Pre-Lecture Video

Hypothalamus: small but essential. ~4 grams.

Sensory, internal, Cognitive

↳ acts as an integrator of diverse inputs to regulate AND coordinate basic functions necessary for life

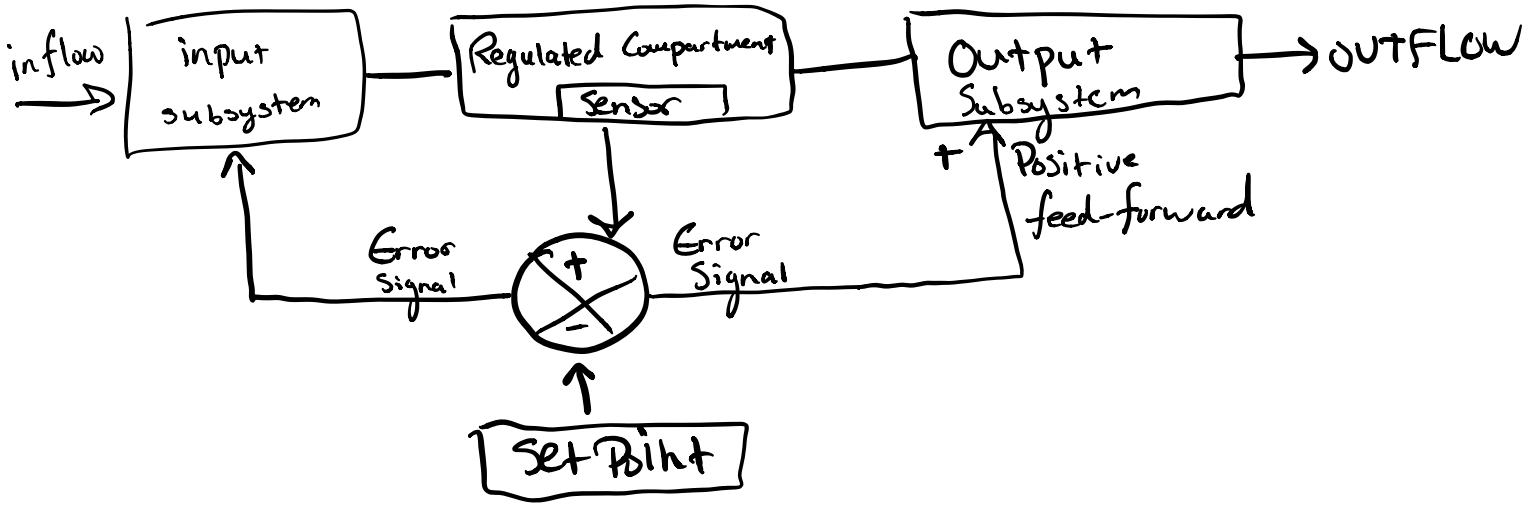
Functions of Hypothalamus

- Energy Homeostasis
- Fluid Homeostasis
- Body Temperature
- Aggressions
- Defensive Behaviors
- Sexual Behavior
- Parental Behavior
- Lactation
- Stress Response
- Sleep

Homeostasis: process through which the body maintains a steady state

- Controlled by **hypothalamus**

Control Diagram of Simple Regulated Systems



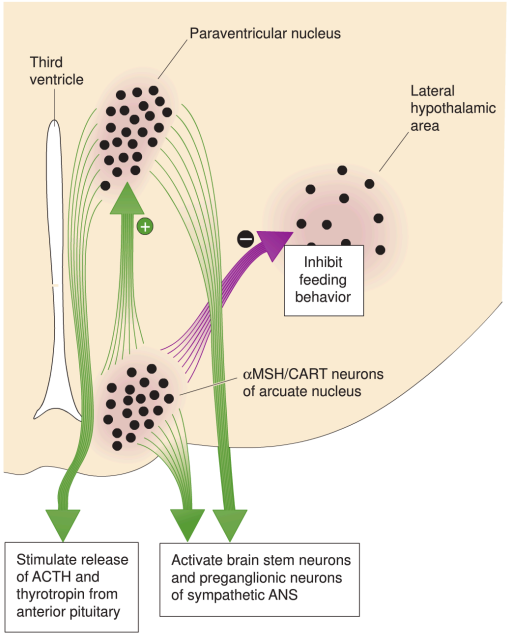
Lecture 35. Hypothalamus and Motivation

Prof. Melissa Warden

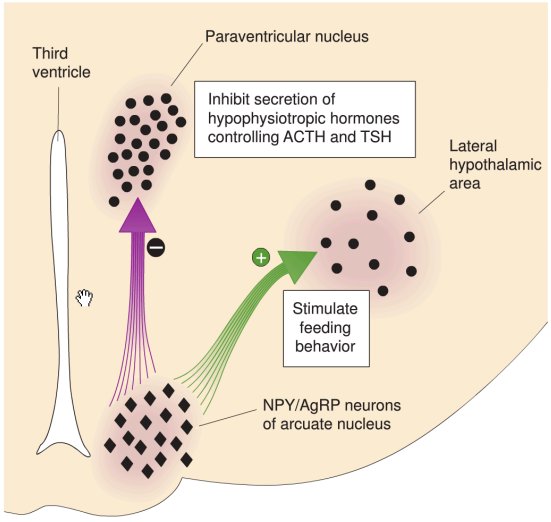
Pre-Lecture Preparation

Watch Video 35-1: Hypothalamic neural circuits and homeostasis
Learn these diagrams:

Response to elevated leptin



Response to decreased leptin



Required Reading

Be able to explain the following figures from Bear et al.: p.524, Fig. 15.2; p.526, Fig. 15.4; p.529, Fig. 15.6; p.555, Fig. 16.4 and 16.5; p.559, Fig. 16.8 and 16.9; p.560, Fig. 16.11.

Optional Reading

1. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Aponte Y, Atasoy D, Sternson, SM.

Learning Objectives

1. To learn what homeostasis is, and how the hypothalamus regulates internal physiological processes and essential behaviors to maintain bodily homeostasis.
2. To learn the three broad categories of function mediated by the hypothalamus (hormonal, autonomic, and behavioral).
3. To learn the neural circuits of the hypothalamus that regulate feeding and body weight, and how dysfunction in these circuits can lead to obesity or starvation.

Lecture Outline

This lecture will focus on the role of the hypothalamus in maintaining bodily homeostasis. We will discuss how they hypothalamus detects deviations from homeostasis and responds by causing the release of hormones into the blood and triggering autonomic and behavioral responses. We will study the hypothalamic neural circuits that mediate feeding behavior as a canonical example of homeostatic regulation, and will also discuss how dysfunction in this system can lead to obesity or anorexia.

1. Hypothalamic control of body systems
    a. Organization of behaviors essential for survival: reproduction, aggression, food/water intake, sleep.
    b. Control over the autonomic nervous system. Homeostasis, sympathetic and parasympathetic nervous systems.
    c. Regulation of the endocrine system. Hormonal signaling, mobilization of energy stores, growth stimulation.

2. Modes of communication
    a. Autonomic nervous system – multiple connections to coordinate systemic regulation (innervation of organs, glands, blood vessels).
    b. Endocrine system – release of hormones into the blood stream (slow and widespread systemic effects).
    c. Point to point synaptic connections.

3. Organization of hypothalamic nuclei

4. Hypothalamic control of the pituitary, and the different functions mediated by the anterior and posterior pituitary

5. Hypothalamic control of feeding behavior
    a. The role of leptin in energy balance; ob/ob mice
    b. Hypothalamic circuits for the control of feeding behavior (arcuate nucleus, lateral hypothalamus, ventromedial hypothalamus)
    c. Bidirectional control of feeding behavior by AgRP and POMC neurons

Study Questions

1. Would you expect that leptin supplementation would always work to reverse obesity? Why or why not?

2. Describe the activity of AgRP neurons in a hungry animal as compared to an animal that is not hungry.

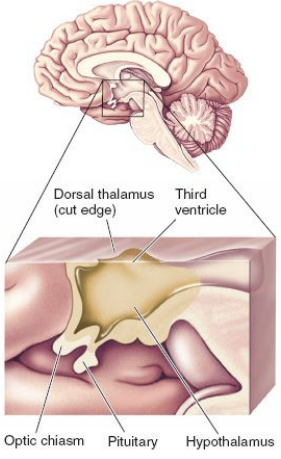
NEUROBIOLOGY AND BEHAVIOR II: INTRODUCTION TO NEUROSCIENCE

BioNB 2220

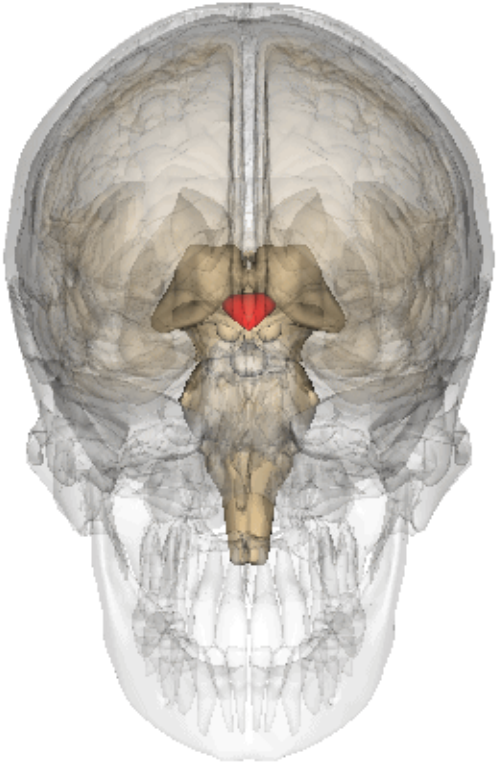
Lecture 35: Hypothalamus and Motivation

April 22, 2019

Melissa Warden, PhD



Hypothalamus: small but essential

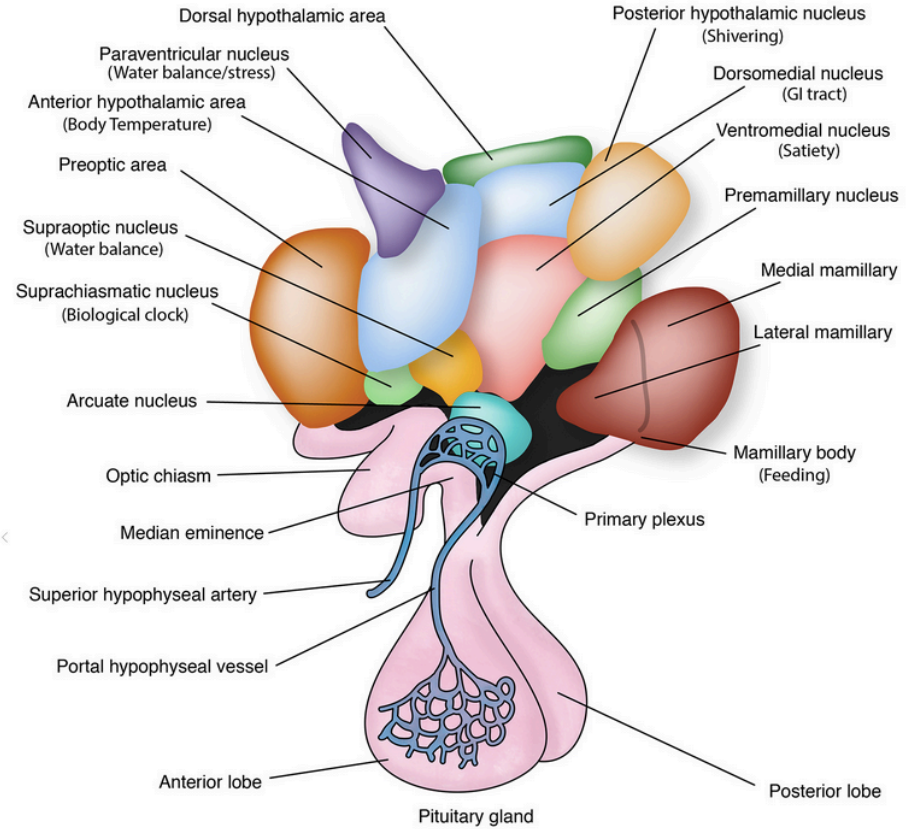


Weighs only 4 grams – brain weighs 1400 grams.

