CHAPTER 2: CAUSES OF OBESITY

Part 3: Appetite Control

References:

1. Peter G. Kopelman, Ian D. Caterson, William H. Dietz - Clinical Obesity in Adults and Children 4e-Wiley-Blackwell (2022): Main reference
2. Understanding Nutrition 13e. Whitney, Rolfes.
3. The Impact of Gastrointestinal Hormones on Human Adipose Tissue Function (2024) by Marcelina Radziszewska,Lucyna Ostrowska, and Joanna Smarkusz-Zarzecka

Definitions

- **Appetite**

The psychological desire for foods or beverages.

- **Hunger**

A range of feelings (irritating) that signal the need to eat.

- **Satiation**

Processes involved in the termination of a meal due to feeling of satisfaction and fullness

- **Satiety**

The inhibition of further intake of food and meal after eating has ended.

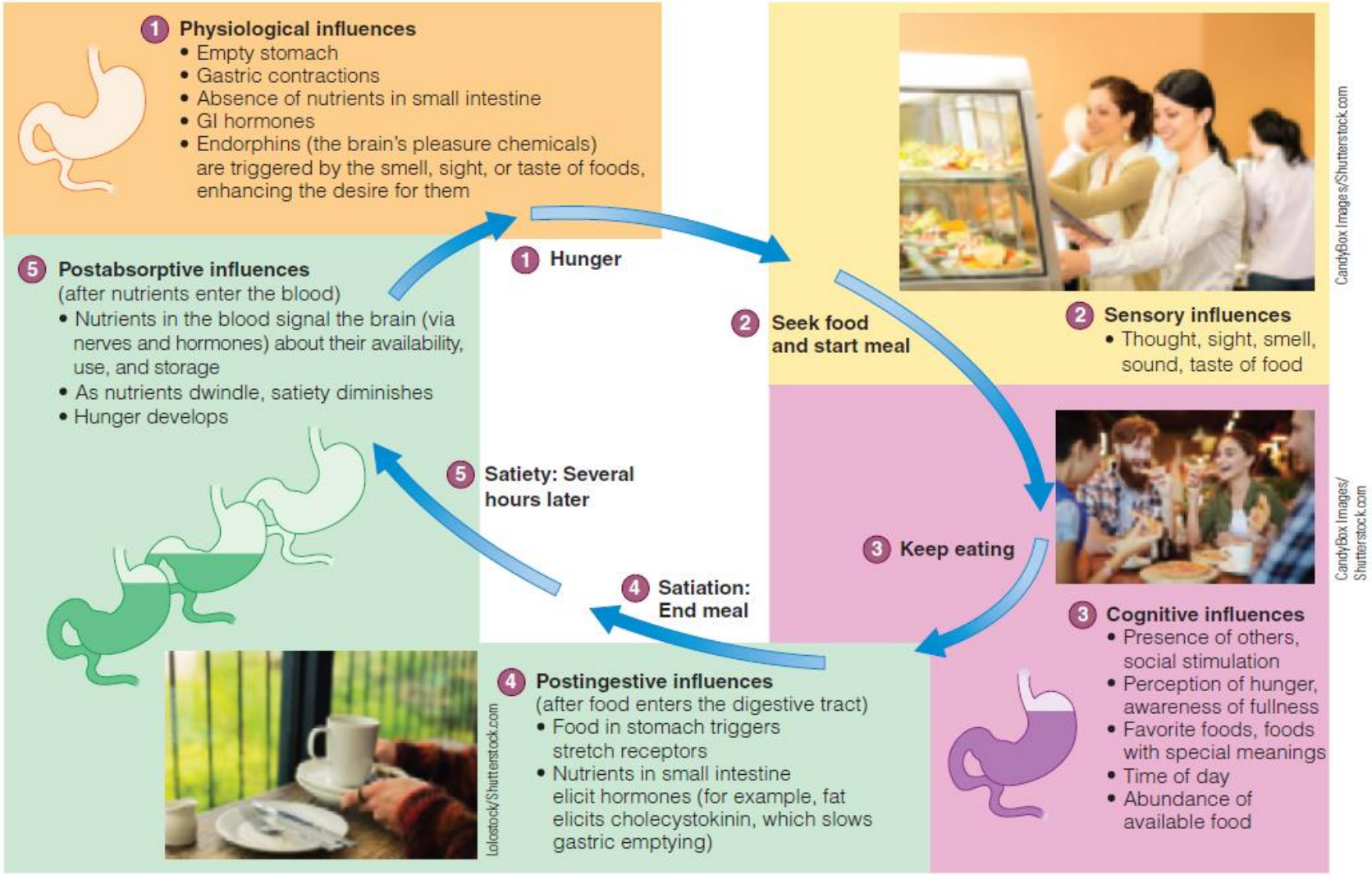
Determines how much time passes between meals

Outline

1. The Satiety Cascade
2. Appetite Control
    I. Homeostatic and Hedonic Processes
    II. Classical Theories of Appetite Regulation
    III. Pathways involved in Appetite regulation

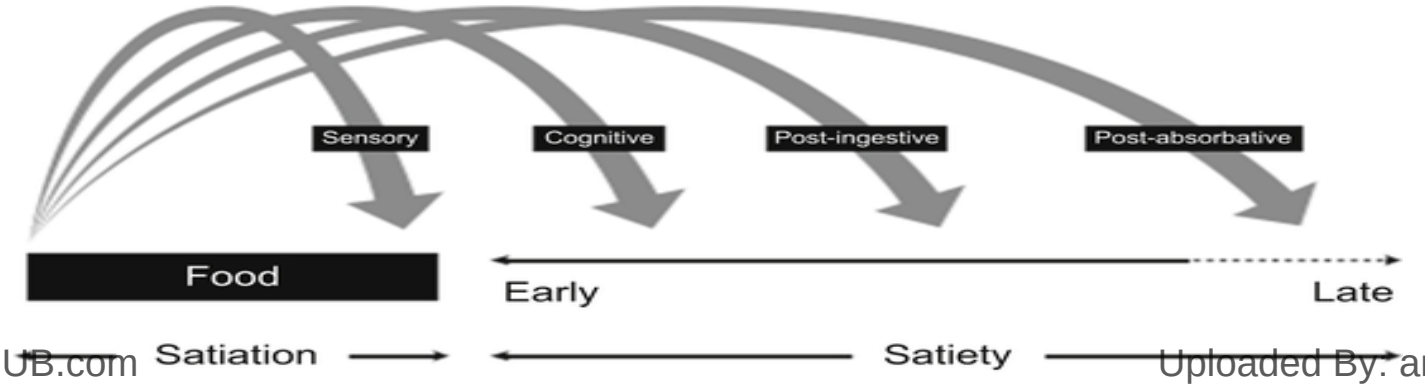
PART 1: THE SATIETY CASCADE

Hunger, Satiation, and Satiety



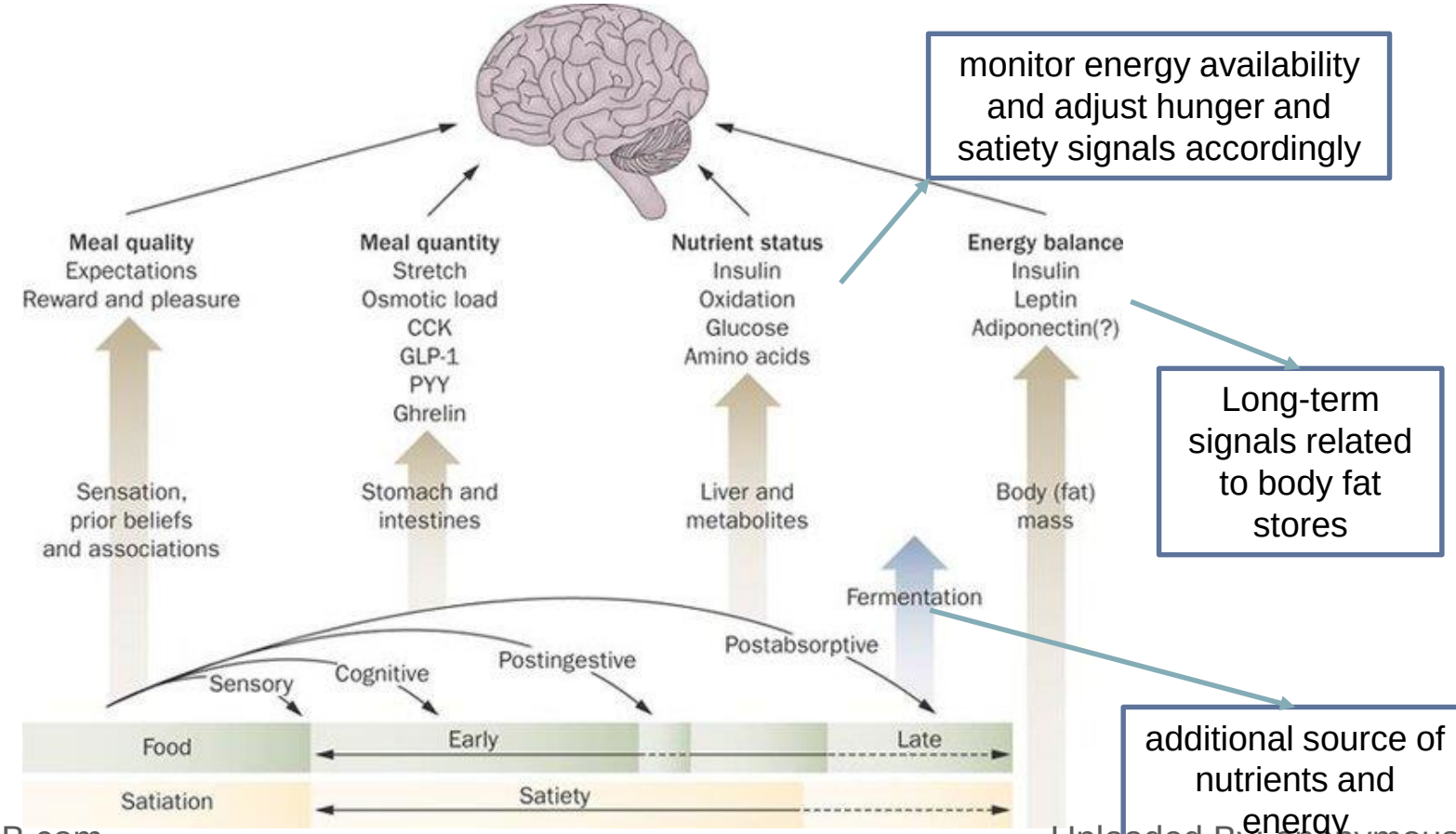
The Satiety Cascade

- Four **overlapping** mediating processes:
  - Sensory: generated by sensory attributes of food (e.g. smell, taste, temperature).
  - Cognitive: beliefs held about food & effects on eater.
  - Post-ingestive: gastric distension, gastric emptying rate, release of satiety hormones, stimulation of receptors in GIT.
  - Post-absorptive: arising from metabolite actions following release into bloodstream.



