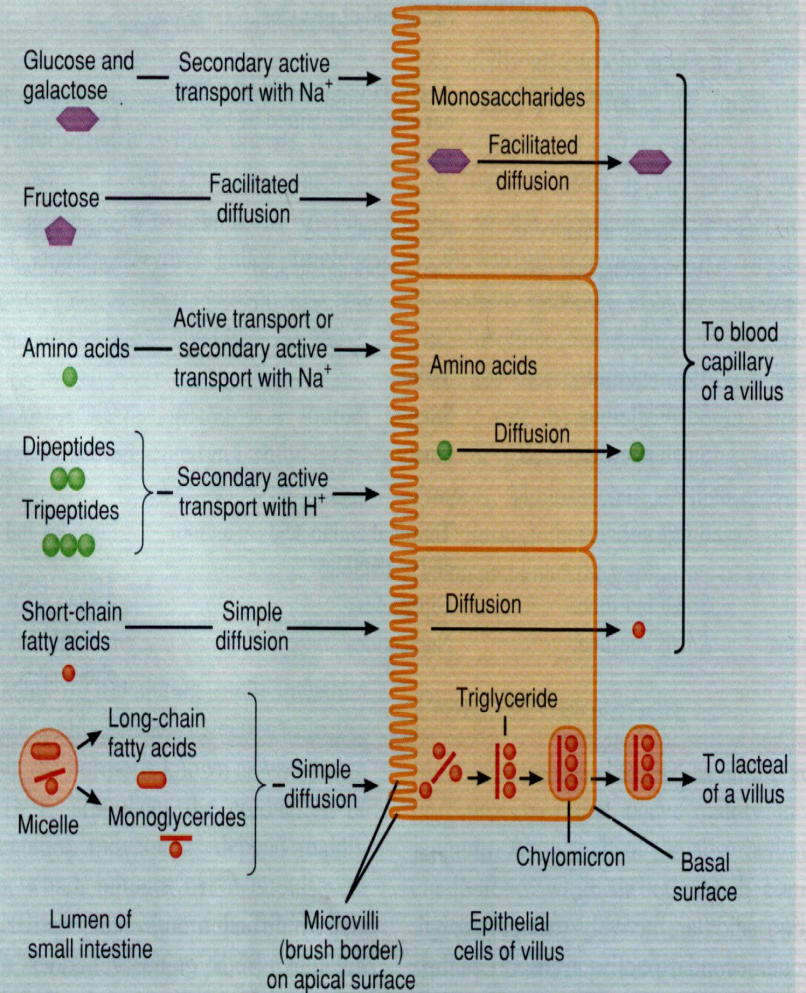


FIGURE 24.25 Absorption of digested nutrients in the small intestine. For simplicity, digested foods are shown in the lumen of the small intestine, even though some nutrients are digested by brush border enzymes.