Essential life functions - tiny lesions can have have dramatic effects.

Functions of the hypothalamus

Energy homeostasis
Fluid homeostasis
Body temperature
Aggression
Parental behavior
Defensive behavior
Sexual behavior
Stress response
Sleep



DO NOT NEED TO MEMORIZE THIS!! Just for illustration

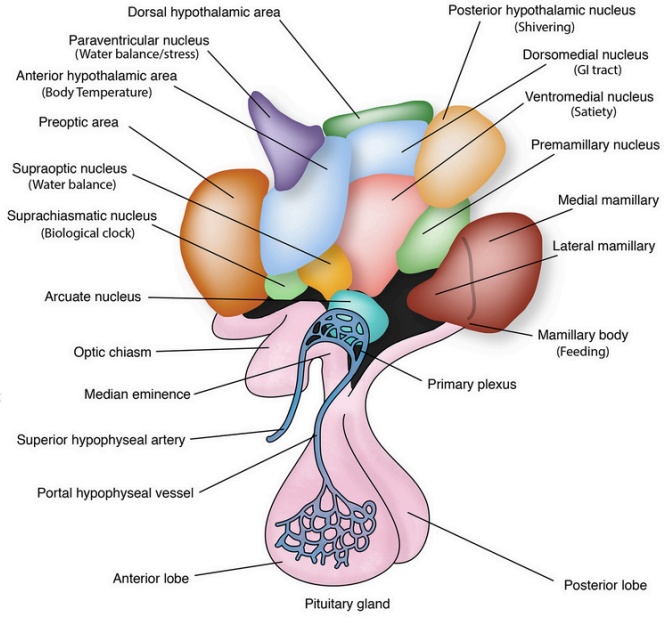
Stimulation of the hypothalamus

Drives a diverse array of behaviors that depend on the precise location of the electrode

Stimulation has been shown to cause animals to:

- Eat
- Drink
- Gnaw
- Attack
- Flee
- Growl/hiss
- Mate
- Seek warmth

wow



These are some of the strongest stimulation-induced behavioral responses in neuroscience

Ice swimmers in Poland. Hypothalamus orchestrates response to cold:

Autonomic: Shivering (generate heat in muscles), goosebumps (fluff up hair), turn blue (shunt blood to core)
Hormonal: Release thyroid-stimulating hormone
Behavioral: Move around. Eventually go inside and warm up.

Homeostasis

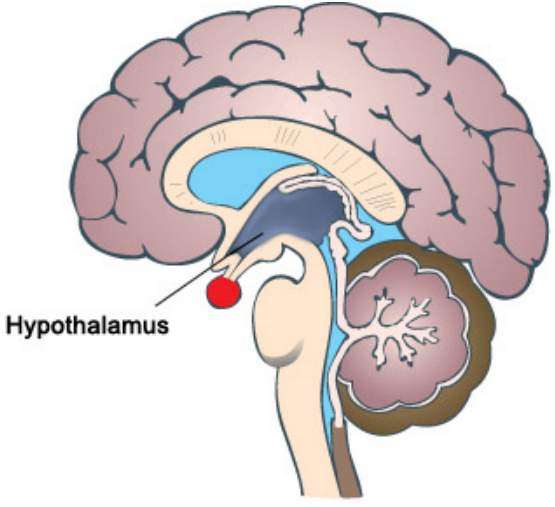
Homeostasis: process through by the body maintains a steady state (meaning: stay the same)

Examples:

blood volume, pressure

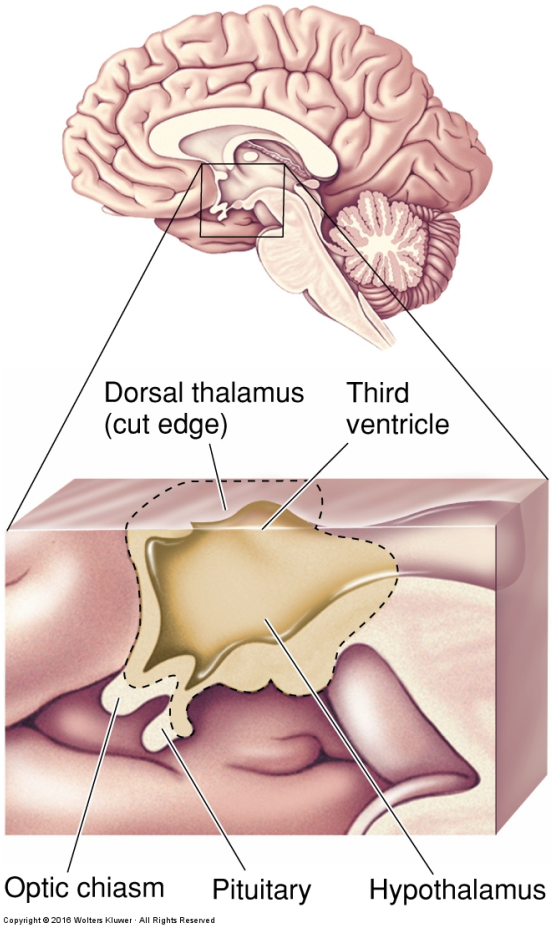
blood glucose level

body temperature



Many of these critical functions are controlled by the **hypothalamus**

Hypothalamic neuroanatomy



Hypothalamic inputs

Internal state: temperature, blood glucose, blood salt, blood volume, hormones (e.g. leptin), and more

Sensory systems: olfactory, gustatory, visual, auditory, and somatosensory systems

Highly processed inputs from limbic system (hippocampus, amygdala, frontal cortex)

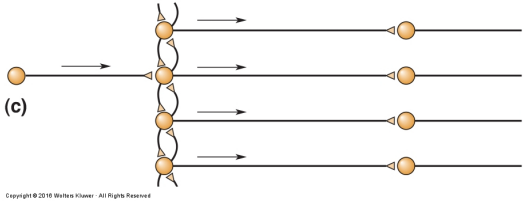
States, systems

Hypothalamic outputs

Controls → { ans; endocrine system; cns }

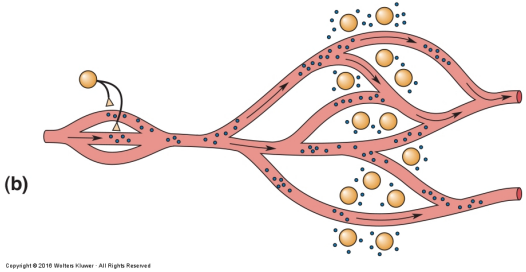
Control of the **autonomic nervous system**

- Sympathetic and parasympathetic nervous systems
- "Fight or flight" vs "rest and digest" (or "feed and breed")