The Satiety Cascade

- “A series of behavioural and physiological events that occur following food intake and that inhibit further eating until the return of hunger signals. ”

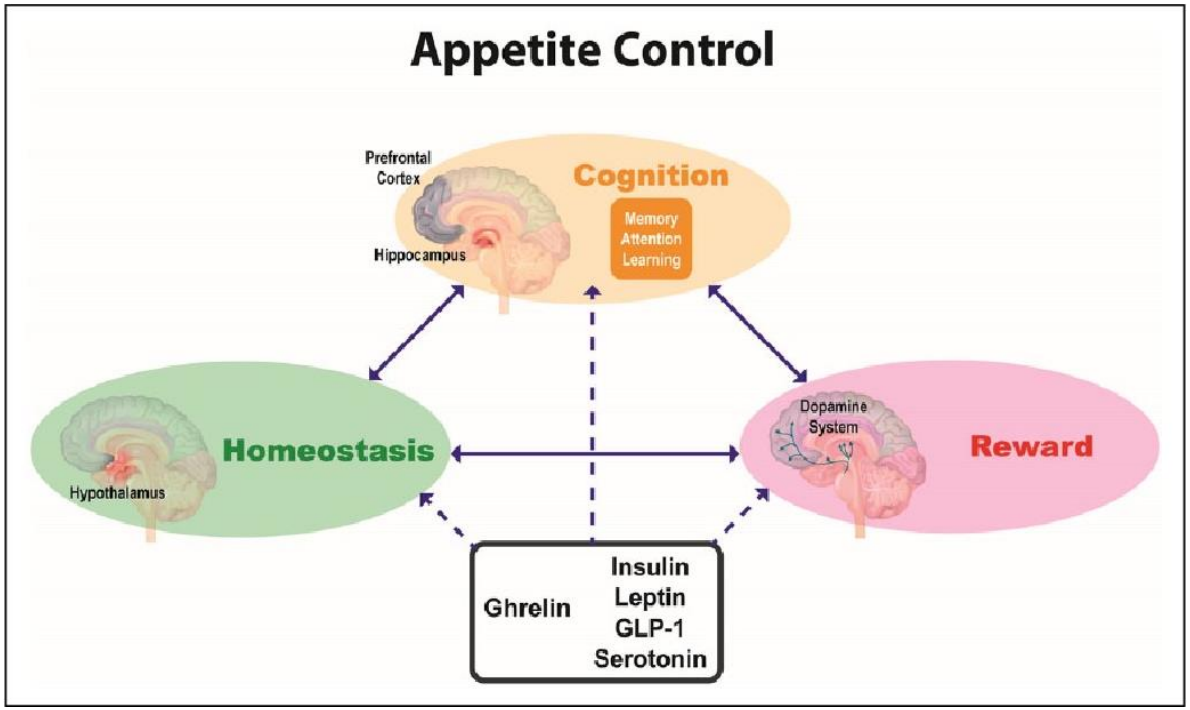


DOI: 10.1080/10408398.2015.1073140

PART 2: APPETITE CONTROL

Appetite Control

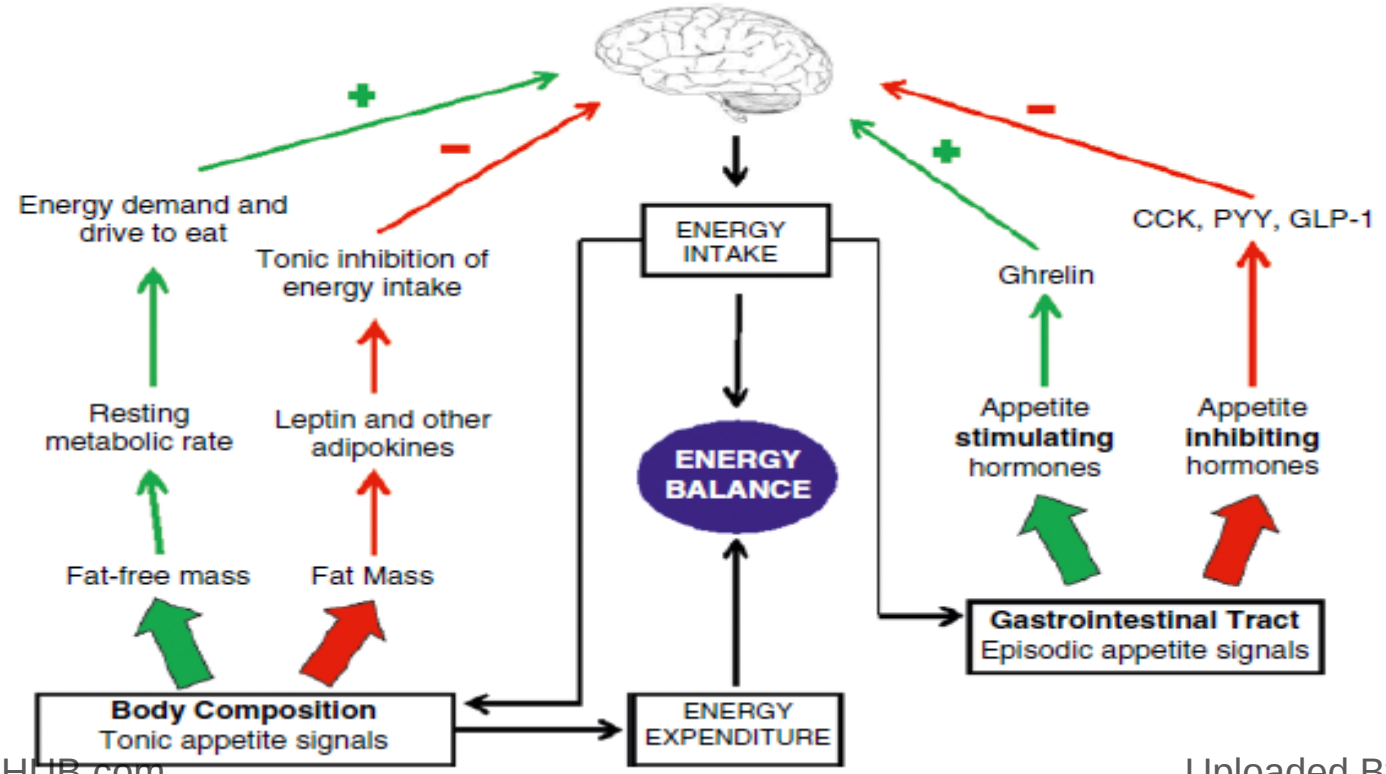
- Appetite Control integrates **cognitive**, **homeostatic** and **hedonic (reward)** mechanisms



•DOI:10.1177/0269881117736917

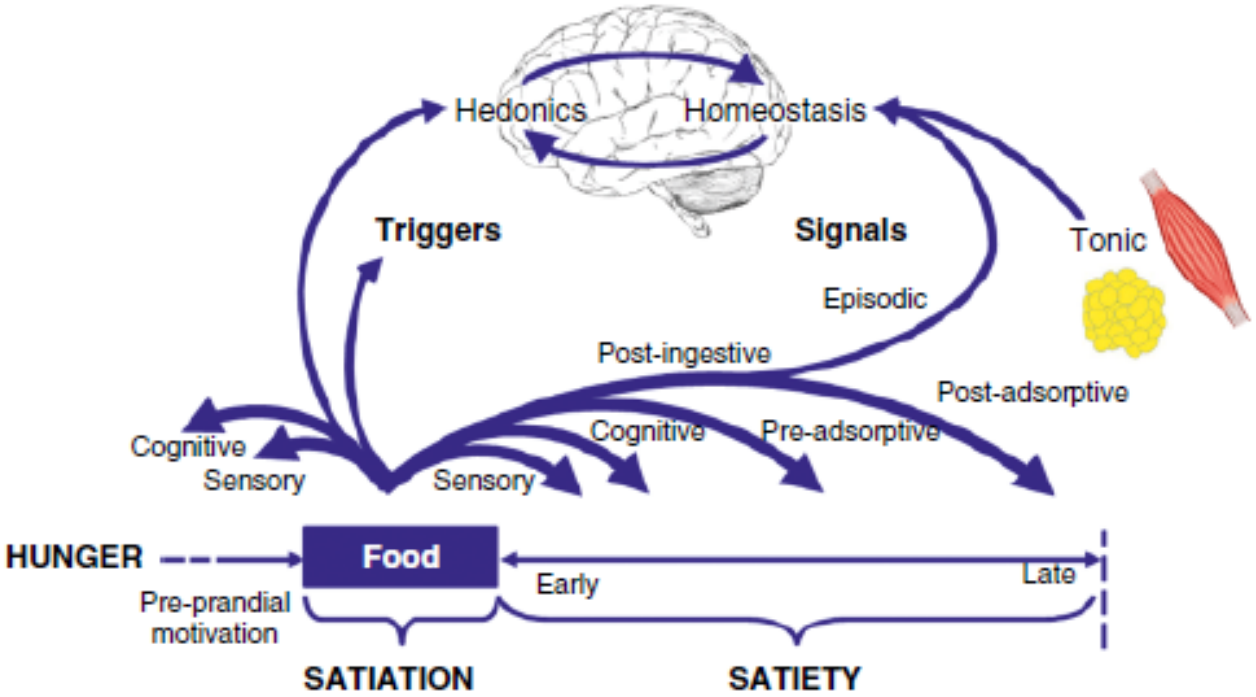
1. Homeostatic and Hedonic Processes

- Homeostatic Processes: Concerned with the ingestion of **food as energy**. They deal with the excitatory & inhibitory processes that influence the "**amount**" of food



Homeostatic and Hedonic Processes

- Sensory aspects of food such as taste and smell, labeling, palatability of foods or their ***hedonic properties***.
- Hedonics (liking and wanting) exerts a huge influence on the choice of foods and **modulates the homeostatic drive** to alter the energy ingested



Homeostatic and Hedonic Processes

- The reward derived from food plays an important role in the **initiation**, **maintenance**, and **termination** of an eating episode.