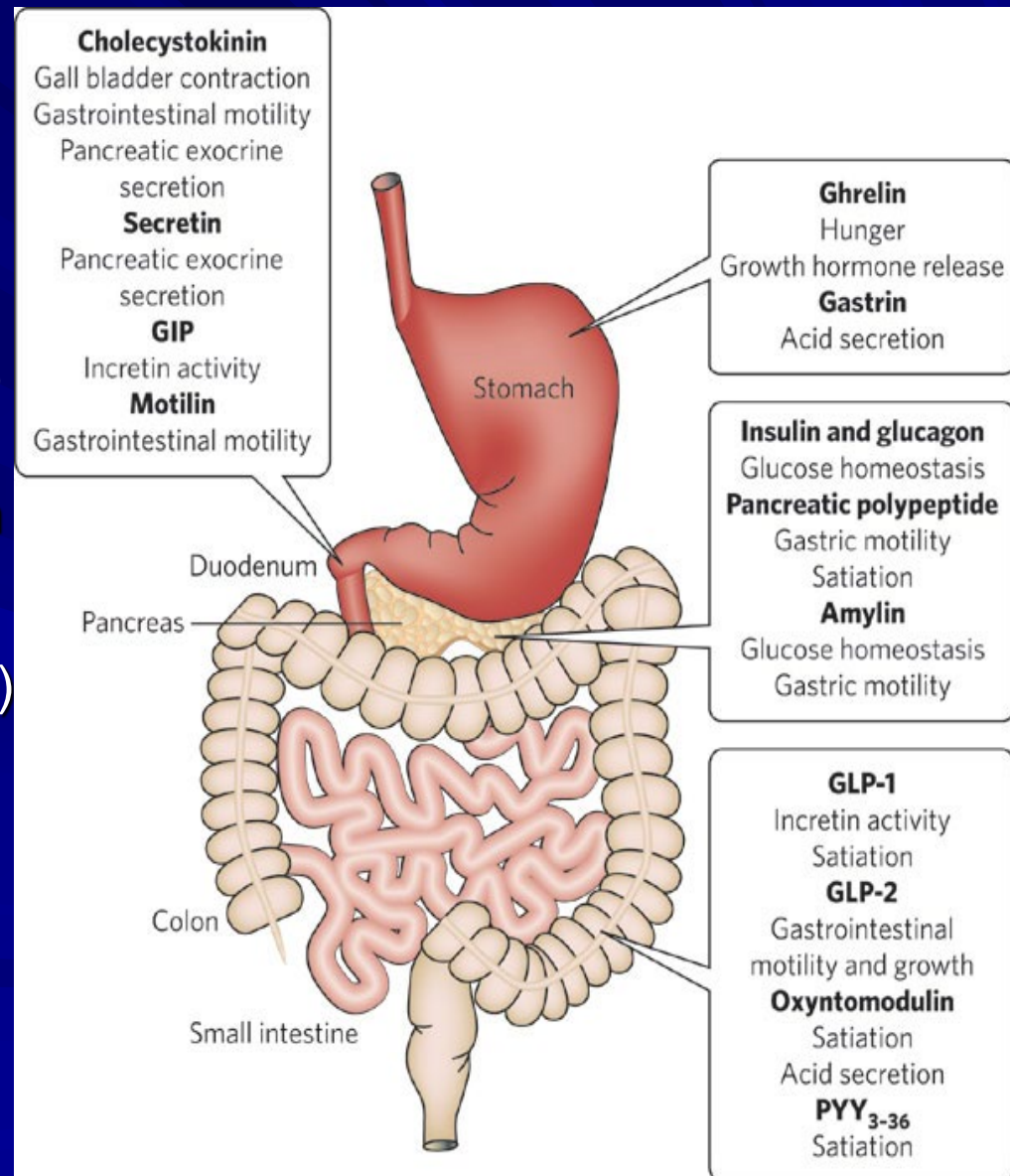


(a) Mechanisms for movement of nutrients through epithelial cells of the villi



Short term control of food intake

- Biological signals that arise in the gastrointestinal tract
 - **Inhibitors (anorexigenic or satiety signals)** such as:
 - cholecystokinin, Glucagon Like Peptide-1 (GLP-1), pancreatic polypeptide (PP) and protein YY (PYY)
 - **Stimulators (orexigenic signals)** such as:
 - ghrelin



Protein YY

- Synthesised and released from enteroendocrine cells (L cells).
- Two forms: PYY1-36 and PYY3-36.
- PYY3-36 is the main circulating and active form.
- Circulating PYY rises in response to nutrient ingestion, caloric load, food consistency and nutrient composition.
- Rise in concentration is seen about 15 min after nutrient ingestion.
- PYY peaks between 1-2 hours after ingestion and then plateaus.

Anorectic Effect of PYY3-36 on Food Intake in Rats

Gut hormone PYY₃₋₃₆ physiologically inhibits food intake

Rachel L. Batterham^{*†}, Michael A. Cowley^{†‡§}, Caroline J. Small^{*}, Herbert Herzog^{||}, Mark A. Cohen^{*}, Catherine L. Dakin^{*}, Alison M. Wren^{*}, Audrey E. Brynes^{*}, Malcolm J. Low[§], Mohammad A. Ghatei^{*}, Roger D. Cone[§] & Stephen R. Bloom^{*}