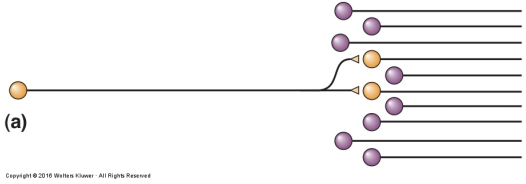
Control of the **endocrine system**

- hormonal signaling
- energy regulation
- fluid regulation
- stress response

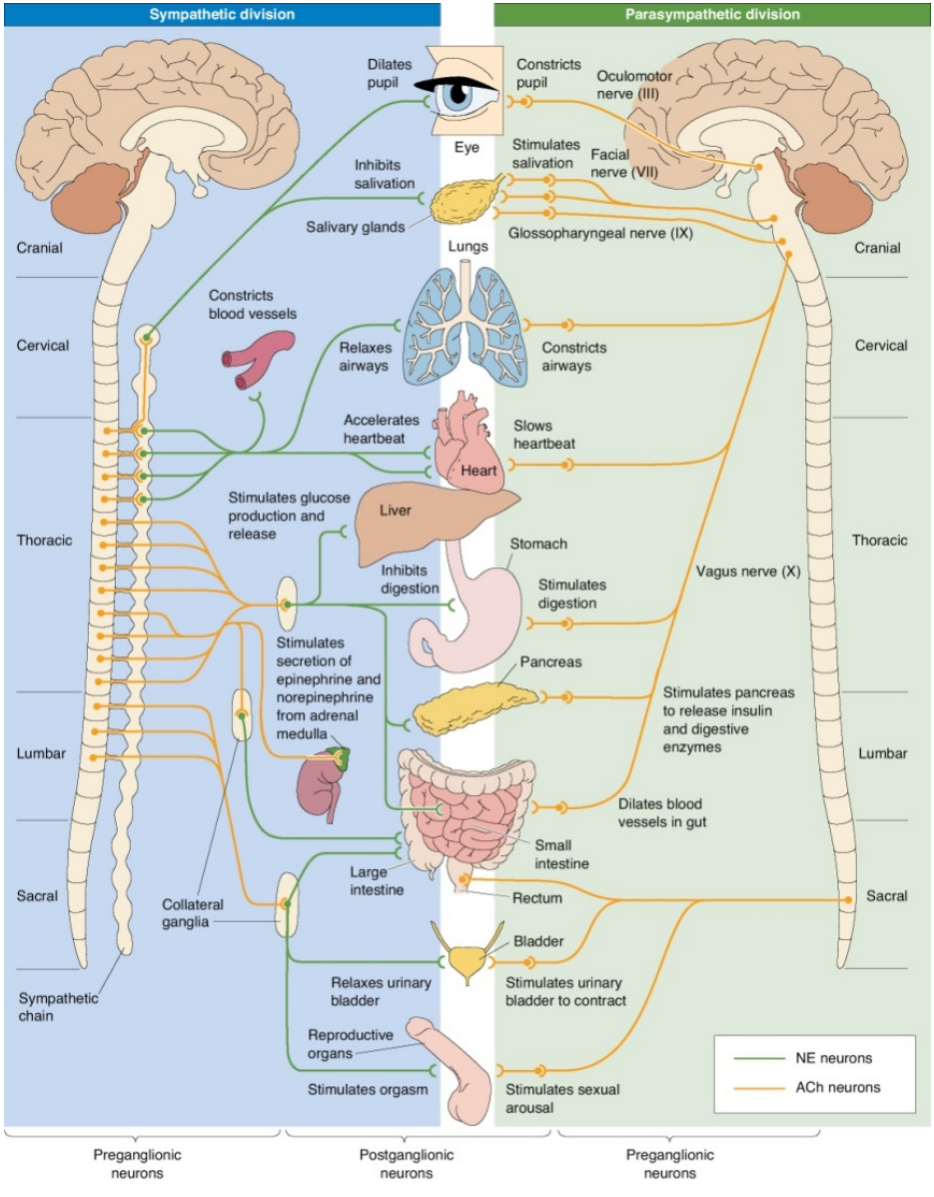


Control of the **central nervous system**

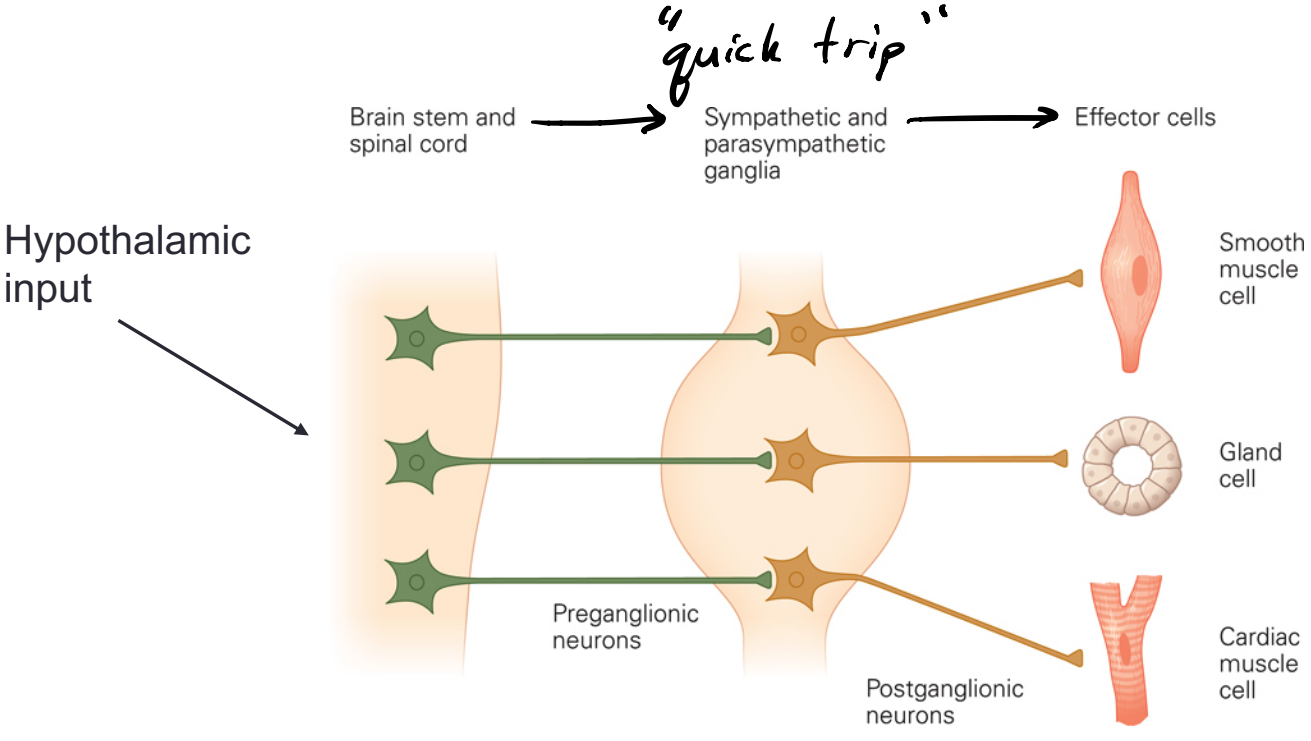
- Organization of behaviors essential for survival: reproduction, aggression, food/water intake, sleep



Autonomic nervous system



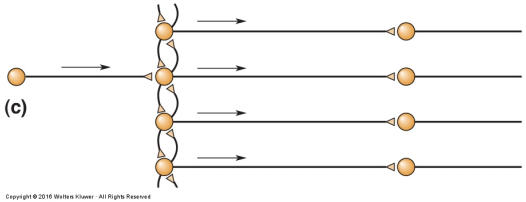
Autonomic pathways



Hypothalamic outputs

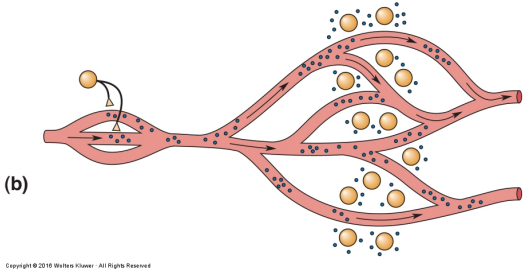
Control of the **autonomic nervous system**

- Sympathetic and parasympathetic nervous systems
- “Fight or flight” vs “rest and digest” (or “feed and breed”)



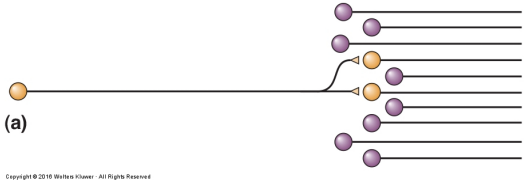
Control of the **endocrine system**

- hormonal signaling
- energy regulation
- fluid regulation
- stress response

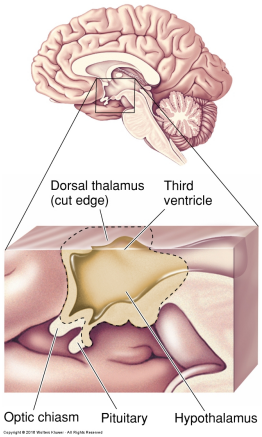


Control of the **central nervous system**

- Organization of behaviors essential for survival: reproduction, aggression, food/water intake, sleep



The hypothalamus controls the pituitary



Hypothalamus

'intermediary hormone released

'indirect pathway

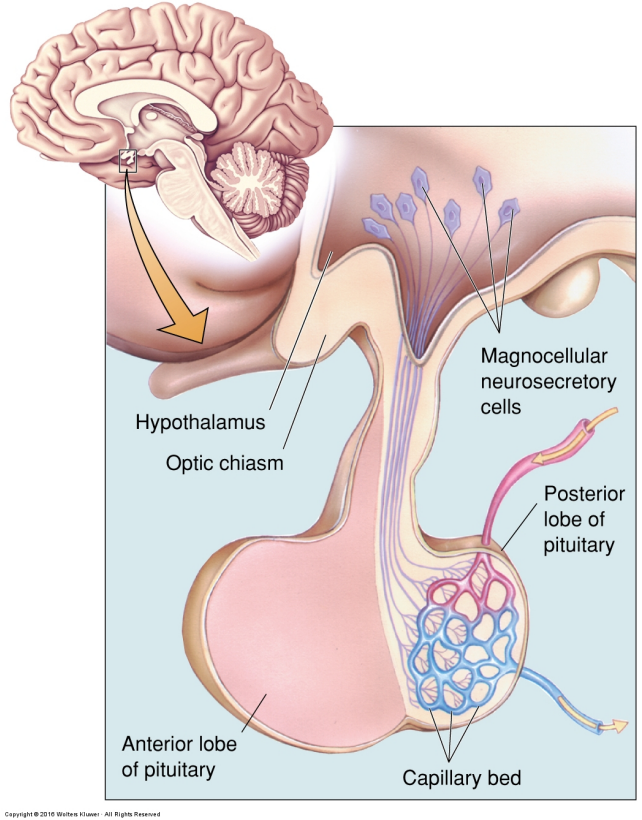
a direct pathway from hypothalamic neurons to bloodstream

Anterior Pituitary

Posterior Pituitary

Second hormone released

Hypothalamic control of the posterior pituitary

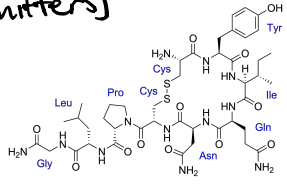


Direct hormone release into the general circulation

- Magnocellular (big cells) neurons secrete oxytocin and vasopressin directly into capillaries in the posterior lobe of the pituitary

(neuropeptides which function as neurotransmitters)

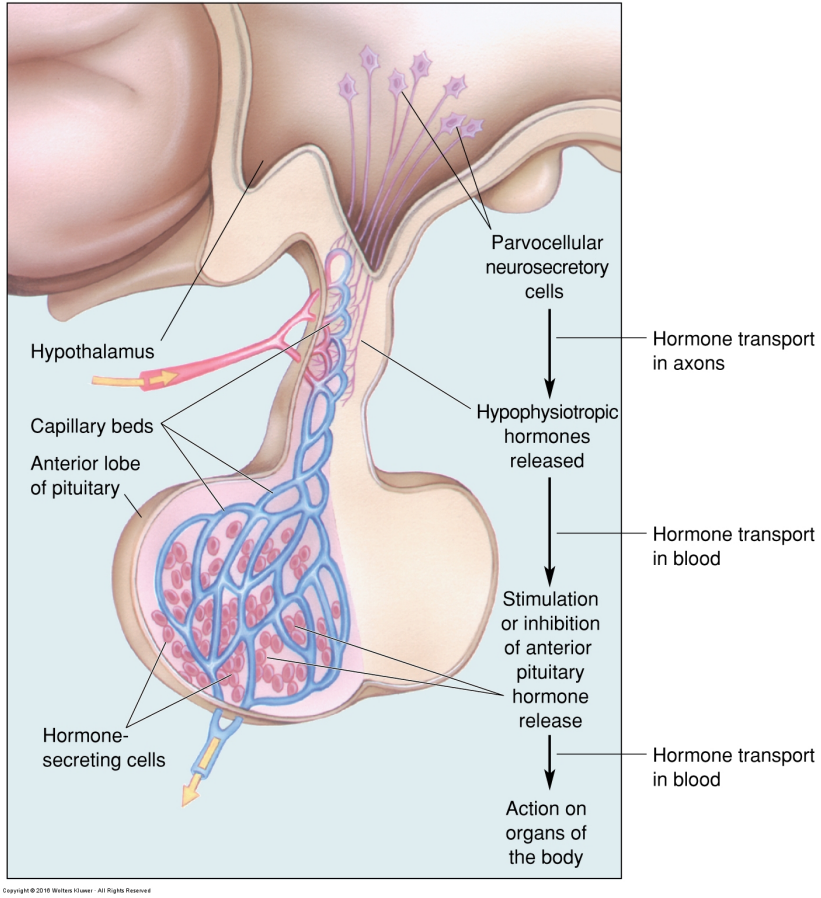
Oxytocin: uterine contraction during childbirth, milk let down during nursing



Oxytocin

Vasopressin (antidiuretic hormone): regulates blood volume and salt concentration

Hypothalamic control of the anterior pituitary



Indirect hormone release – first into local circulation, which triggers release into general circulation

Parvocellular (small cells) neurons secrete hormones into local capillary beds.