- Palatable food stimulates an **orexigenic drive** that is able to override homeostatic signals of satiety

- Consuming a highly palatable food → Activates the reward pathways within the brain → release of neurotransmitters including dopamine.

- These pathways have connections with the hypothalamus → release of hunger peptides (NPY and orexins) & inhibit satiety peptides (leptin and CCK)

- Hedonic processes exert a **powerful influence** over food consumption

Homeostatic and Hedonic Processes

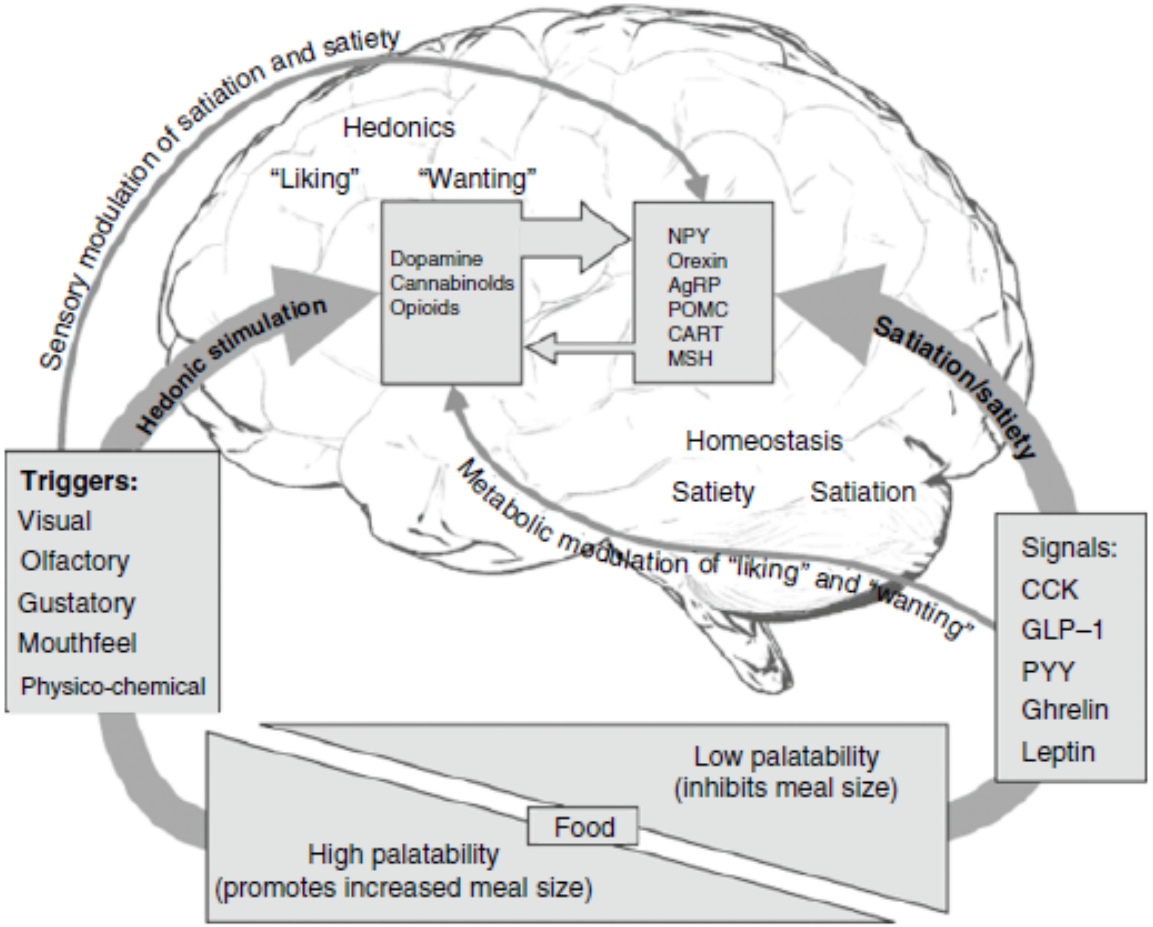


Figure 8.4 Model to explain overconsumption with highly palatable food [27]. Exposure to highly palatable food causes an imbalance between hedonic and homeostatic processes. Sensory properties act as triggers causing the upregulation of reward mediators implicated in "liking" and "wanting." These triggers may also modulate homeostatic processes directly (e.g. [30]). The hedonic system connects with appetite-controlling neurons in the hypothalamus to override homeostatic signaling in favor of continued eating.

2. Classical Theories of Appetite Regulation

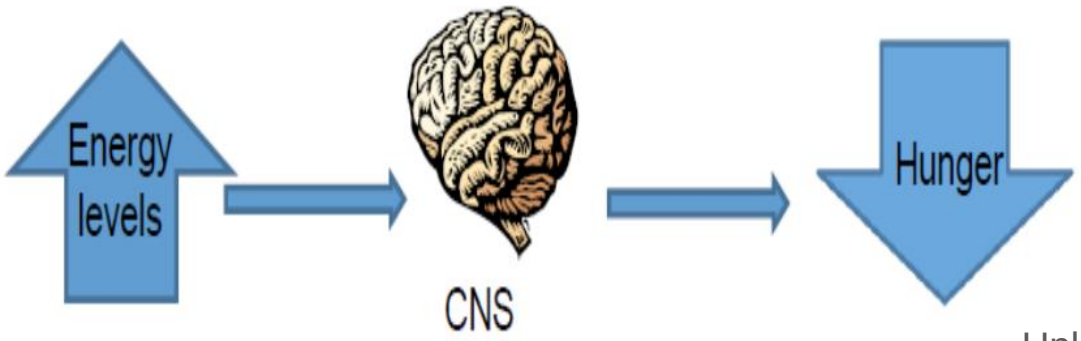
Main early theories:

- Energostatic
- Glucostatic
- Lipostatic
- Aminostatic

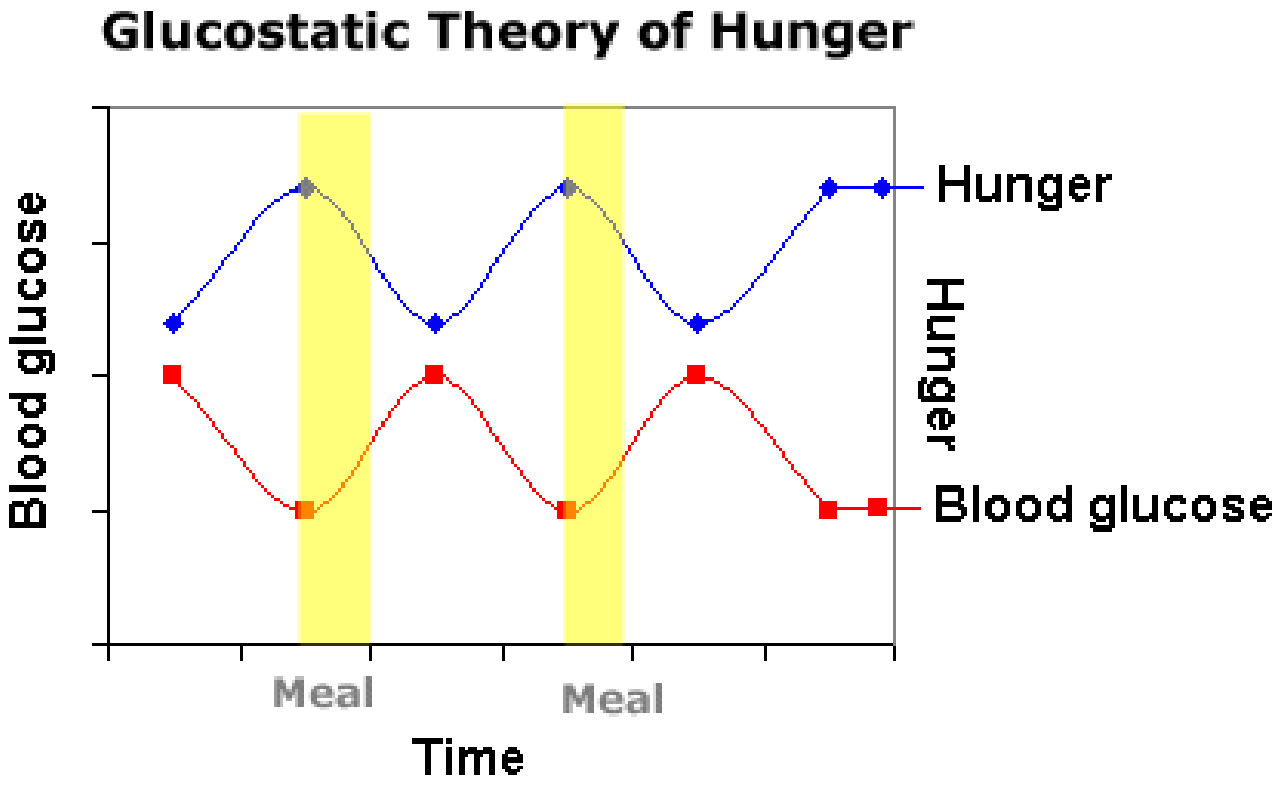
Energostatic Theory

- Proposed **energy supply** was the main factor controlling appetite, with each macronutrient having equally isocaloric satiating effects

- Evidence against:
  - Passive overconsumption of high energy density foods
  - Protein more satiating macronutrient



Glucostatic signals



Glucostatic signals

- A glucostatic theory for the regulation of feeding behavior

There are chemoreceptors in the hypothalamic satiety center that would be sensitive to the **arteriovenous difference in glucose** or to the **availability and utilization of glucose**.

(a) the small decreases of blood glucose observed prior to spontaneous meal consumption

(b) the suppression of food intake induced by infusion of glucose

(c) the spontaneous decrease in total intake observed when dietary CHO content is increased.