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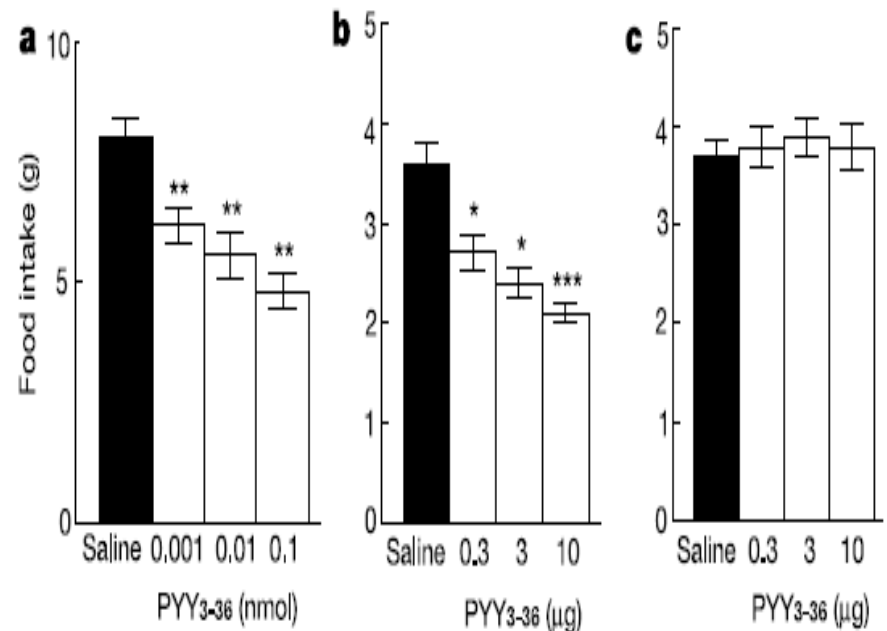
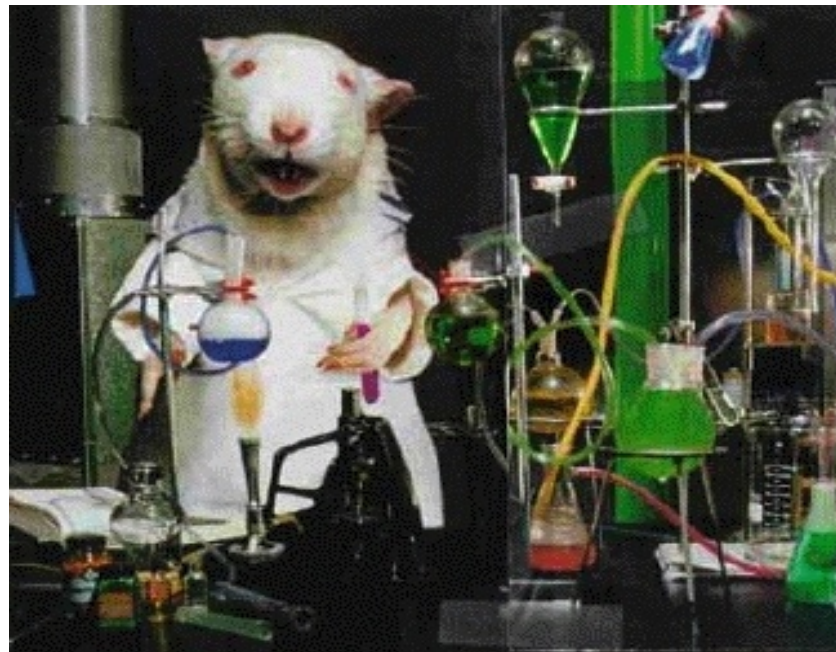


Figure 2 Feeding effects of intra-arcuate injection of PYY₃₋₃₆ in rats and of i.p. PYY₃₋₃₆ in Y2r-null mice. **a**, Food intake after intra-arcuate injection of PYY₃₋₃₆. Fasted rats were injected with saline or PYY₃₋₃₆ into the arcuate nucleus at the doses indicated, and 2-h cumulative food intake was measured; double asterisk, $P < 0.01$ versus saline.