These hormones travel in this local bloodstream to the anterior lobe of the pituitary. Here, they trigger or inhibit the release of a variety of pituitary hormones from secretory cells into the general circulation.

Hormones of the anterior pituitary

Corticotropin-releasing hormone (CRH) release from hypothalamic neurons into anterior pituitary triggers release of ACTH into general circulation

Table 15.1 **Hormones of the Anterior Pituitary**

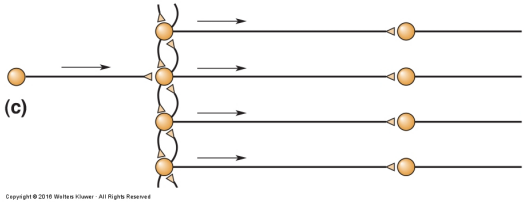
HORMONE	TARGET	ACTION
Follicle-stimulating hormone (FSH)	Gonads	Ovulation, spermatogenesis
Luteinizing hormone (LH)	Gonads	Ovarian, sperm maturation
Thyroid-stimulating hormone (TSH); also called thyrotropin	Thyroid	Thyroxin secretion (increases metabolic rate)
Adrenocorticotropic hormone (ACTH); also called corticotropin	Adrenal cortex	Cortisol secretion (mobilizes energy stores; inhibits immune system; other actions)
Growth hormone (GH)	All cells	Stimulation of protein synthesis
Prolactin	Mammary glands	Growth and milk secretion

DO NOT NEED TO MEMORIZE THIS!! Just for illustration

Hypothalamic outputs

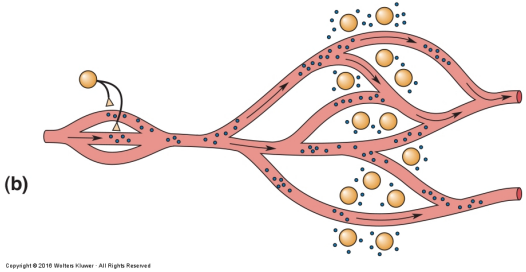
Control of the **autonomic nervous system**

- Sympathetic and parasympathetic nervous systems
- “Fight or flight” vs “rest and digest” (or “feed and breed”)



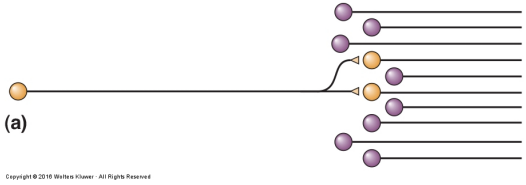
Control of the **endocrine system**

- hormonal signaling
- energy regulation
- fluid regulation
- stress response



Control of the **central nervous system**

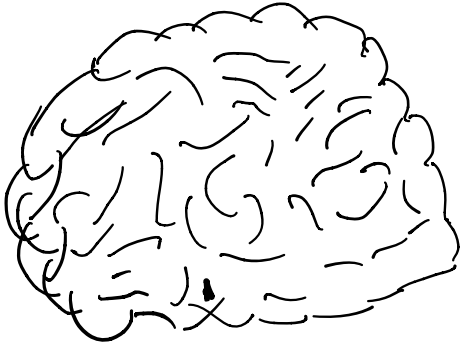
- Organization of behaviors essential for survival: reproduction, aggression, food/water intake, sleep



Feeding behavior and energy homeostasis

Activation of specific regions in the hypothalamus can cause animals to prioritize food seeking and consumption over other behaviors.

Very important! The brain would die just as quickly without glucose as it would without oxygen.



The brain is highly dependent on glucose

PET image of glucose utilization superimposed on structural MRI.

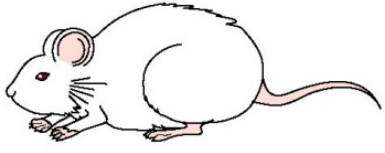
Brain cells begin dying within minutes if glucose is unavailable

Oxygen always surrounds us, but food is not always nearby

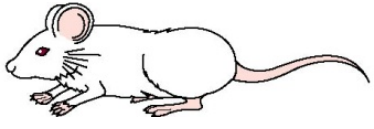
Energy balance and body fat

	Energy balance	Body fat
(a)	Intake = expenditure	Normal

(b)	Intake > expenditure	Obesity



(c)	Intake < expenditure	Starvation



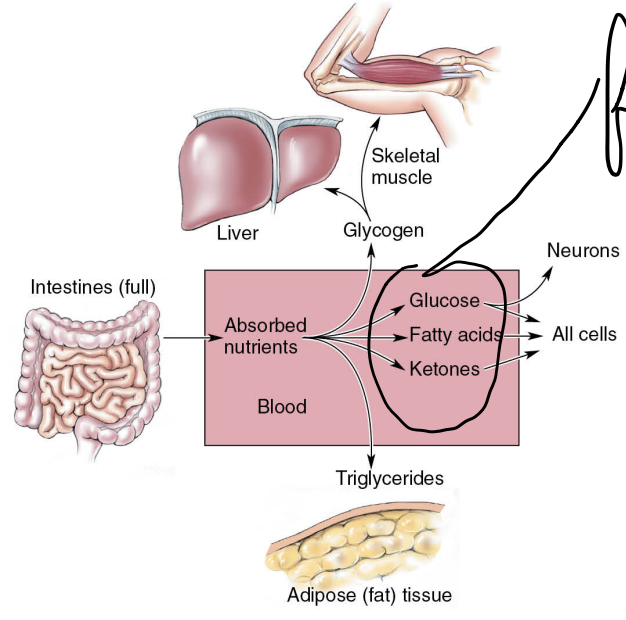
(a) Normal energy balance leads to normal adiposity.

(b) Prolonged positive energy balance leads to obesity.

(c) Prolonged negative energy balance leads to starvation.

This system must be regulated by the amount of energy in storage and the rate of replenishment

Loading and emptying the body's energy reserves



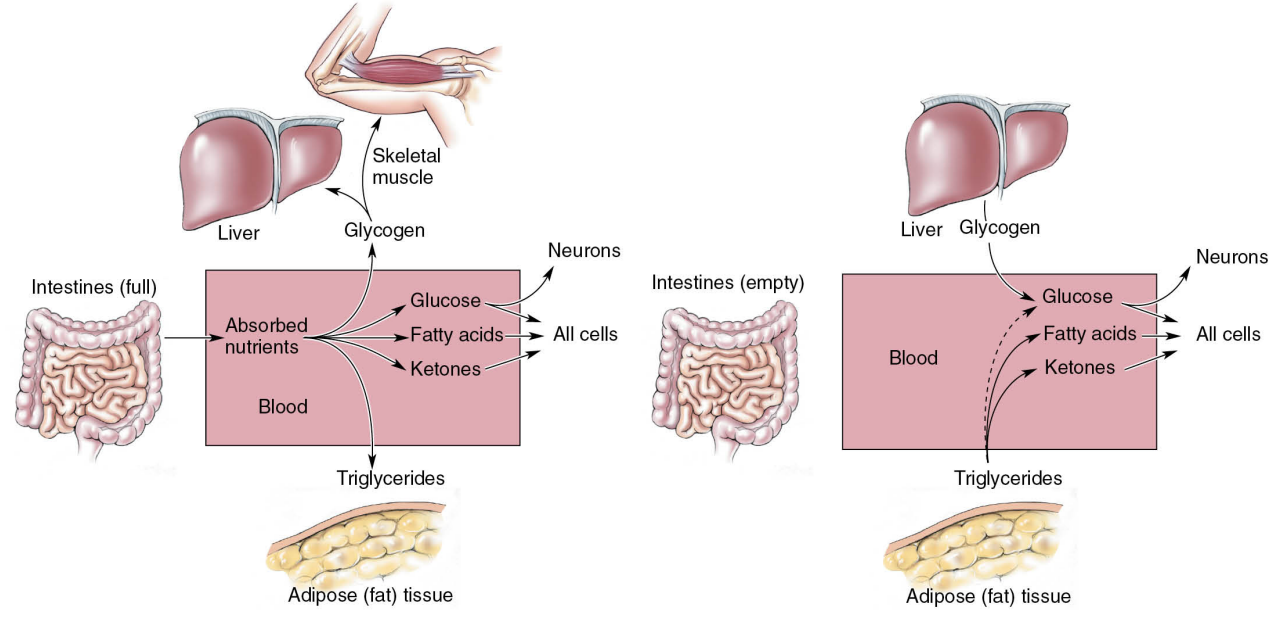
fuel for cells

(a) Anabolism during the prandial state

Prandial = during meal consumption

During and after a meal, excess energy is stored as glycogen or triglycerides.

Loading and emptying the body's energy reserves



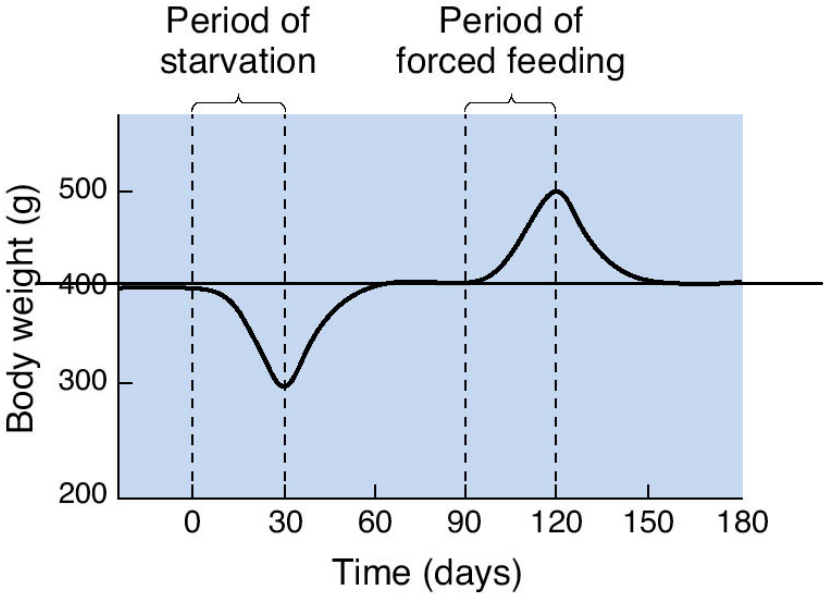
(a) Anabolism during the prandial state

(b) Catabolism during the postabsorptive state

During and after a meal, excess energy is stored as glycogen or triglycerides.