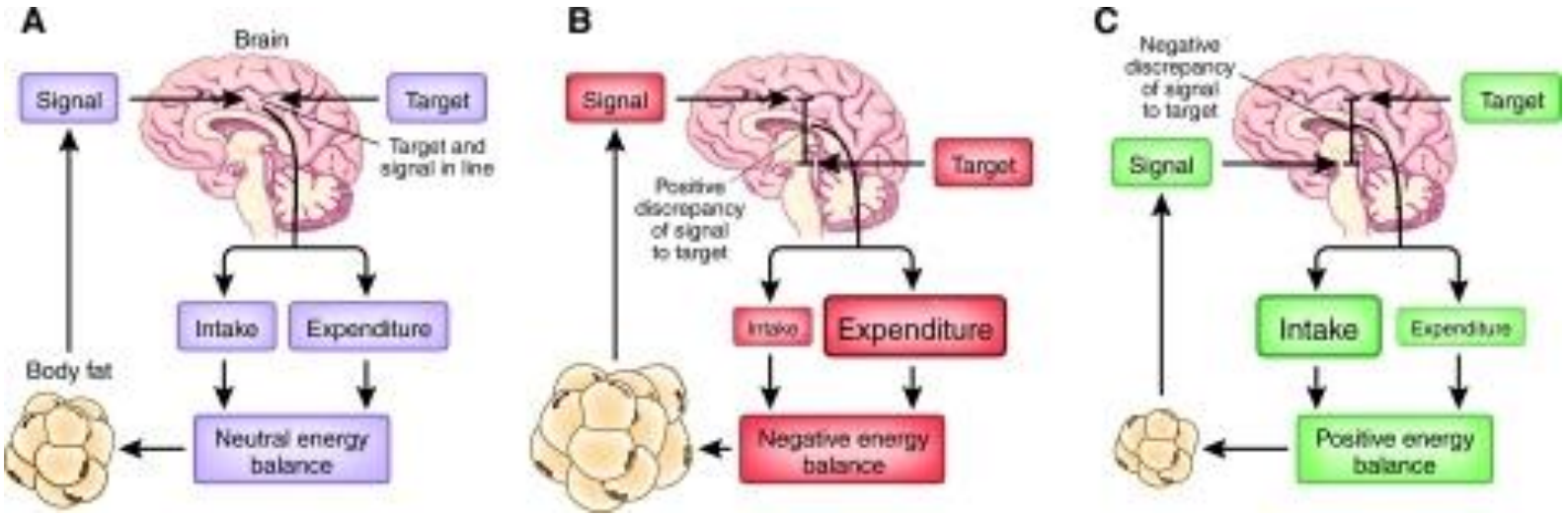
Evidence against?

Aminostatic or protein- static signals

- Food intake is determined by the level of plasma amino acids.
- Dietary protein induces satiety in the short term, and consumption of low- protein diets leads to an increased appetite for protein- containing foods.
- Further:
  - Administration phenylalanine and tryptophan (monoamine neurotransmitters precursors) leads to reduced food intake
  - The ratio of plasma tryptophan to other amino acids affects brain serotonin → has an inhibitory influence on food intake.

Lipostatic and adiposity signals

- Substances released from fat stores function as afferent signals relaying to the brain the amount of stored energy in the form of triglycerides that affects feeding behavior.
- The lipostatic hypothesis is perhaps the one that provides the most plausible explanation for the long- term regulation of fat stores.



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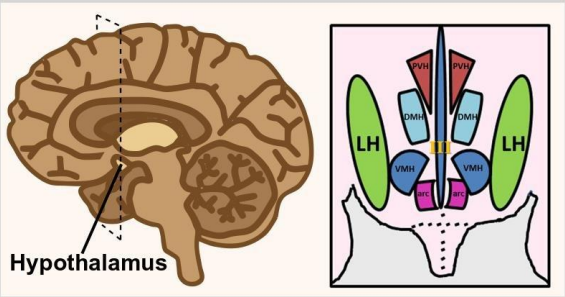
Lipostatic and adiposity signals

Humans who are predisposed to obesity may have a homeostatic mechanism in which the set- point for weight regulation is set at a higher level than those who are more resistant to obesity.

BUT **this is only part of the complex processes** to regulate appetite

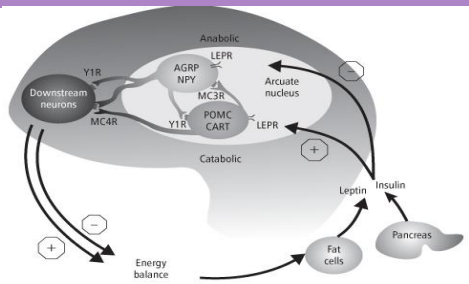
3. Pathways involved in Appetite regulation



- "Centers" localized in the hypothalamus are involved in the control of feeding behavior.
  1. **Ventromedial hypothalamic** (VMH) region is implicated in satiety
  2. **Lateral hypothalamic** (LH) region is implicated in the initiation of feeding
  3. **Paraventricular nucleus** (PVN) is implicated in the cessation of feeding.

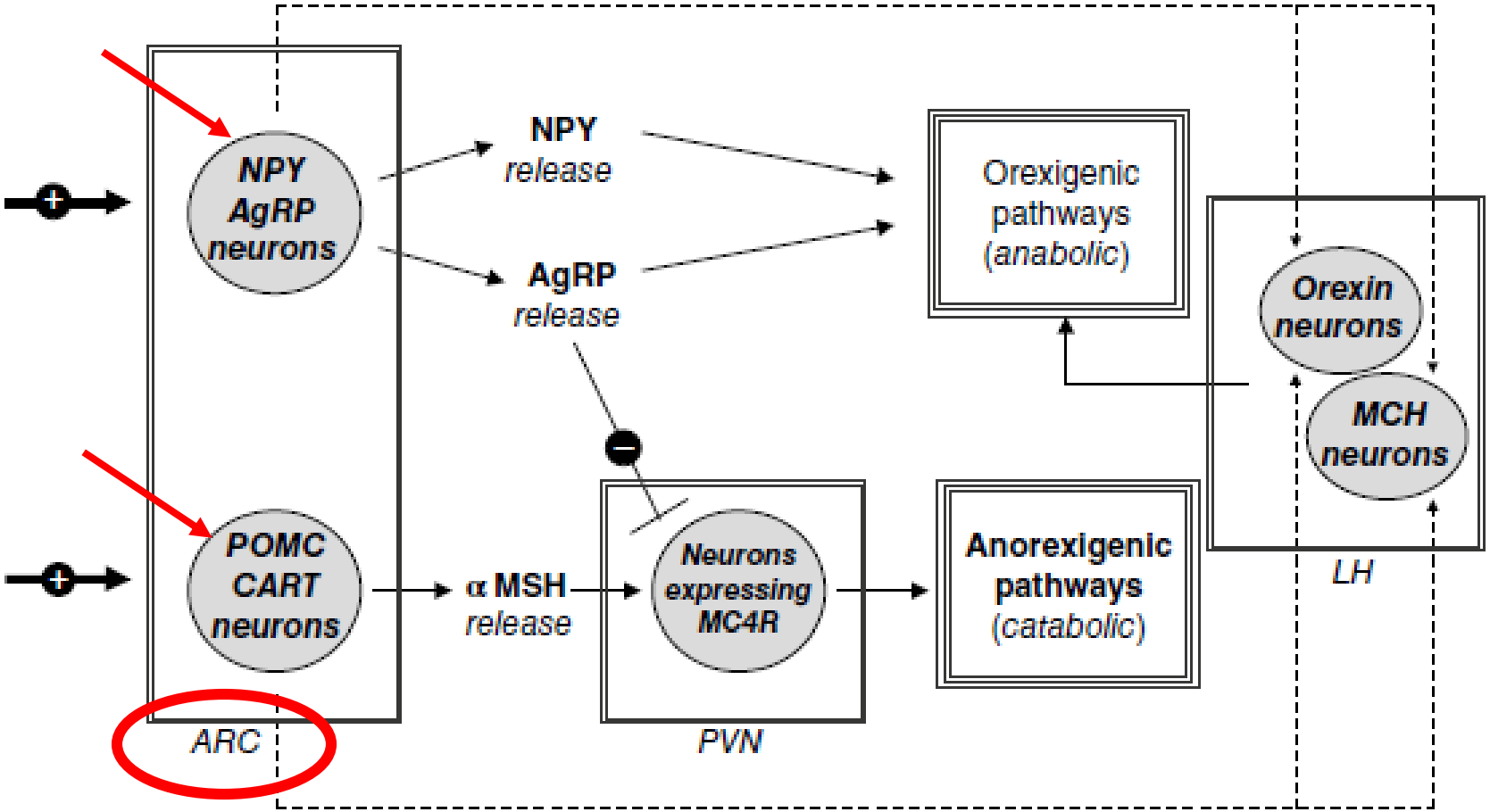
These analyze and integrate afferent signals that are neural or humoral.