b, c, Feeding response to PYY₃₋₃₆ in Y2r-null mice after i.p. administration. Wild-type littermates (**b**) and Y2r-null mice (**c**), fasted for 24 h, were injected with PYY₃₋₃₆ at the doses indicated (µg per 100 g) or saline, and 4-h cumulative food intake was measured. Results are the mean $\pm$ s.e.m. ($n = 5$ per group); asterisk, $P < 0.05$; double asterisk, $P < 0.01$; triple asterisk, $P < 0.001$ versus saline.

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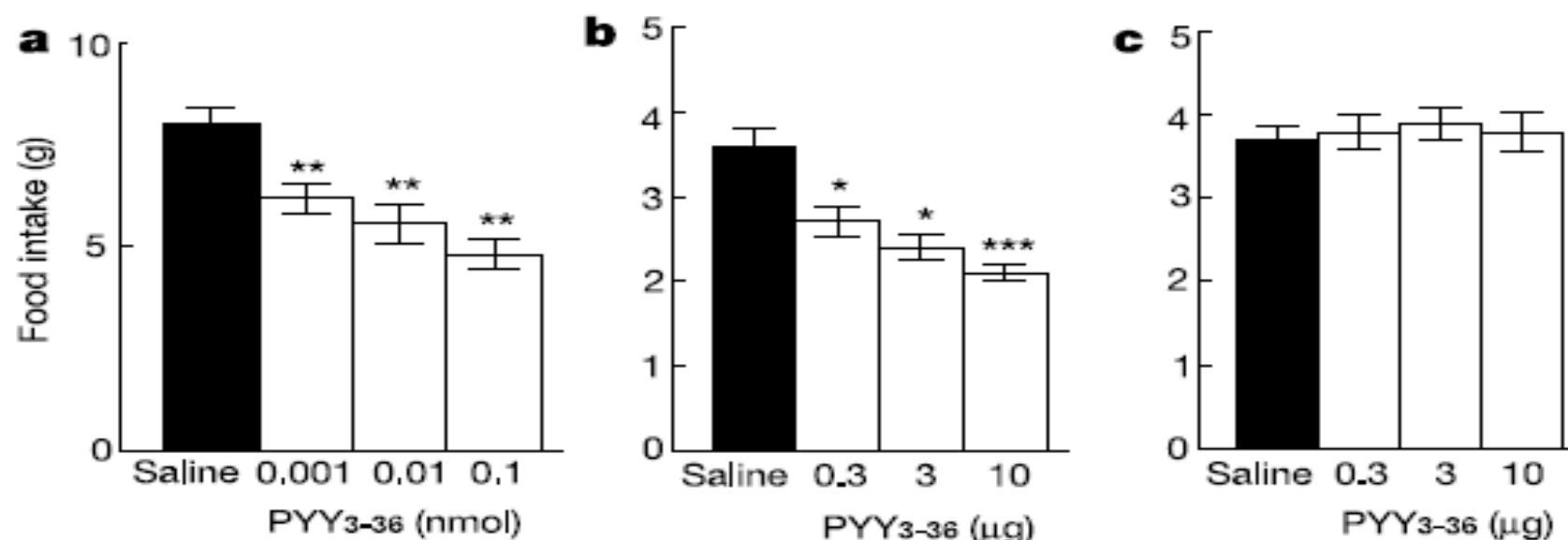