During the time between meals, glycogen and triglycerides are broken down into smaller molecules that can be used as fuel by the cells of the body

Body weight is maintained around a set value

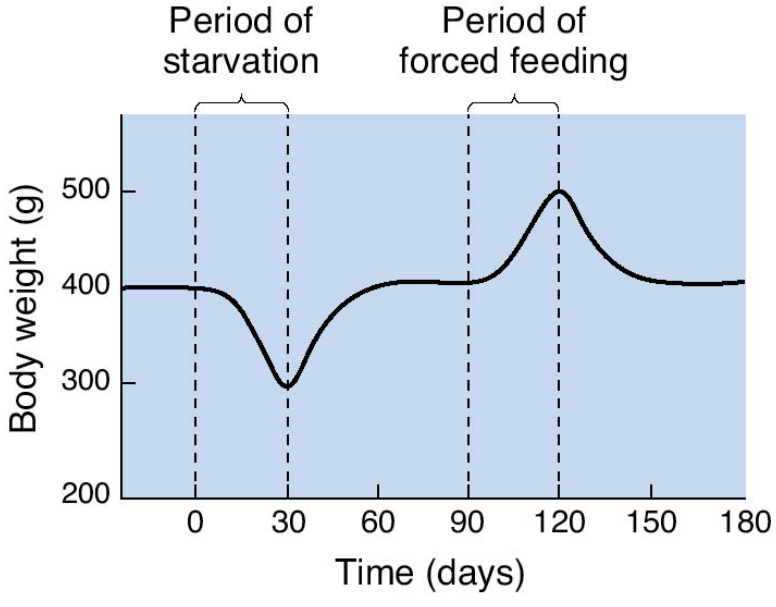


Body weight is normally very stable.

If an rat is force-fed, it will gain weight. However, the weight is lost as soon as the animal can regulate its own food intake.

Similarly, weight lost during a period of starvation is rapidly gained when food is freely available.

Body weight is maintained around a set value



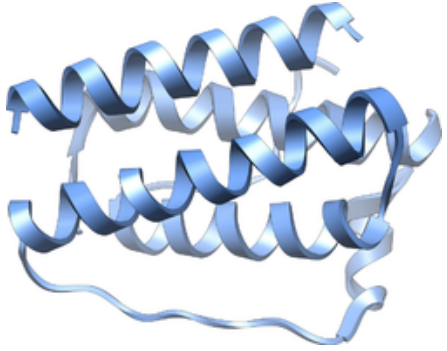
How is this set-point maintained? Very interesting question!

Researchers observed a connection between body fat and feeding behavior.

Lipostatic hypothesis: fat sends a signal to the brain to regulate feeding behavior.

More fat = less feeding until reach set point.

The reversal of obesity in ob/ob mice by a blood-borne factor: leptin



Both of these mice have a defect in the ob gene that encodes the fat hormone leptin.

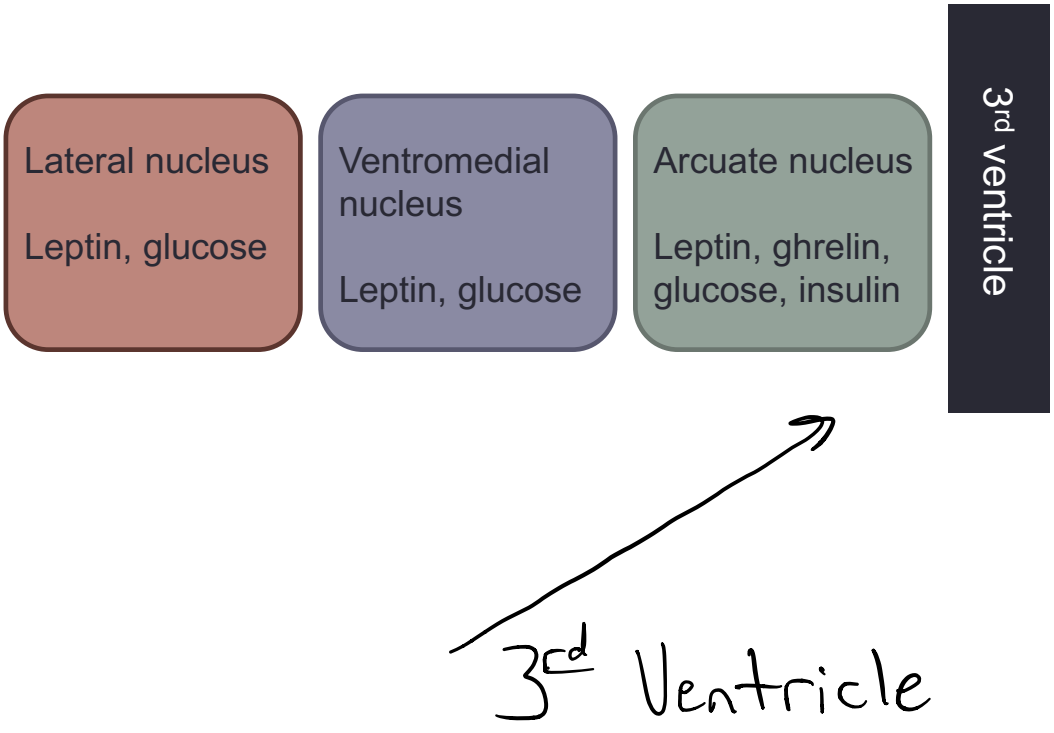
The animal on the right received daily leptin replacement treatment, which prevented the obesity that is apparent in the animal on the left.

Leptin is released by adipocytes and regulates body mass by acting directly on neurons in the hypothalamus that decrease appetite and increase energy expenditure.

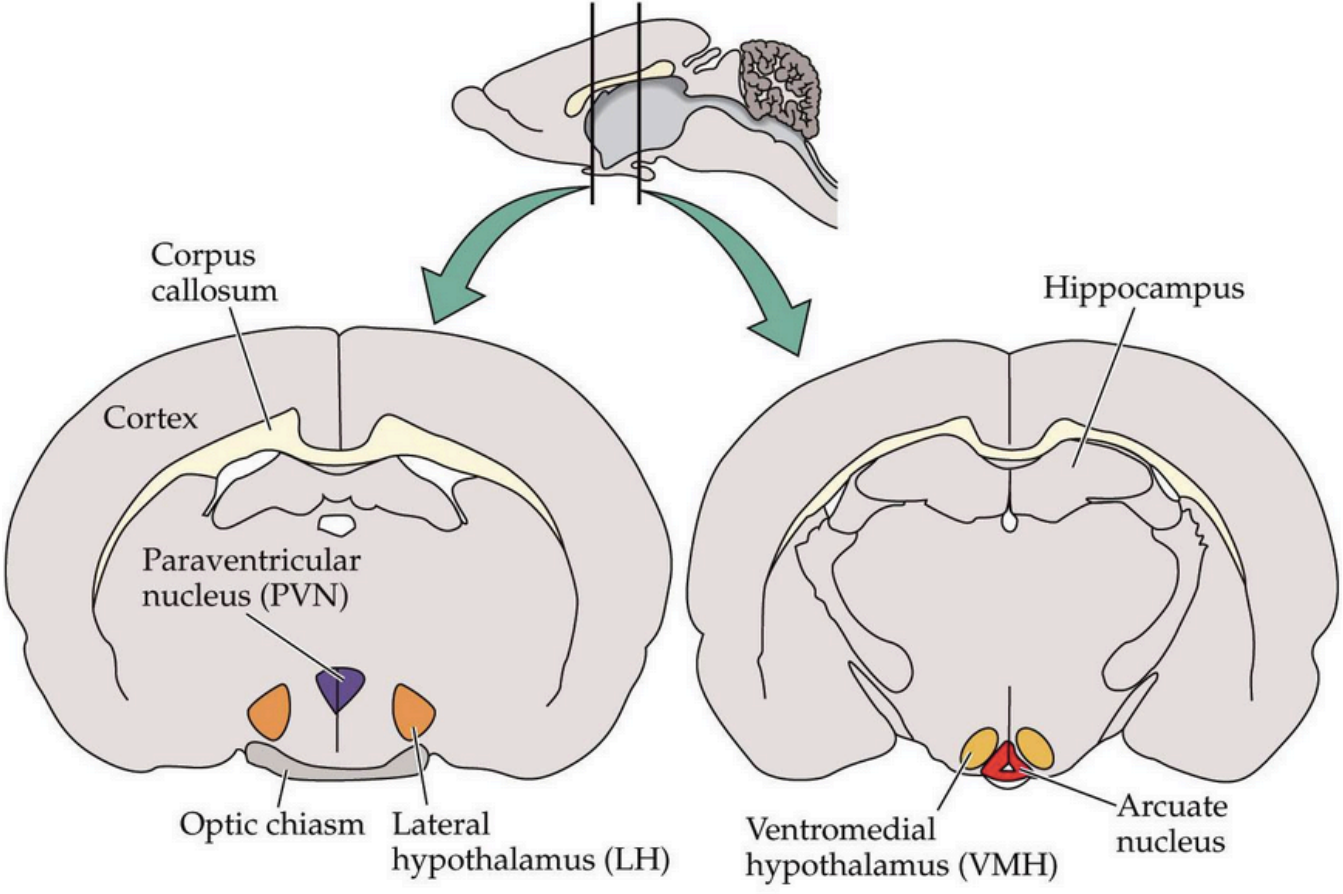
The effect of hormone replacement in a leptin-deficient person

Daily leptin treatment begun at age 5 (left) brought this girl's weight down to a normal level, shown here at age 9 (right)

