Hypothalamus and Limbic System

Daniel Salzman
Center for Neurobiology and Behavior
cds2005@columbia.edu
212-543-6931 ext. 400
Pages 972-1013 in PNS

Lecture I: The hypothalamus

- Overview of hypothalamus and limbic system purpose, function and some examples of clinical conditions mediated by hypothalamic and/or limbic system neural circuitry.
- Brief overview of hypothalamus anatomy.
- Information flow into and out of the hypothalamus: inputs, outputs and pathways.
- Servo-control systems as a model for hypothalamic function.
- Two detailed examples of hypothalamic function:
  - Temperature regulation
  - Feeding behavior

Hypothalamus and Limbic System: Homeostasis

- A major function of the nervous system is to maintain homeostasis, or the stability of the internal environment.
- The hypothalamus, which comprises less than 1% of the total volume of the brain, is intimately connected to a number of structures within the limbic system and brainstem.
- Together the hypothalamus and the limbic system exert control on the endocrine system the autonomic nervous system to maintain homeostasis.

Hypothalamus and Limbic System: Emotion and Motivated Behavior

- Emotions and motivated behavior are crucial for survival:
  - Emotional responses modulate the autonomic nervous system to respond to threatening stimuli or situations.
  - Emotional responses are adaptive. If you are prepared to deal with threatening stimuli, you are more likely to survive and reproduce.
  - Motivated behavior underlies feeding, sexual and other behaviors integral to promoting survival and reproduction.
  - The hypothalamus and limbic system mediate these behaviors.

Hypothalamus and Limbic System: Clinical Context

- A large number of clinical conditions have symptoms that arise from hypothalamic and/or limbic system brain circuits.
- For example, regardless of medical or dental specialty, all of you will encounter patients who have one or more of the following:

Hypothalamus and Limbic System: Clinical Context (cont.)

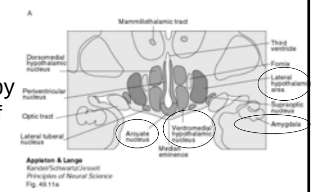
- Fever
  - Need to detect temperature changes and modulate the autonomic nervous system to either retain or dissipate heat.
- Addiction
  - Many recreational drugs work through neural pathways involved in reward and motivated behavior that form an important part of limbic system function.
- Anxiety Disorders
  - Many anxiety disorders, such as Panic Disorder and Post-traumatic stress disorder have physiological symptoms mediated by the autonomic nervous system and by the limbic system.
- Obesity.
  - Feeding behavior is in part controlled by the hypothalamus, and interactions between limbic reward circuitry and the hypothalamus are important to feeding behavior.

Hypothalamus: Integrative Functions

- The hypothalamus helps regulate five basic physiological needs:
  1) Controls blood pressure and electrolyte (drinking and salt appetite).
  2) Regulates body temperature through influence both of the autonomic nervous system and of brain circuits directing motivated behavior (e.g. behavior that seeks a warmer or cooler environment).
  3) Regulates energy metabolism through influence on feeding, digestion, and metabolic rate.
  4) Regulates reproduction through hormonal control of mating, pregnancy and lactation.
  5) Directs responses to stress by influencing blood flow to specific tissues, and by stimulating the secretion of adrenal stress hormones.

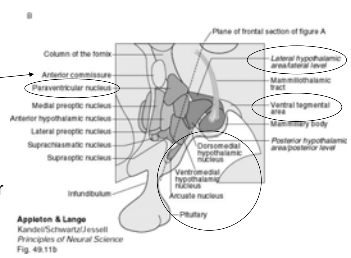
Hypothalamus Anatomy

- Lines the walls of 3rd ventricle, above the pituitary.
- Divided into medial and lateral regions by the fornix, bundles of fiber tracts that connect the hippocampus to the mamillary bodies.



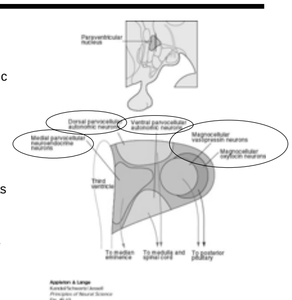
Hypothalamus Anatomy

- The hypothalamus is limited at the anterior by the optic chiasm and anterior commissure, and at the posterior by the mamillary bodies.
- The paraventricular nucleus is of particular importance, as it controls both endocrine and autonomic processes.

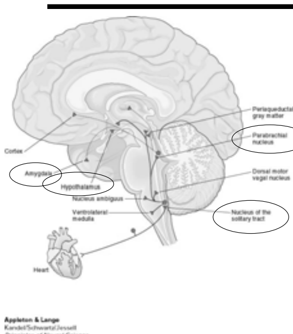


The Paraventricular Nucleus

- Contains two types of cells:
  - Parvocellular
    - Medially, parvocellular neurons secrete hypothalamic releasing hormones, such as CRH.
    - Dorsally and ventrally, neurons project to the medulla and spinal cord to exert autonomic control. Some of these neurons secrete oxytocin and vasopressin, which can act as neuromodulators.
  - Magnocellular
    - Two distinct populations control endocrine function by secreting oxytocin and vasopressin directly into the posterior pituitary.



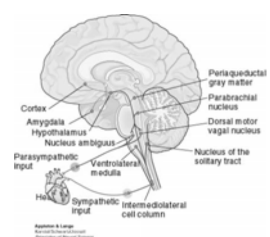
What pathways deliver visceral information to the hypothalamus?



- The nucleus of the solitary tract receives visceral information from cranial nerves VII, IX, and X.
- Besides directly regulating certain autonomic functions, the nucleus of the solitary tract relays information to the parabrachial nucleus, which projects to the hypothalamus and other limbic structures.