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Anorectic Effect of PYY3-36 in Humans

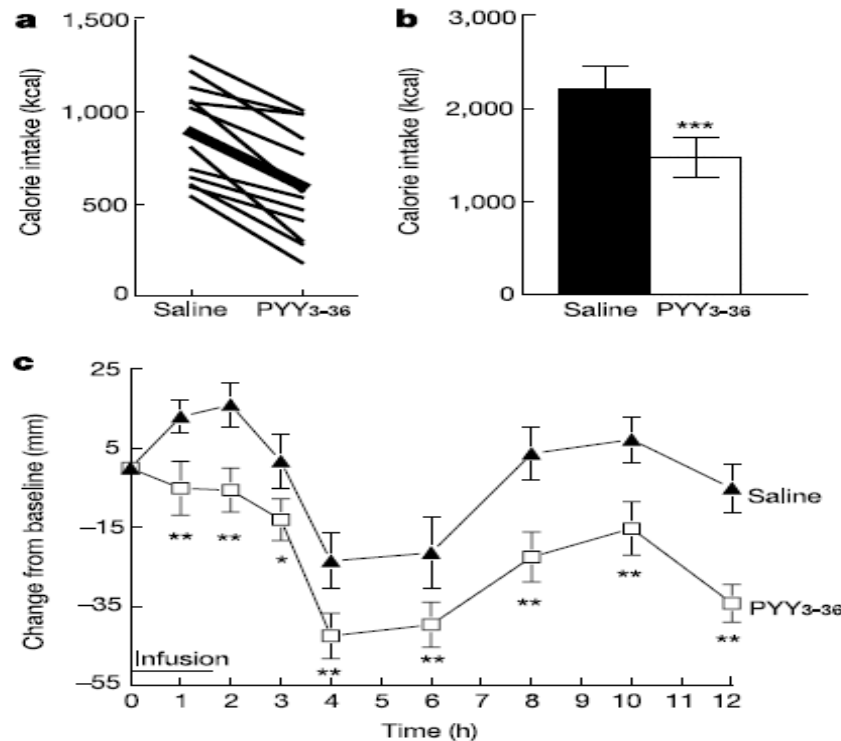


Figure 4 Effect of PYY₃₋₃₆ infusion on appetite and food intake in humans. **a**, Calorie intake from free-choice buffet meal 2 h after infusion with saline or PYY₃₋₃₆. The thin lines indicate individual changes in calorie intake for each subject between saline and PYY₃₋₃₆ administration. The thick line represents mean change between the two infusions ($n = 12$). **b**, Total calorie intake, as assessed by food diaries, for the 24-h period after either saline or PYY₃₋₃₆ infusion. Data are expressed means $\pm$ s.e.m. ($n = 12$); triple asterisk, $P < 0.0001$ versus saline. **c**, Appetite score (relative scale). Visual analogue scores¹⁶ show perceived hunger during and after infusions. The results are presented as change from baseline scores and are the mean $\pm$ s.e.m. for all 12 subjects. Asterisk, $P < 0.05$; double asterisk, $P < 0.01$ versus saline.