Hypothalamic interoceptors: primary sensory neurons for internal body state

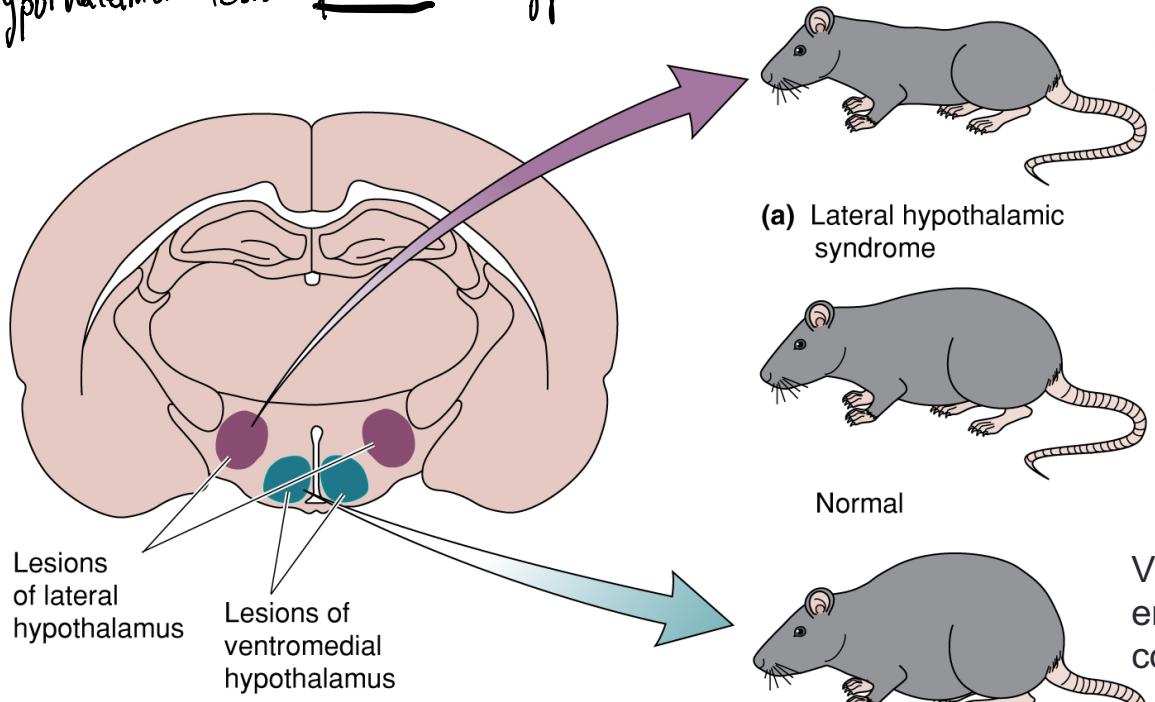


Hypothalamic nuclei important for the control of feeding and energy balance



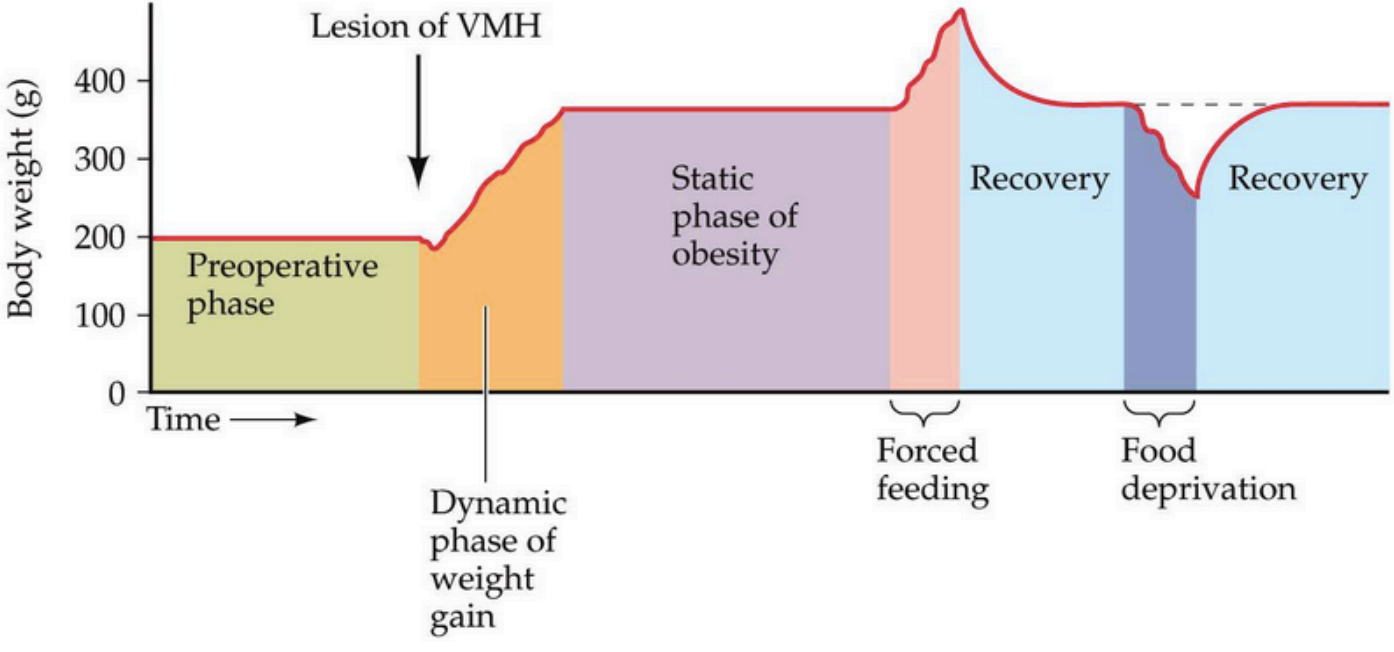
Hypothalamic lesions and feeding behavior

Lateral hypothalamus lesion promotes energy conservation

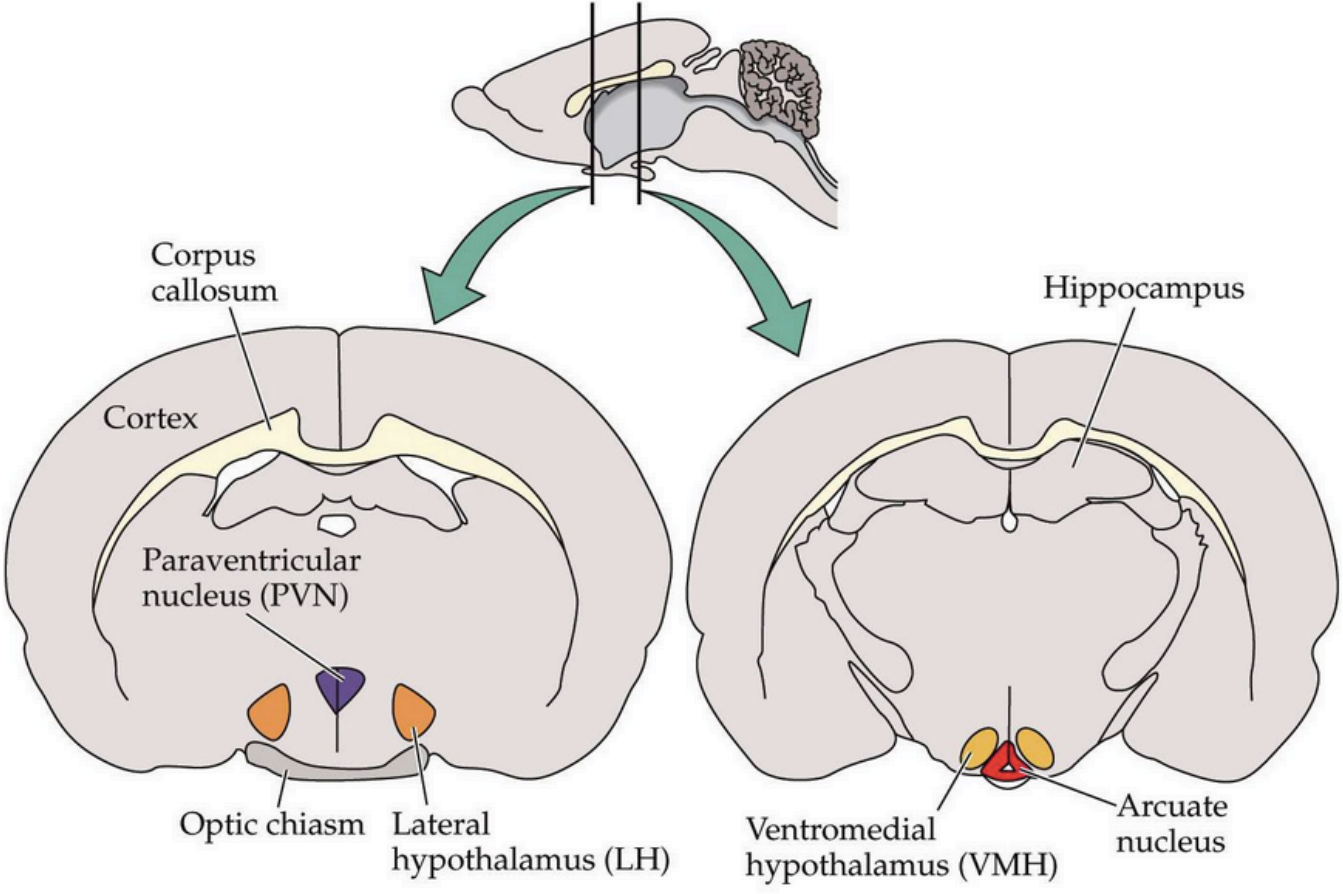


Ventromedial hypothalamus inhibits energy conservation

Ventromedial hypothalamus lesions induce a new set point



Hypothalamic nuclei important for the control of feeding and energy balance



Neural subtypes in the arcuate nucleus

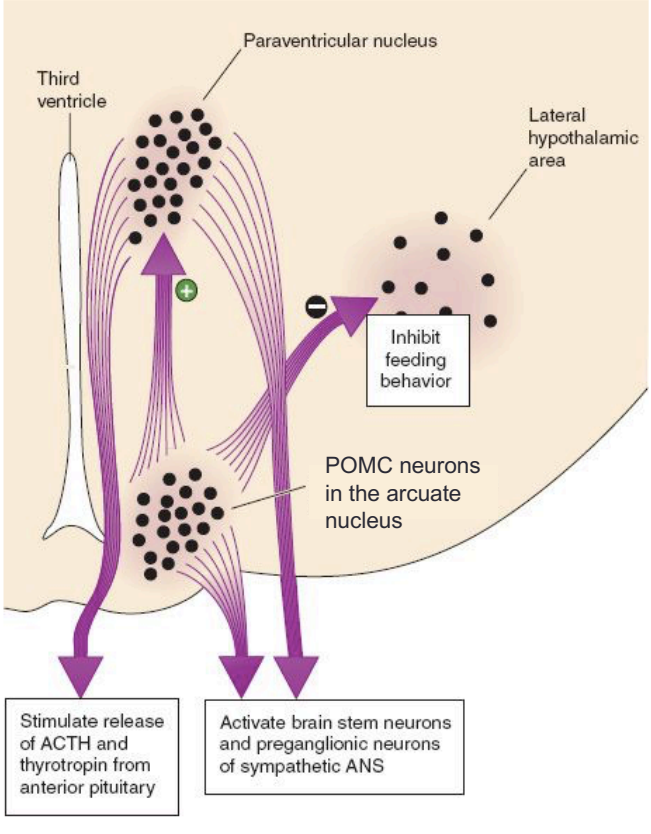
AgRP (agouti-related peptide) neurons

- Characterized by expression of AgRP (agouti-related peptide)
- Leptin inhibits these neurons
- Stimulating these neurons increases feeding, decreases metabolic rate

POMC (pro-opiomelanocortin) neurons

- Characterized by expression of αMSH (alpha melanocyte stimulating hormone) peptide
- Leptin activates these neurons
- Stimulating these neurons decreases feeding, increases metabolic rate

The response to elevated leptin levels



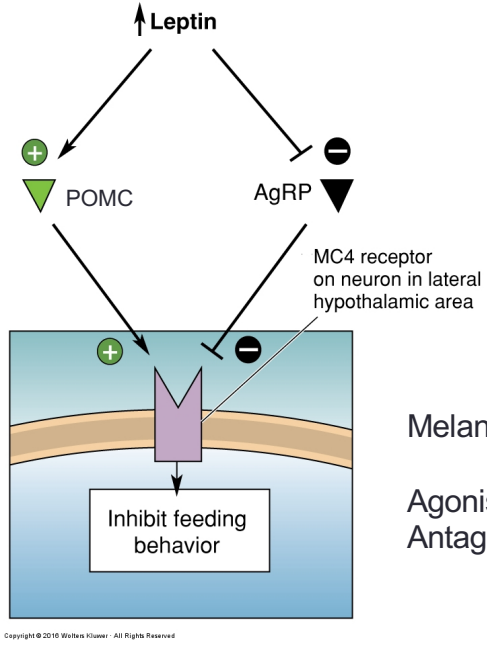
Coordinated response to elevated leptin levels (hormonal, autonomic, behavior)

POMC projection to lateral hypothalamic area inhibits feeding behavior

POMC projection to paraventricular nucleus results in increased secretion of thyroid stimulating hormone and adrenocorticotropic hormone to raise metabolic rate

Paraventricular nucleus and arcuate nucleus also project to preganglionic neurons to activate sympathetic nervous system and raise metabolic rate.