The arcuate nucleus (ARC)



- Two primary neuronal populations in ARC integrate signals of nutritional status & influence E homeostasis: –
- Inhibit food intake (anorexigenic) & ↑EE
  - Via expression of CART (cocaine- and amphetamine–regulated transcript) & POMC (pro-opiomelanocortin)
- Stimulate food intake (orexigenic) & ↓EE
  - Via expression of NPY (neuropeptide Y) & AgRP (agouti-related peptide)

Satiety Control Centers



Satiety Control Centers (summary)

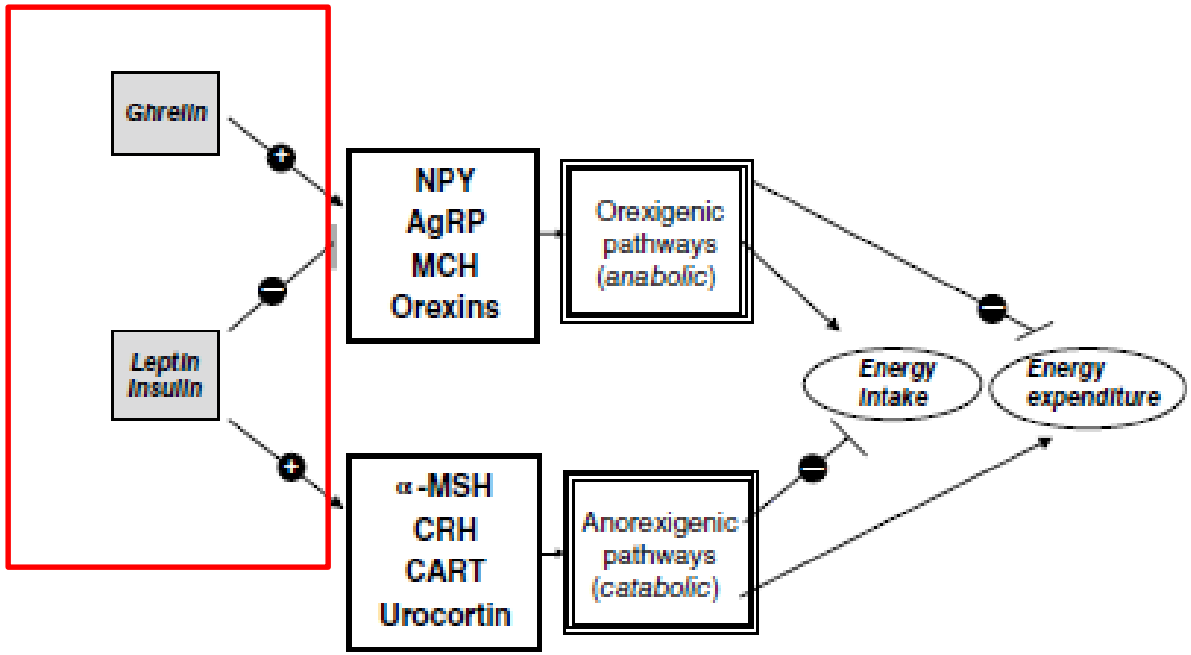
(i). The *NPY/AgRP* neurons, which coexpress NPY (neuropep-tide Y) and AgRP (agouti- related peptide) – are orexigenic, i.e. their activation stimulates food intake.

(ii). The *POMC/CART* neurons are anorexigenic, i.e. their activation reduces food intake.

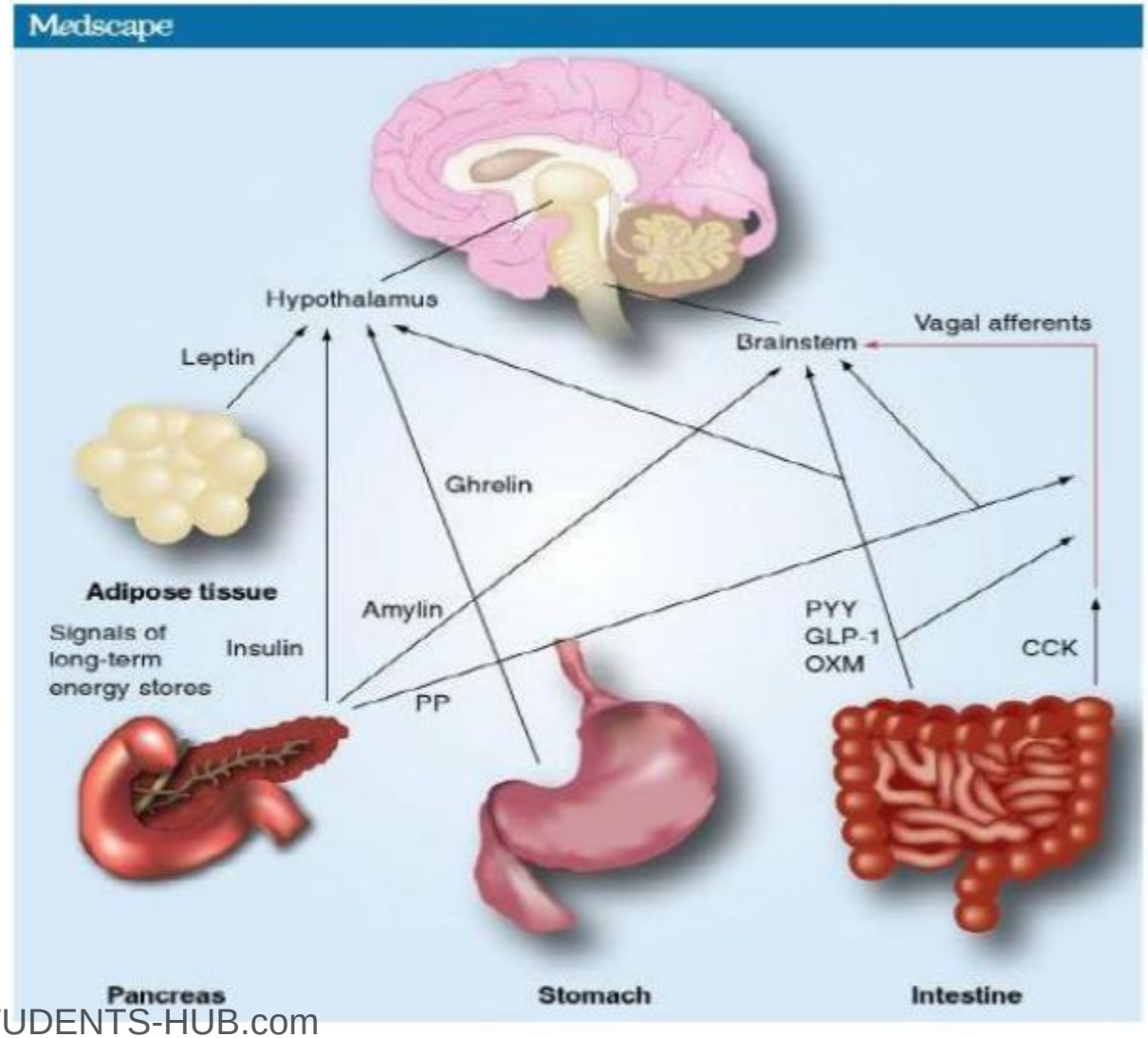
All these neurons project to other regions of the hypothalamus where further signal processing occurs

Satiety signals from the periphery

- The sensations of hunger and satiety result from the central integration of numerous signals originating from a variety of **peripheral tissues and organs** (GI tract, liver, pancreas, adipose tissue, skeletal muscle)



Satiety signals from the periphery



- Vast array of peripheral signals
- Centrally integrated mainly in hypothalamus

Signals from the GI tract

- The progression of food through the stomach and small intestine (a short- term nutrient reservoir) – initiates peripheral satiety signals

  - **Stretch- and mechano- receptors**.

  Inhibit feeding, partly **inhibition of AgRP neurons** (vagal pathways)

  - **Chemoreceptors**

  Respond to the products of digestion (vagal pathways)

These neural signals are integrated with those transmitted by **hormones** released from the GI system.

→ mediate **short- term feelings** of hunger and satiety

Stretch Signals from the GI tract

As food arrives into stomach → Stomach muscle wall distended → Activate stretch receptors (mechanoreceptors)

Influenced by rate of gastric emptying (rate by which stomach contents emptied into intestine)

Physical state of meal

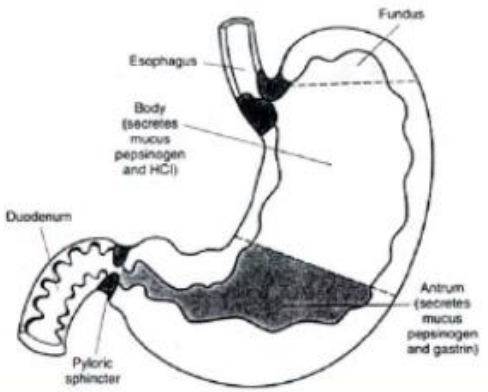
Solid/liquid

Viscosity

pH

Temperature

Fibre/digestibility



Meal volume vs meal energy content

(rate increases with meal volume but decreases with energy density)

The individual

Gender

Body size

Age

Macronutrients

Carbohydrate - empties more rapidly than protein or fat

Protein and fat - delay gastric emptying due to CCK secretion

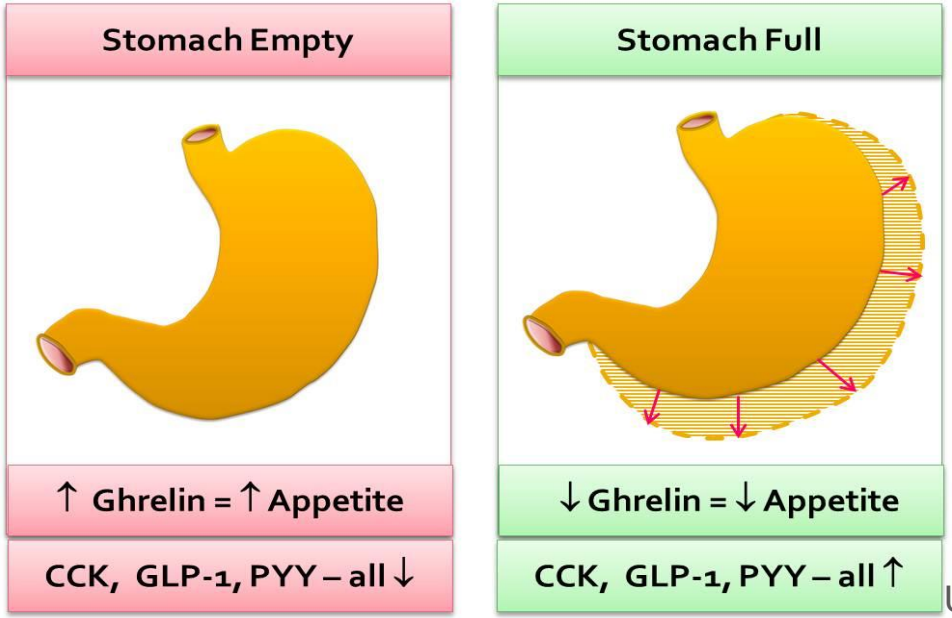
Endocrine Signals from the GI tract

1. **Ghrelin**: the only known circulating factor to increase hunger.