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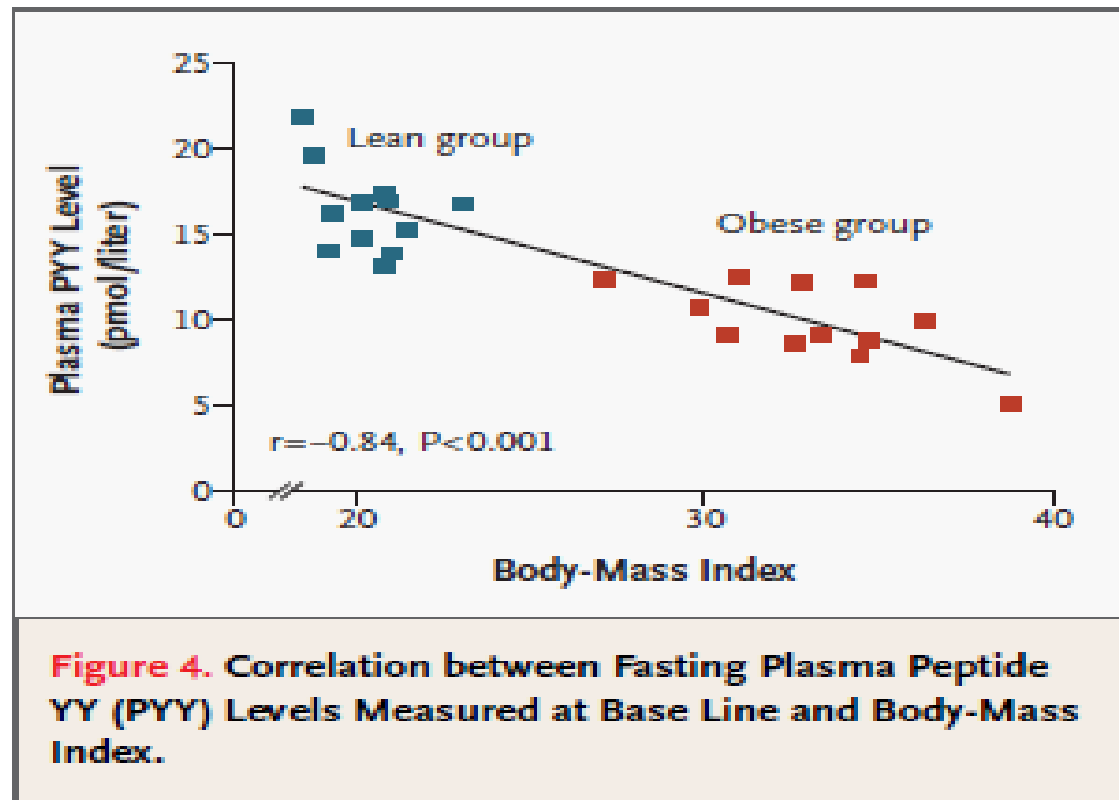
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PYY3-36 in Lean and Obese Humans

Inhibition of Food Intake in Obese Subjects by Peptide YY₃₋₃₆

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Sandra M. Ellis, B.Sc., Carel W. Le Roux, M.B., Ch.B.,
Dominic J. Withers, M.B., B.S., Ph.D., Gary S. Frost, Ph.D.,
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N Engl J Med 2003;349:941-8.

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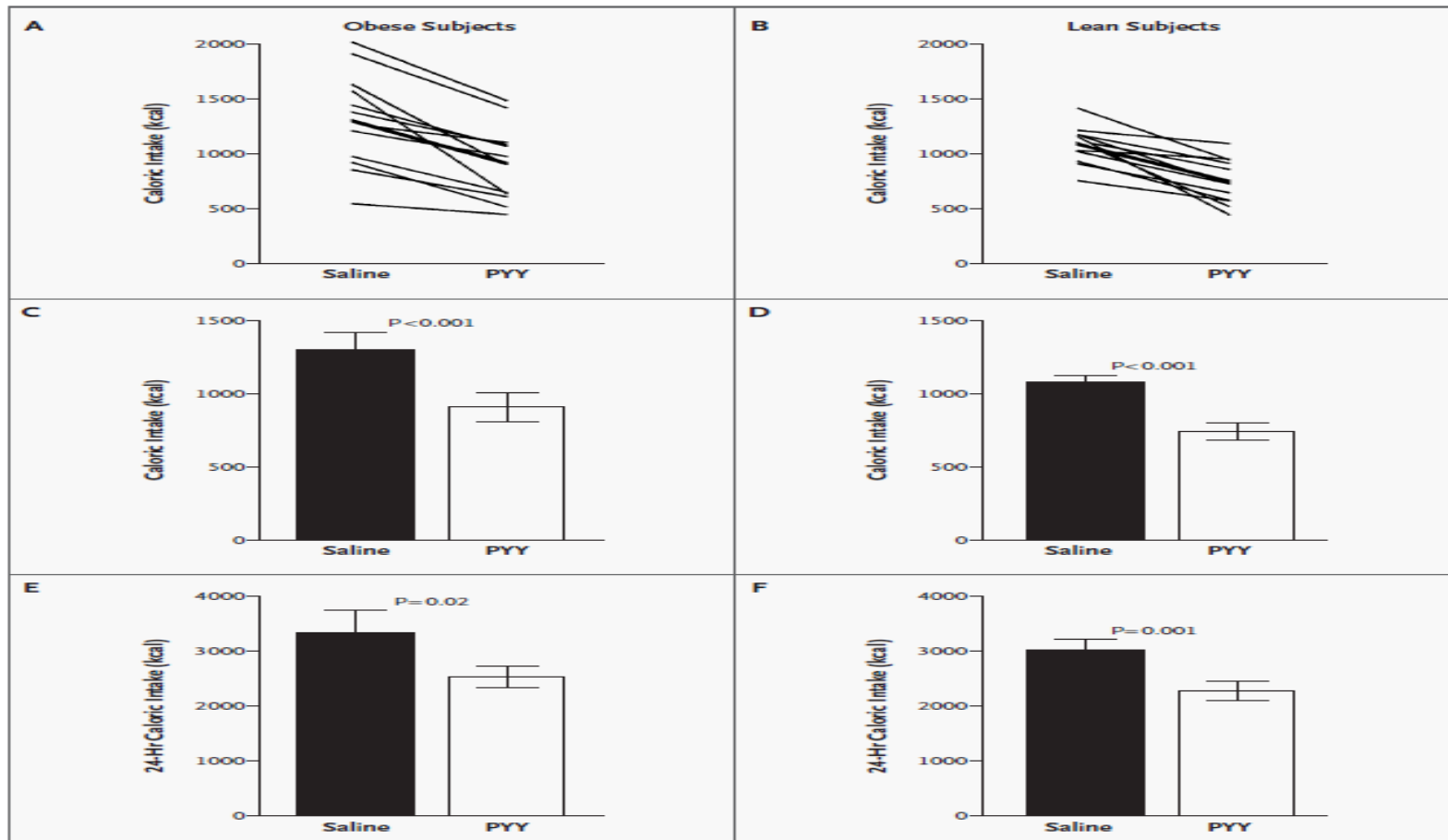