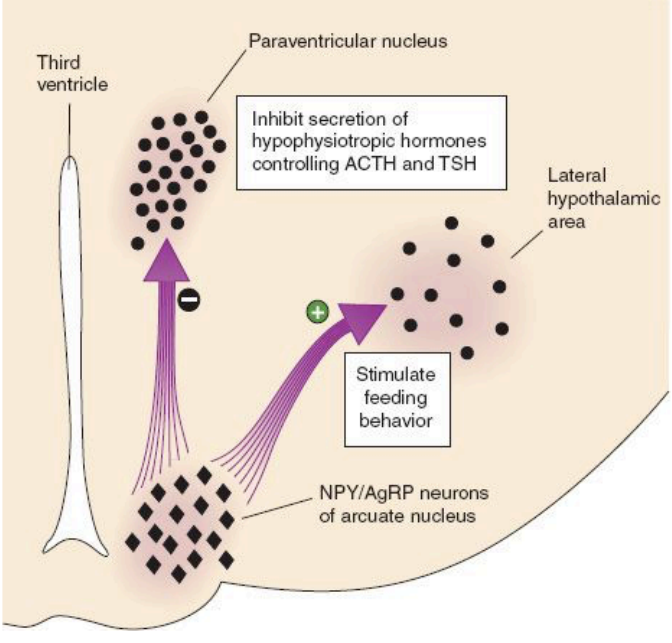
Lateral hypothalamic neurons express the melanocortin 4 (MC4) receptor



Melanocortin 4 receptor

Agonist: αMSH (from POMC neurons)
Antagonist: AgRP (from AgRP neurons)

The response to decreased leptin levels



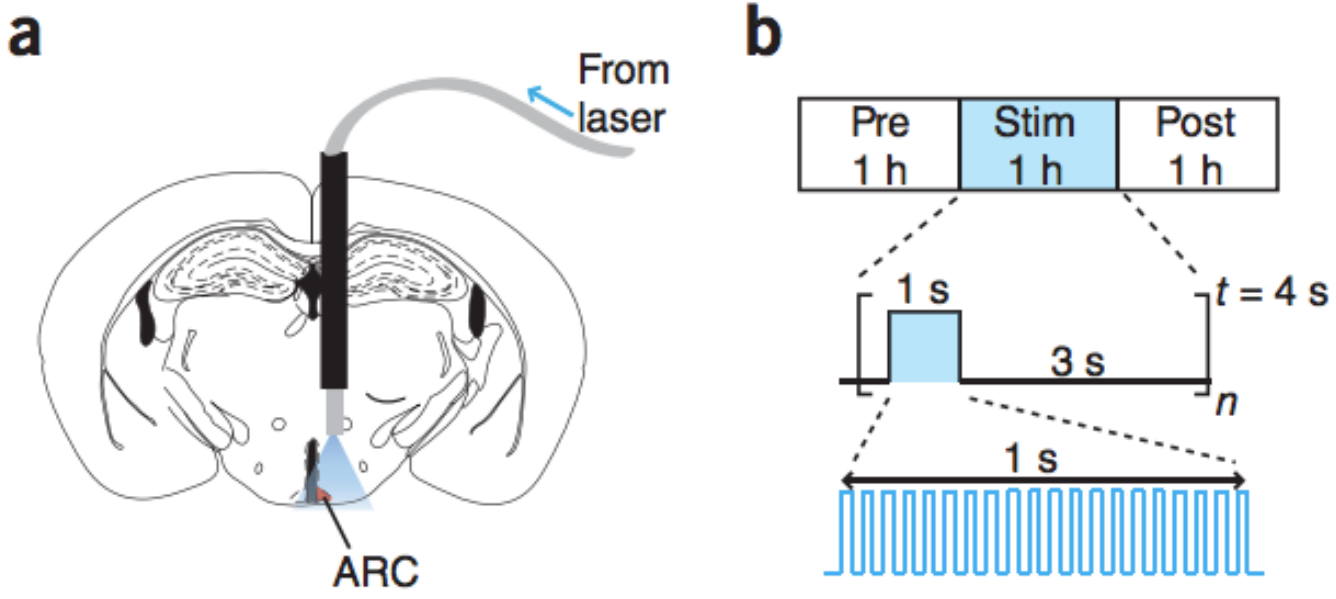
Coordinated response to decreased leptin levels (hormonal, autonomic, behavioral)

AgRP projection to lateral hypothalamic area stimulates feeding behavior

AgRP projection to paraventricular nucleus inhibits secretion of TSH and ACTH hormone to decrease metabolic rate

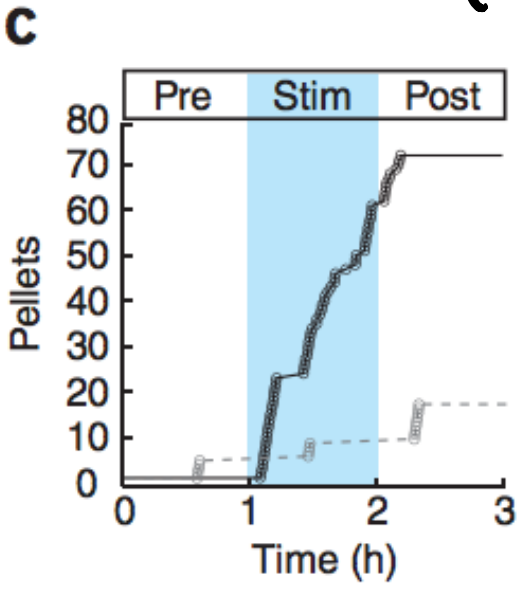
Parasympathetic nervous system activated

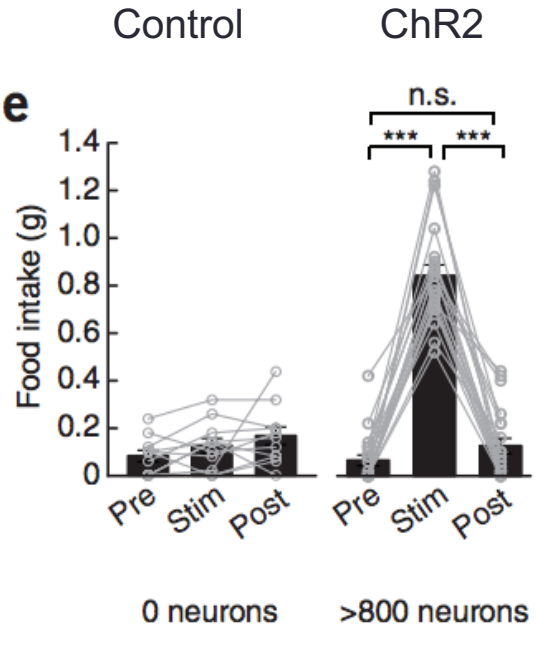
Optogenetic stimulation of AgRP neurons in the arcuate nucleus increases feeding



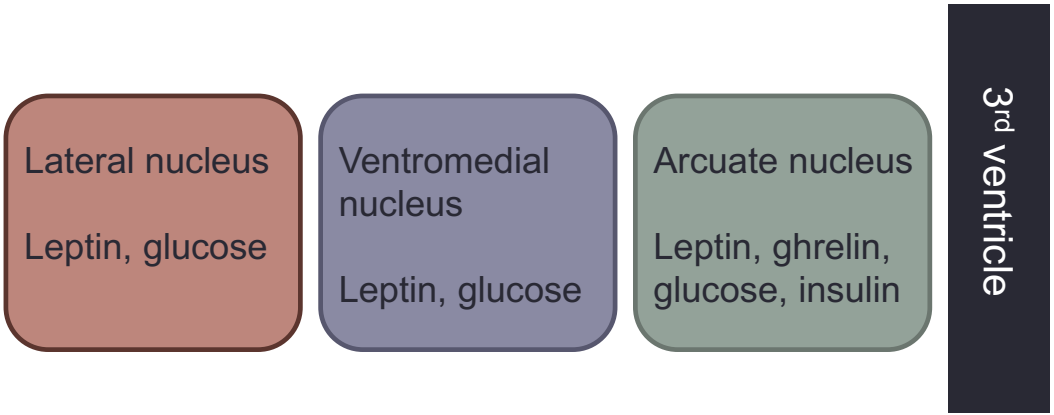
Optogenetic stimulation of AGRP neurons in the arcuate nucleus increases feeding

Profound

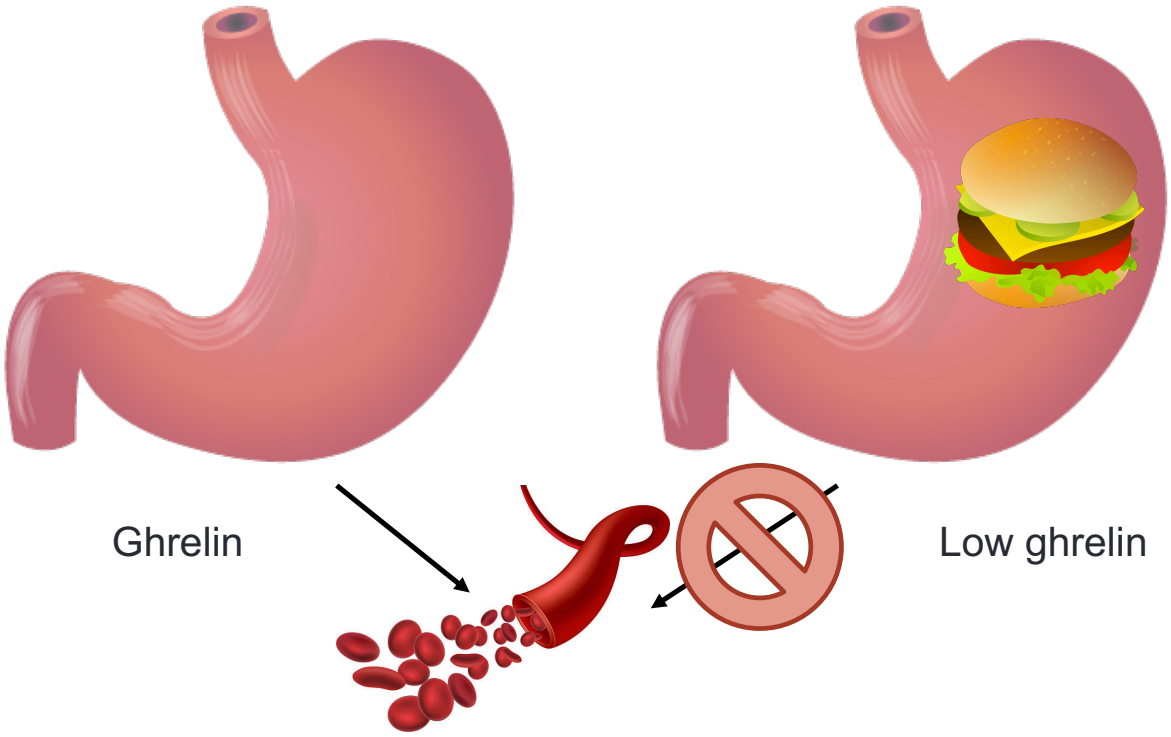




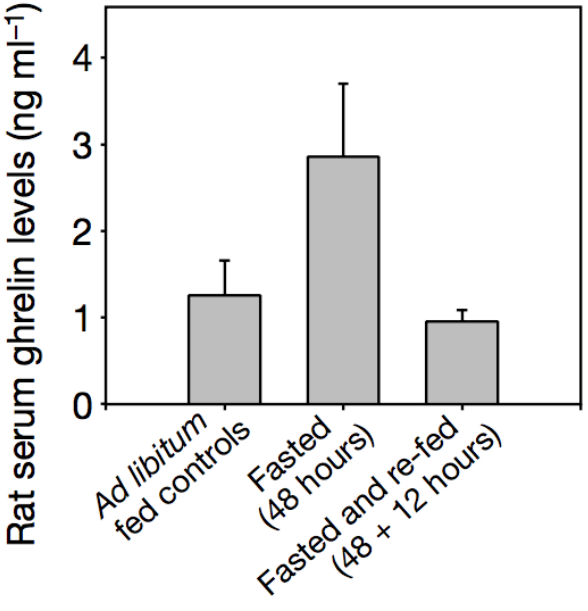
Hypothalamic interoceptors: primary sensory neurons for internal body state