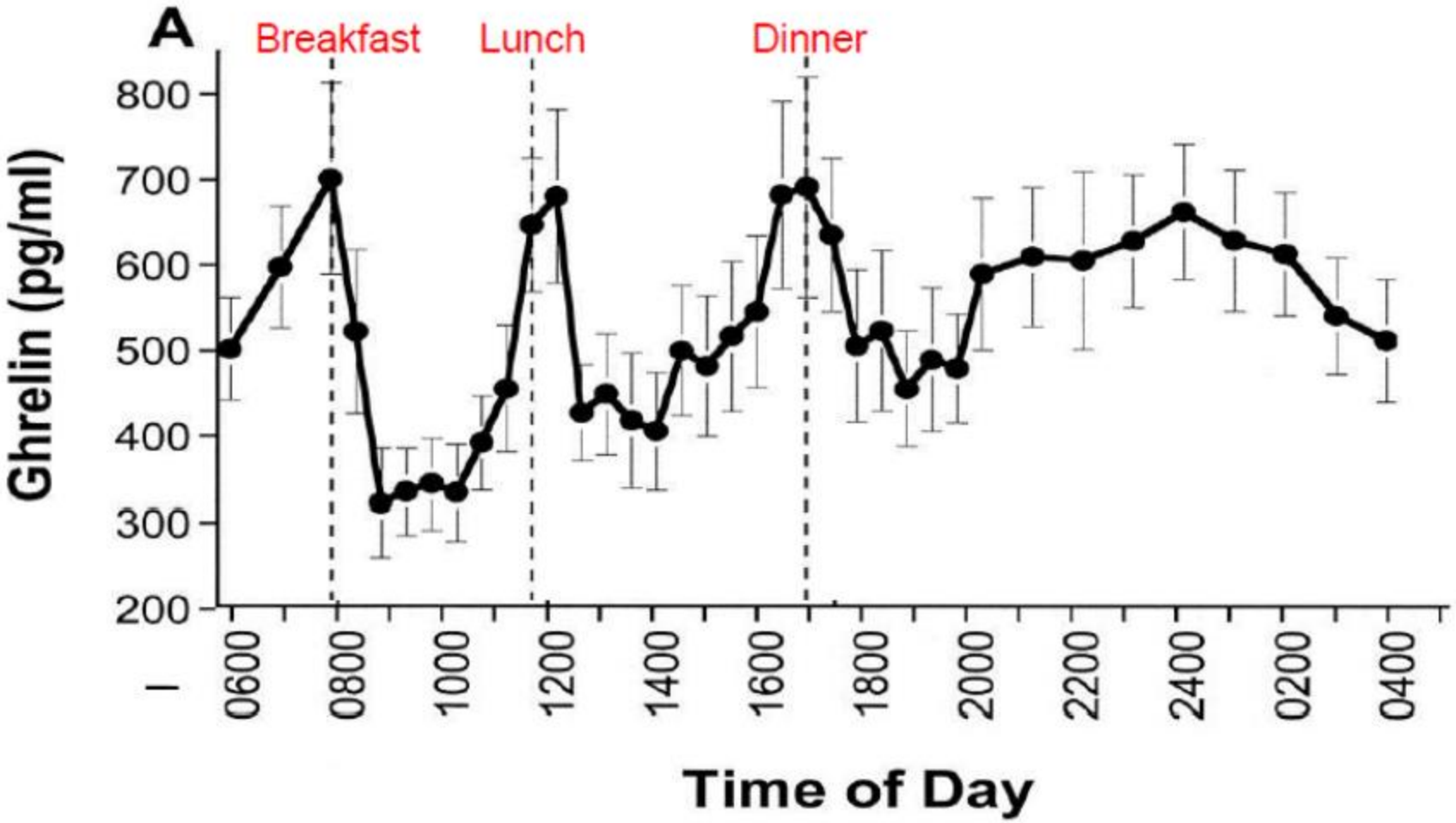
Ghrelin is primarily secreted by cells located in the gastric fundus.

Fasting leads to increased ghrelin production in the stomach and elevated ghrelin concentrations in the blood

→ stimulates gastric motility and gastric emptying, enhances taste perception

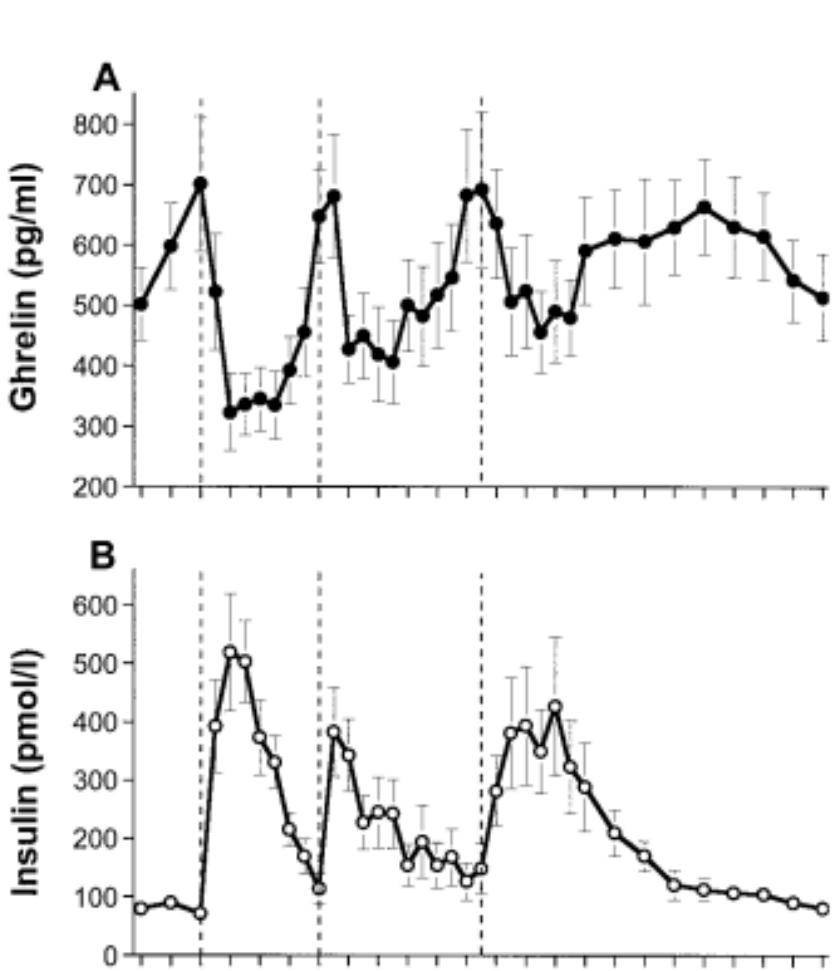


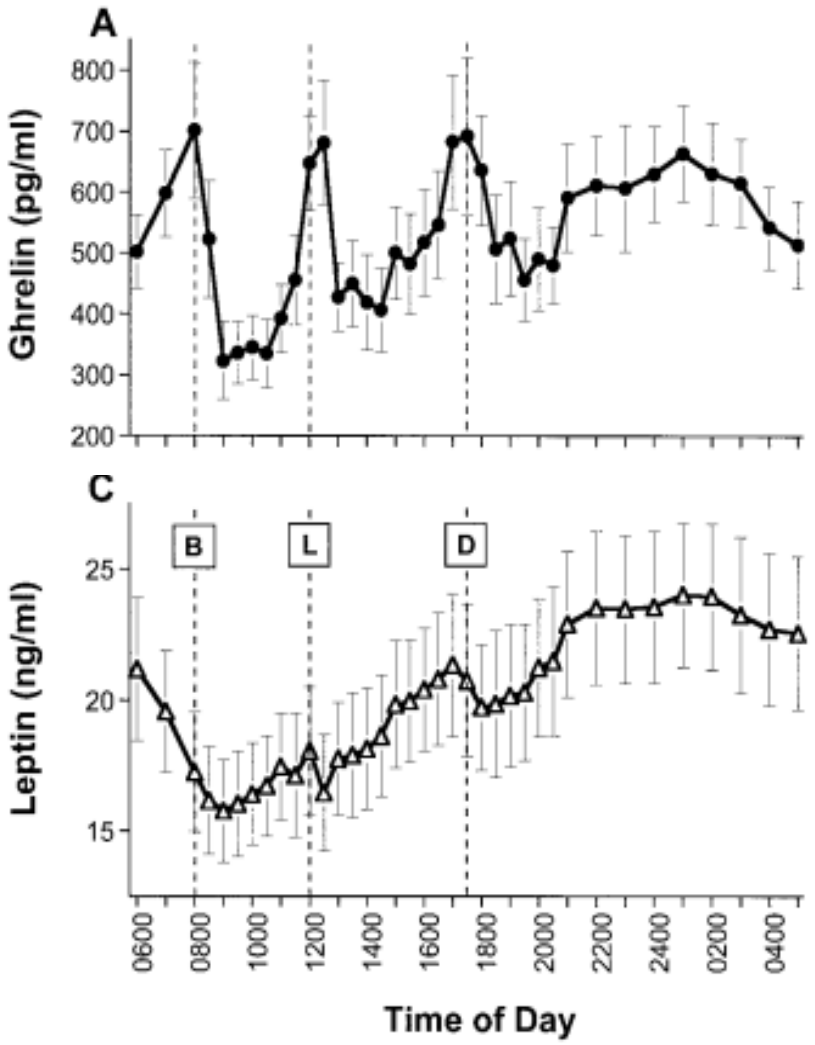
Plasma ghrelin concentrations during a 24h period in 10 human subjects consuming breakfast, lunch, and dinner