Figure 1. Caloric Intake by Obese and Lean Subjects after Infusion of Peptide YY₃₋₃₆ (PYY) or Saline.

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 ($\pm$ 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 ($\pm$ 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.

PYY3-36 and Bariatric Surgery

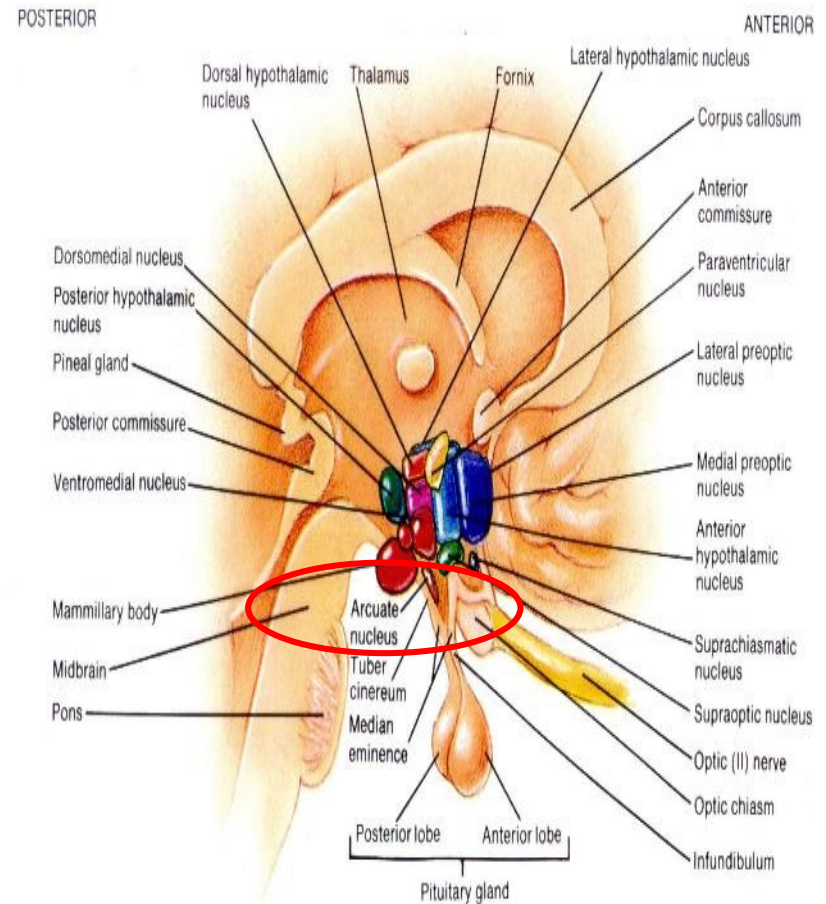
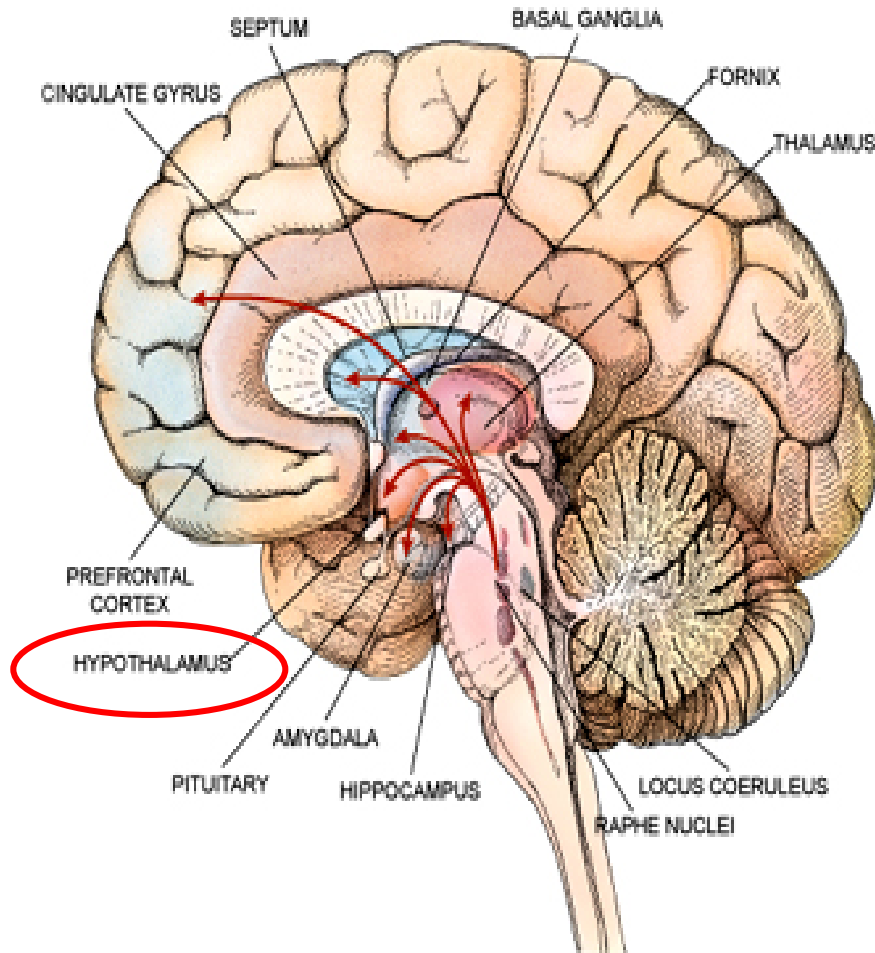
Surgery Comparison Chart

- PYY3-36 is increased following Roux—en Y gastric bypass.
- This suggests that changes in PYY3-36 may partly explain the weight loss with this type of surgery.
- Possibly also the improvement in metabolic health.
- PYY3-36 also appears to reduce motivation to seek high fat foods.