Ghrelin is secreted by cells in the wall of the stomach when it is empty

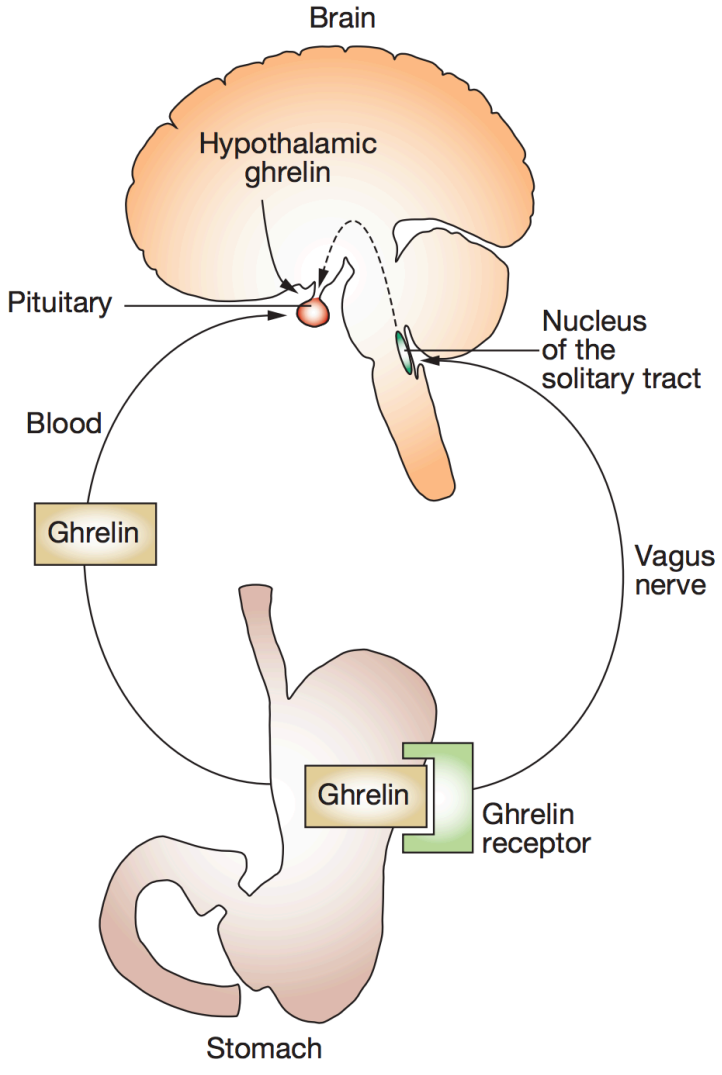


Serum ghrelin is high when hungry

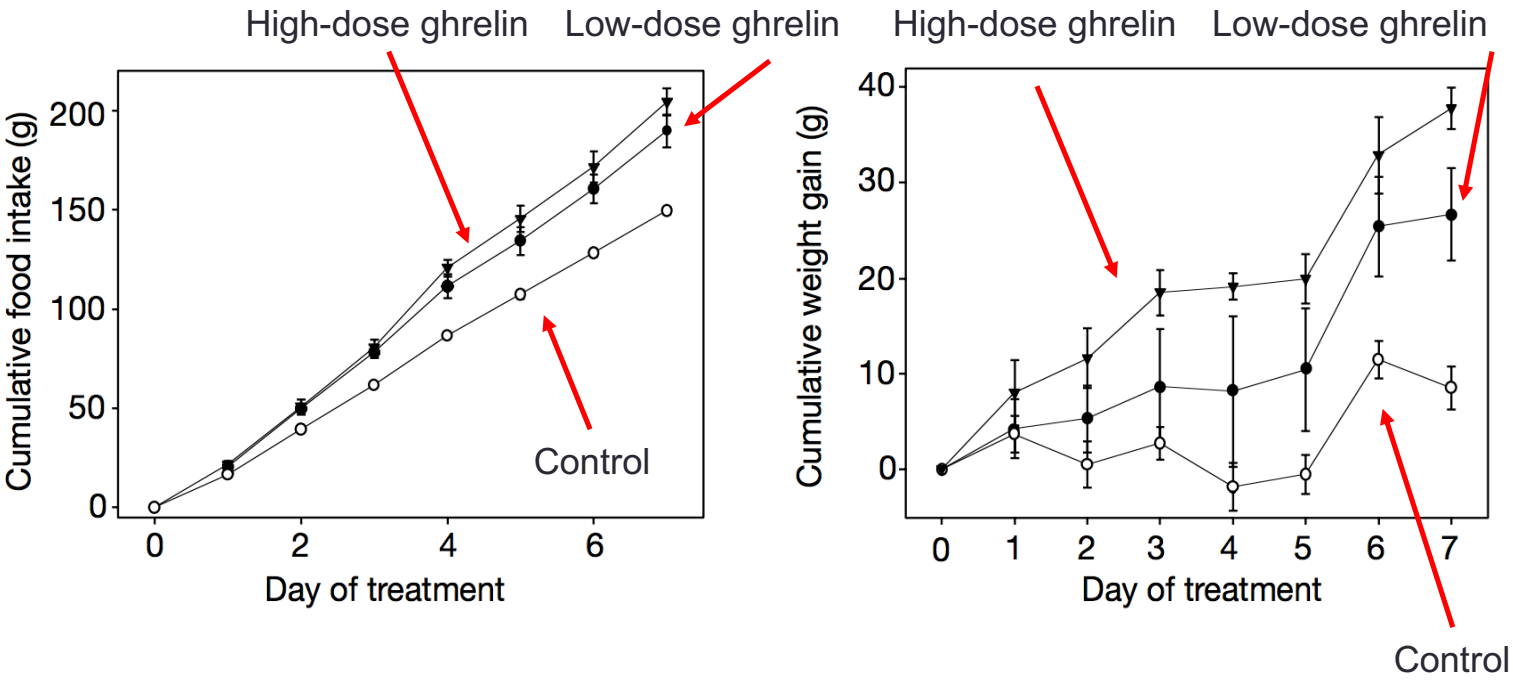


Ghrelin is secreted by the stomach

Ghrelin makes you hungry, decreases metabolic rate, promotes fat storage

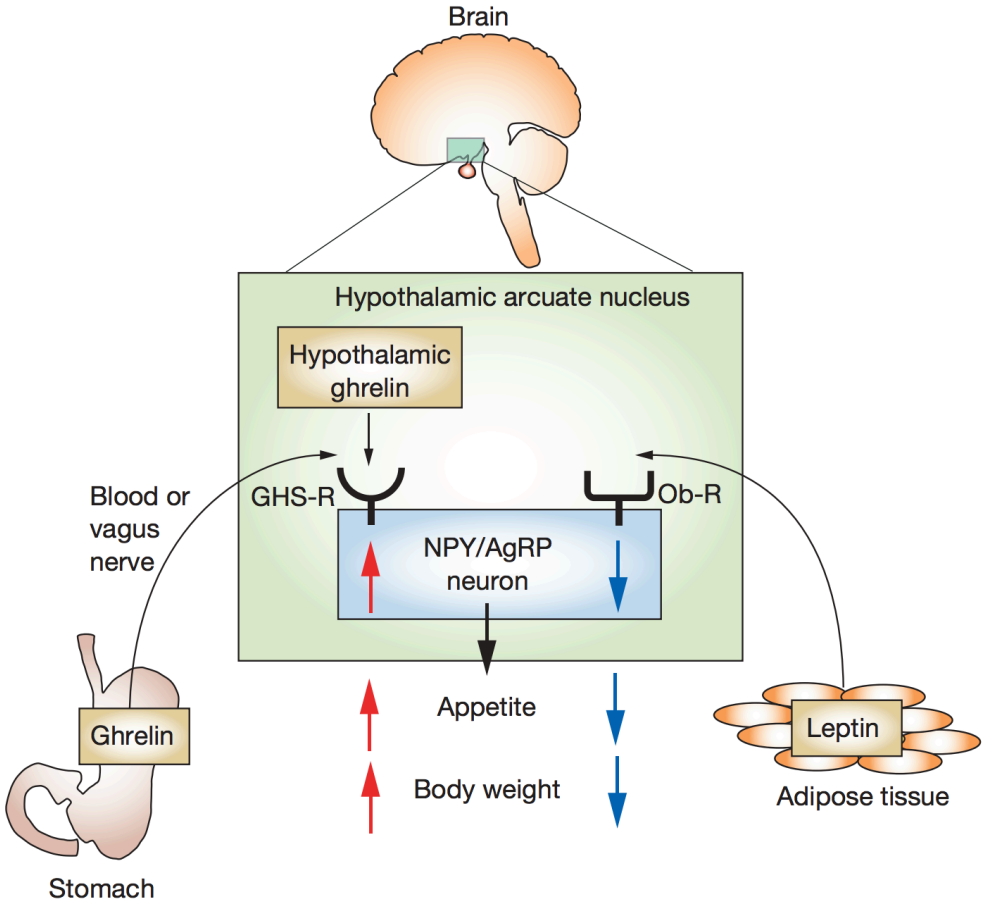


Ghrelin makes rats eat more and gain weight



Each day, rats were given an injection of ghrelin directly into the cerebral ventricle

Appetite regulation by ghrelin and leptin



Conclusions

The hypothalamus is important for homeostatically regulating many important bodily functions.

The hypothalamus can control hormones, the autonomic system, and the central nervous system (behavior) to maintain homeostasis.

Energy balance is one of the best understood examples of hypothalamic function

- Should understand what leptin is
- Should understand how leptin affects hypothalamic function