Cummings D E et al. Diabetes 2001;50:1714-1719

Ghrelin, Leptin, and Insulin Changes

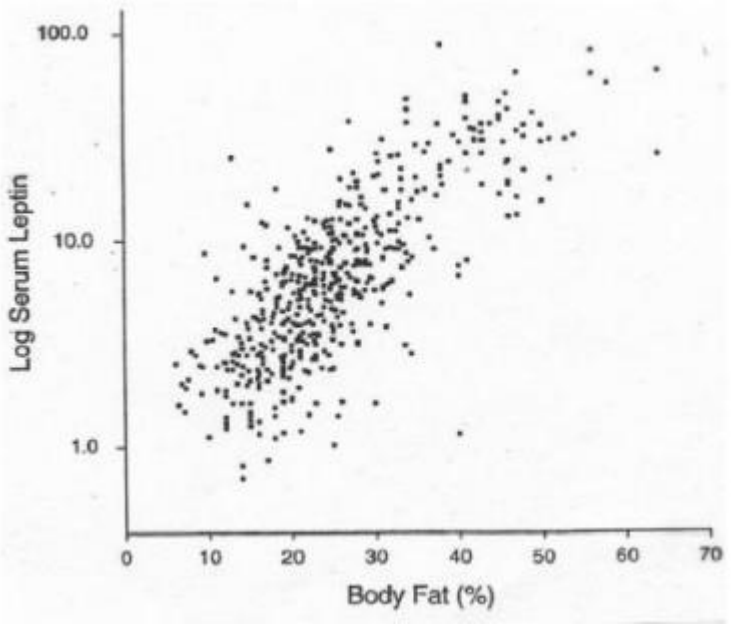




Ghrelin, Leptin, and Insulin Changes

- Leptin is secreted by adipocytes (fat cells)
- Circulating leptin concentrations proportional to adipose tissue mass, correlate better with total fat mass than body weight
- Reflect energy stores

Food restriction suppresses circulating leptin concentrations, reversed by refeeding -i.e. circulating levels also reflect food intake



Ghrelin, Leptin, and Insulin Changes

Leptin

- Activates anorexigenic POMC/CART neurons
- Inhibits orexigenic NPY/AgRP neurons

- Majority of obese humans have high circulating leptin levels (high levels do not prevent obesity)

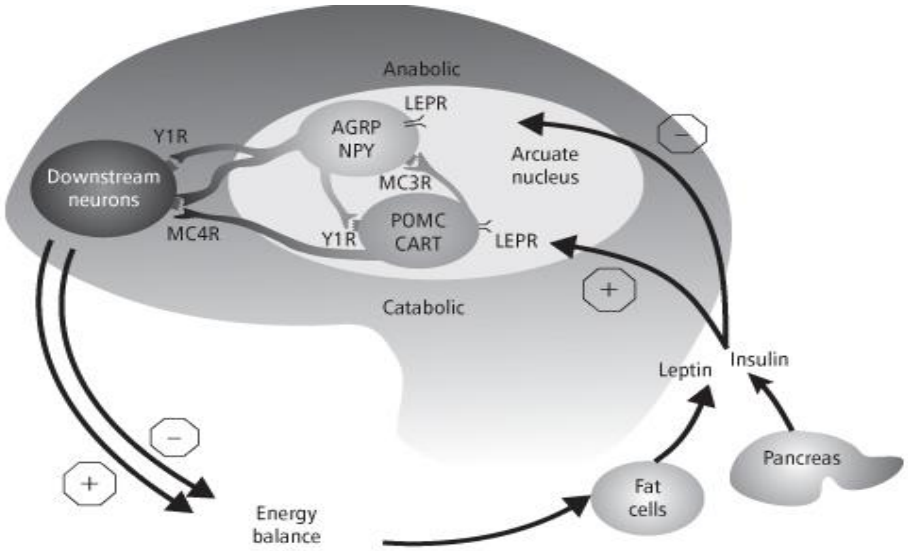
– Suggestive of **relative resistance** to leptin action

– Leptin resistance seems to result from obesity, but a lack of sensitivity to leptin will further contribute to aetiology of obesity

Ghrelin, Leptin, and Insulin Changes

- Insulin secretion rapidly increases following a meal – Unlike leptin which is relatively insensitive to acute food intake

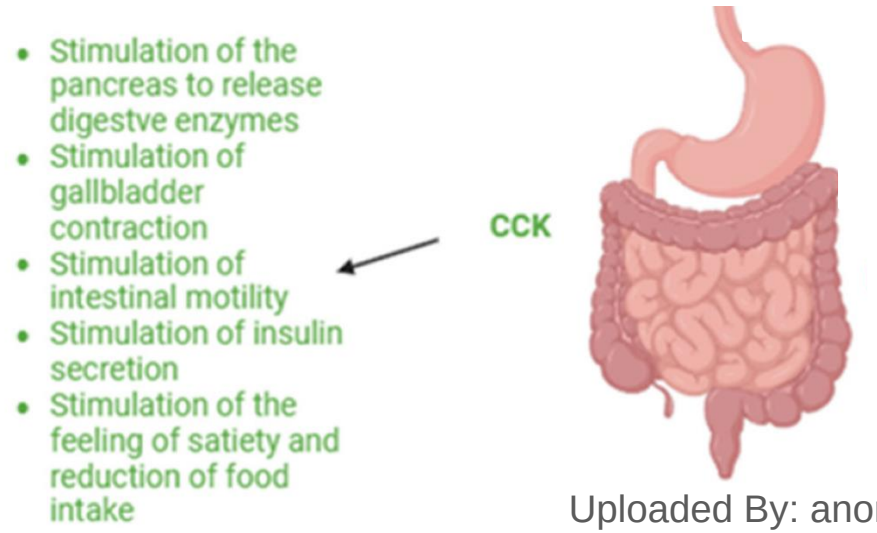
- insulin ↑ activation POMC increases, food intake ↓



Continued .. Endocrine Signals from the GI tract

2. **Cholecystokinin (CCK)** –

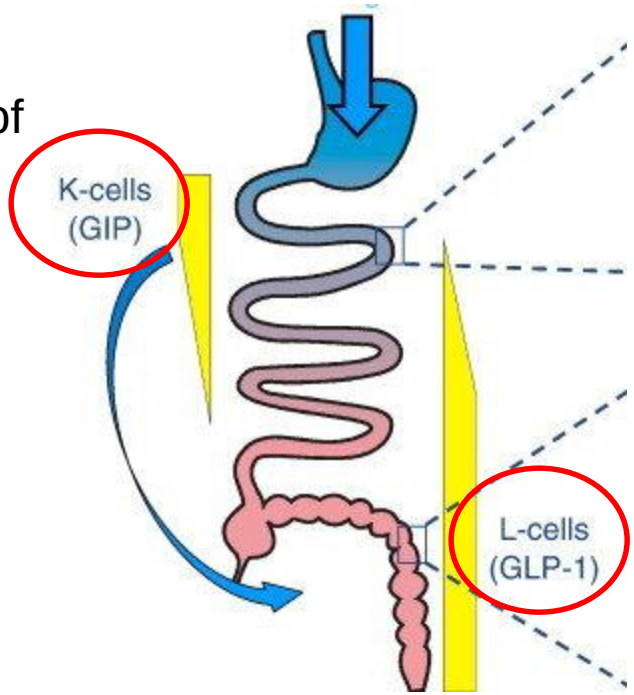
- It is released from the small intestine into the circulation in response to luminal nutrients (particularly proteins and fats)
- CCK release delays gastric emptying
- CCK enhances the sensation of fullness and helps to reduce meal size and regulate food intake



Endocrine Signals from the GI tract

3. Other Postprandial Peptides: **Gastric inhibitory peptide (GIP), Glucagon- like peptide- 1 (GLP- 1) and Peptide (PYY)**

- **GIP** secretion is stimulated by food intake (particularly a few minutes after the consumption of glucose or other easily absorbed carbohydrates), but fats and proteins also stimulate GIP release.
- Its concentration increases most rapidly within 30 min of the start of a meal (Consistently high for three hours after meal ingestion)
- GIP inhibits of gastric acid secretion & reduces food intake by stimulating the satiety center



Endocrine Signals from the GI tract

2. Peptides that are released postprandially and reduce appetite include: **Gastric inhibitory peptide (GIP), Glucagon- like peptide- 1 (GLP- 1) and Peptide (PYY)**

- PYY is released by the L-cells
- PYY reduces appetite by acting on the central nervous system and inhibiting neuropeptide Y activity.
- It stimulates the feeling of satiety → reduction in the amount of food intake.
- It also delays gastric emptying by limiting gastric peristalsis and decreasing the secretion of pancreatic hormones.

Endocrine Signals from the GI tract

2. Peptides that are released postprandially and reduce appetite include: **Gastric inhibitory peptide (GIP), Glucagon- like peptide- 1 (GLP- 1) and Peptide (PYY)**

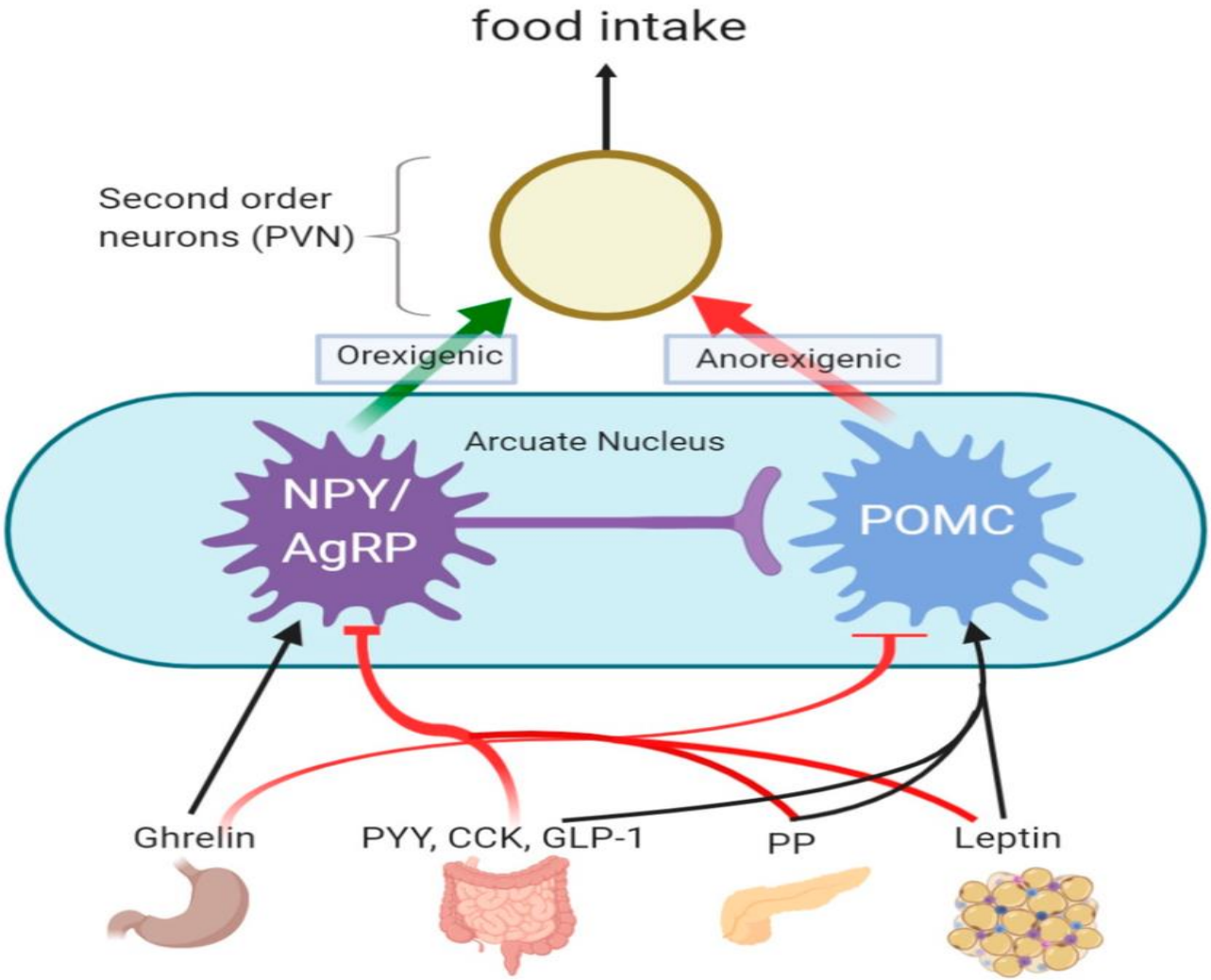
GLP-1 is mainly released by enteroendocrine L-cells located within the intestines (highest concentration observed in the ileum and the colon)