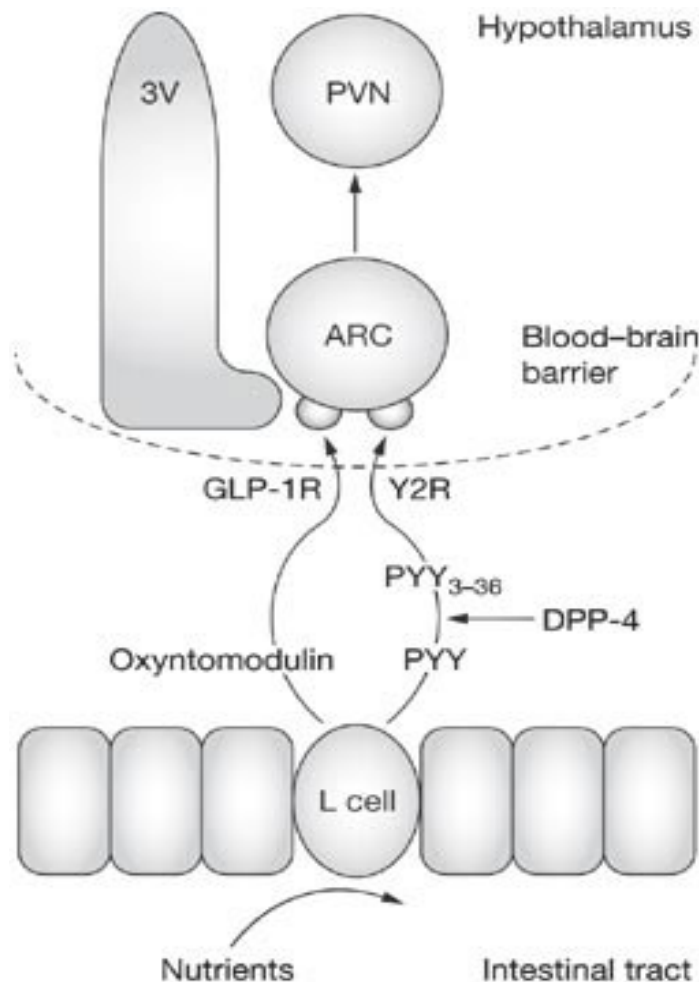


TYPE OF SURGERY	ROUX-EN-Y GASTRIC BYPASS	VERTICAL GASTRECTOMY WITH DUODENAL SWITCH (DS)	VERTICAL GASTRECTOMY (VG)	ADJUSTABLE GASTRIC BAND (LAP-BAND®)
WHAT SURGERY ENTAILS	Small pouch (about 1 ounce/20-30cc) Pouch is connected to the small intestine where food and digestive juices are separated for the first 3 to 5 feet. The RnY significantly restricts the volume of food that can be eaten.	Long vertical pouch (about 4-5 oz or 120-150cc). The duodenum (first portion of the small intestine) is attached to the last 6 feet of small intestine, where food and digestive juices are rejoined after 12 feet. Moderate restriction of volume of food that can eaten. Provides moderate malabsorption of fat, which can cause diarrhea and bloating.	Long narrow vertical pouch (about 2-3 oz or 60-100cc). Same shape as the duodenal switch pouch but smaller. No intestinal bypass. The VG significantly restricts the volume of food that can be eaten. There is no malabsorption of nutrients or dumping.	The Lap-Band is an adjustable silicone ring that is placed around the top part of the stomach creating a small (1-2 ounce or 15-30cc) pouch. The Lap-Band moderately restricts the volume and type of foods the patient is able to consume. The Band delays emptying of the pouch and creates the sensation of satiety. There is no malabsorption of nutrients.
REALISTIC EXPECTATIONS	Provides mild malabsorption of nutrients. Patients can expect to lose 70% of excess weight. Less effective (patients who lose <50% excess weight) than with the DS.	Patients can expect to lose 75% - 80% of excess weight. Some patients can lose too much weight. More risk of nutritional deviances than with the RnY.	Patients can expect to lose 60%-70% of excess weight loss at about 2 years. Long term results not available at this time. Easily converted to DS or RnY, if needed.	Patients can expect to lose 60% of their excess weight. This procedure requires the most effort of all of the procedures in order to be successful. Patient must be committed to good eating habits and exercise.
POST-SURGERY EATING AND REQUIRED SUPPLEMENTS	Patients must eat 3 small meals a day. Patients must avoid sugar and fats to prevent "Dumping Syndrome" Patients must take vitamin and protein supplements to avoid deficiency. (Multivitamin, Calcium, Vitamin B12 and Iron for -menstruating women)	Patients must eat 3 meals a day. Patients must strictly adhere to protein and vitamin supplements to avoid deficiencies. (Multivitamins, ADEK vitamins, Calcium and Iron for menstruating women)	Patient must eat 3 meals a day containing 600-800 calories per day (recommended for the first 24 months) and about 1000-1200 thereafter. There is no dumping or diarrhea.	Patients must eat 3 meals per day consisting of less than 1000 calories per day during weight loss. Patients will need to avoid certain foods that can become "stuck" such as bread, rice, nuts, dense meats that may cause pain and vomiting. Patients must not drink fluids with meals.
HOW EFFECTIVE IS THIS SURGERY?	The RnY is effective for patients with a BMI of 35-55 and those with a "sweet tooth".	The DS is effective for patients with a BMI of > 50 kg/m2. Those with BMI of <45 kg/m2 may lose too much weight. The DS has a higher incidence of complications than any of the other procedures.	The VG is effective for high risk or very high BMI patients (BMI > 60 kg/m2) patients as a "first-stage" procedure. Much lower complication rate than the RnY or DS due to there being no intestinal bypass performed.	The Lap-Band is most effective for patients that are more disciplined in following a strict diet and will commit to an exercise program

How does PYY3-36 work?



How does PYY3-36 work?



- The Y2R receptor is critical.
- Blocking the Y2R receptor or giving PYY3-36 to Y2R KO mice = no anorectic effect.
- PYY3-36 may exert its effect on feeding via the homeostatic (need) and hedonic (enjoyment and reward) brain pathways (Batterham et al., 2007).

Summary

- Food intake is influenced by a wide array of factors including a number of biological signals that arise in the gut and adipose tissue.
- These signals transmit their signal via a number of intricate pathways that involves the neuroendocrine system.
- Individual sensitivity to these pathways may partly explain the variation we see in energy balance and weight control.
- How these pathways are affected by exercise has not been studied extensively and are incompletely understood...more later.