GLP-1 secretion is stimulated by nutrients in ingested food (occurs more rapidly after the consumption of proteins and carbohydrates)

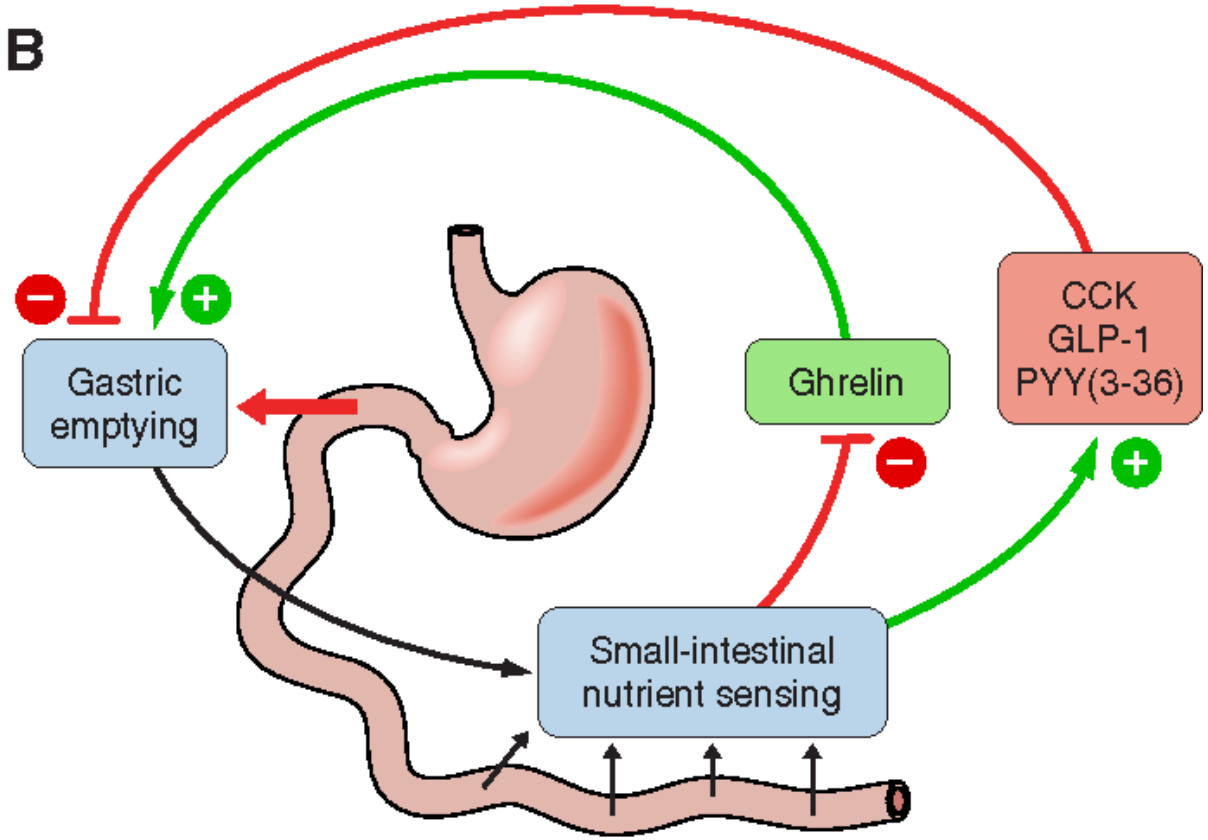
Satiety-related roles: GLP-1 suppresses appetite and food intake, delays gastric emptying

Role in weight management?

Summary



Summary



In-Class Exercise: Reading a Systematic Review

- About GLP-1 Agnosits

GLP-1 AGONIST DRUGS

Brand Name	Generic Name	Indication
Ozempic®	Semaglutide	Type 2 Diabetes
Rybelsus®	Semaglutide	Type 2 Diabetes
Wegovy®	Semaglutide	Weight Loss
Trulicity®	Dulaglutide	Type 2 Diabetes
Victoza®	Liraglutide	Type 2 Diabetes
Saxenda®	Liraglutide	Weight Loss
Byetta®	Exenatide	Type 2 Diabetes
Bydureon BCise®	Exenatide	Type 2 Diabetes
Mounjaro®	Tirzepatide	Type 2 Diabetes

In-Class Exercise : Reading a Systematic Review

Refer to the paper shared on Ritaj:

Introduction

1. What is the objective of this paper?

Methods

1. What is the search strategy?
2. What is the inclusion criteria

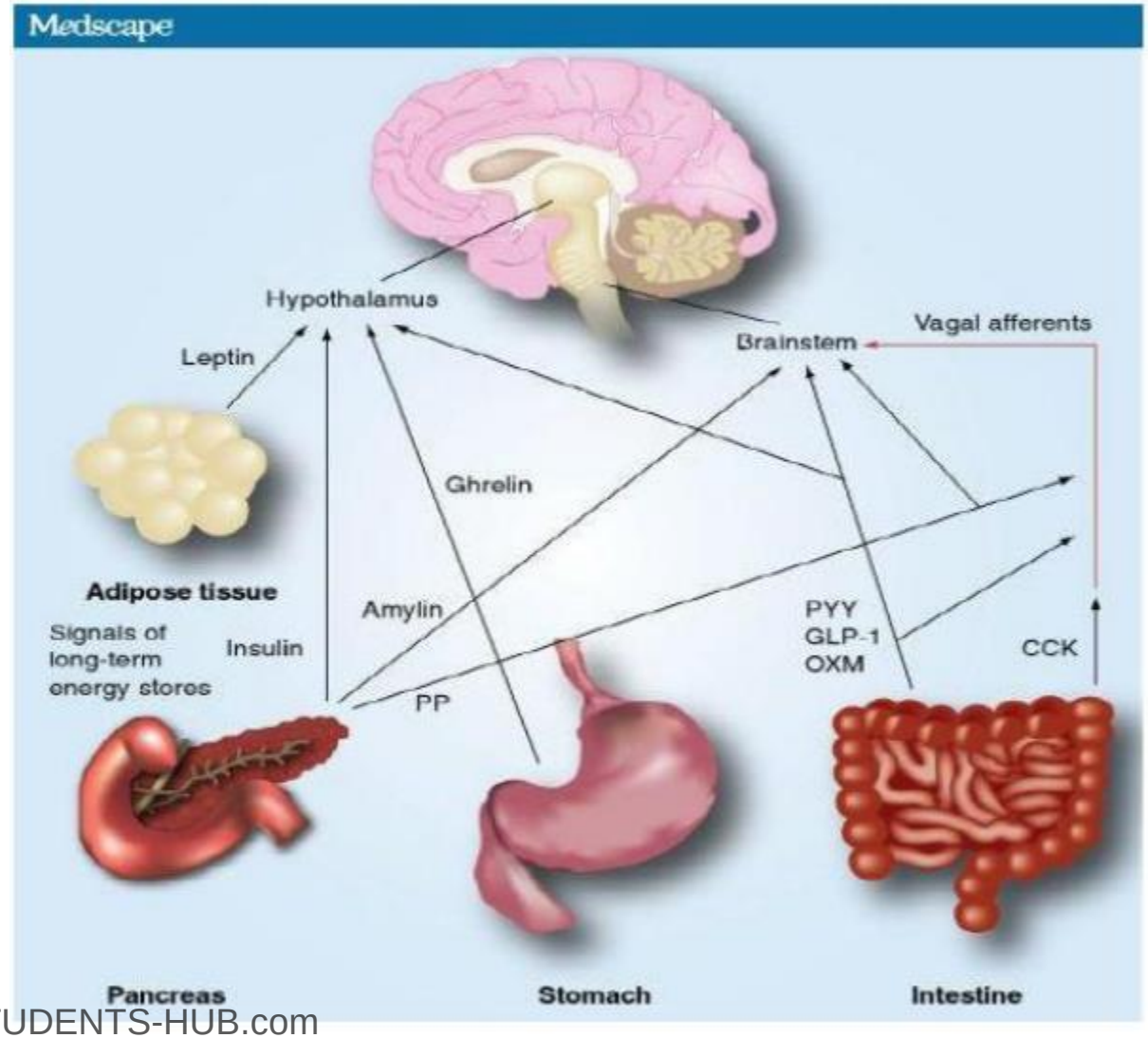
Results

1. How many studies were included?
2. What is the effect on body weight?
3. Figure 2: Discuss the results presented here

Conclusion

1. What is the clinical implication of this study?

Review of Peripheral Signals



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- Centrally integrated mainly in hypothalamus