What pathways control autonomic responses?

- Direct control of autonomic preganglionic neurons arises from the hypothalamus, the parabrachial nucleus, the nucleus of the solitary tract, and neurons in the ventrolateral medulla.
- Indirect control of autonomic responses originates from the cortex, amygdala , and the periqueductal gray matter.



Hypothalamus: Inputs and Outputs

	Neural Output	Hormonal Output
Neural Input	Controls the autonomic nervous system (e.g. emotion)	Controls release of oxytocin for milk lactaction
Hormonal Input	Used for drives and motivated behavior	Controls release of vasopressin for fluid regulation

Neural Input and Hormonal Output: oxytocin release and lactation

- Supraoptic and paraventricular nuclei contain magnocellular neurons that secrete oxytocin into the general circulation in the posterior pituitary.
- When a baby sucks on a mother's nipples, mechanoreceptors are stimulated. These receptors activate neurons that project to the magnocellular hypothalamic neurons, causing those cells to fire brief bursts, releasing oxytocin.
- Oxytocin, in turn, increases contraction of myoepithelial cells in the mamillary glands, leading to milk ejection.

Vasopressin release: an example of humoral input and humoral output

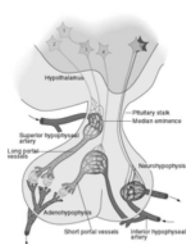
- Magnocellular neurons containing vasopressin are sensitive to changes in blood tonicity, releasing more vasopressin upon water loss. Vasopressin increases water resorption in the kidney.
- Transecting the neural inputs to the hypothalamus does not disrupt the ability to increase vasopressin release upon water loss. This finding confirms that the signal used by hypothalamic neurons is humoral, and not neural, to modulate vasopressin release.

Hormonal input and Neural output: Endocrine Control of Behavior

- Classic experiments by Geoffrey Harris demonstrated how hormones may influence motivated behavior.
- Harris and colleagues implanted crystals of stilboestrol esters in the hypothalamus of ovariectomized cats. These cats had atrophic genitalia. Implantation of these esters elicited full mating behavior from the cats. Thus although the cats were anestrous from the point of view of the endocrine system in the periphery, the animals were estrous from the point of view of the CNS.
- These experiments established the concept that the brain is a target for specific feedback action from gonadal steroids, leading to modulations in motivated behavior through neural circuits almost certainly connected to the hypothalamus.

What hypothalamic pathways influence endocrine function?

- The hypothalamus controls the endocrine system by secreting oxytocin and vasopressin into the general circulation from nerve terminals ending in the posterior pituitary (5 in figure).
- The hypothalamus also secretes regulatory hormones into local portal circulation that drains into the anterior pituitary (3 and 4).
- Finally, some hypothalamic neurons influence peptidergic neurons, synapsing at those neurons cell bodies or axon terminals (1 and 2).



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 49.12

How do we know that regulatory factors travel through the portal circulation to the pituitary?

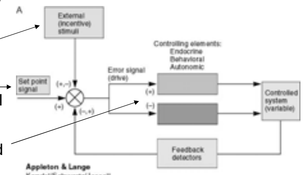
- Geoffrey Harris was a famous neurobiologist responsible for showing that that the hypothalamus exerts control of the pituitary gland.
- In the 1950s, Harris and colleagues carried out a series of transplantation experiments.
  - It had already been shown that endocrine glands (e.g. testes, ovaries, adrenal cortex) can function in a regulated manner when transplanted to a remote location in the body.
  - Harris showed that when the anterior pituitary was transplanted away from its original site, it did not function normally.

How do we know that regulatory factors travel through the portal circulation to the pituitary (2)?

- Harris and colleagues then transplanted the anterior pituitary back under the midline hypothalamus, near the portal vessels. Normal endocrine function was restored, and subsequent histology showed that the restoration of function depended upon the successful revascularization of the anterior pituitary by the primary capillary plexus of portal vessels in the median eminence.
- These experiments provided definitive proof of the functional importance of the portal vascular system in connecting hypothalamic regulation to anterior pituitary function.

Homeostatic processes: servo-control systems

- 3 main mechanisms in the hypothalamus make its function analogous to servo-control systems
  - Receives sensory information from external body
  - Compares sensory information with biological set points.
  - Adjusts an array of autonomic, endocrine and behavioral responses aimed at maintaining homeostasis



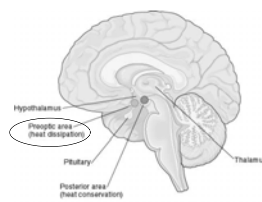
Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 51.01a

Temperature regulation is a good example of a hypothalamic servo-control system

- To regulate temperature, integration of autonomic, endocrine, and skelatomotor systems must occur. The hypothalamus is positioned anatomically to accomplish this control and integration.
- The set point for the system is normal body temperature.
- The hypothalamus contains “feedback detectors” that collect information about body temperature. These come from two sources:
  - Peripheral receptors transmit information through temperature pathways to the CNS.
  - Central receptors are located mainly in the anterior hypothalamus. Temperature-sensitive neurons in the hypothalamus modulate their activity in relation to local temperature (blood temperature).

Distinct regions of the hypothalamus mediate heat dissipation and heat conservation

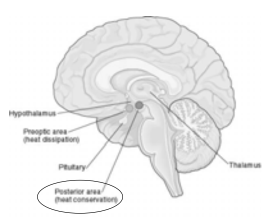
- The anterior hypothalamus (preoptic area) mediates decreases in heat.
- Lesions cause:
  - Chronic hyperthermia
- Electrical stimulation causes:
  - Dilation of blood vessels in the skin
  - Panting
  - Suppression of shivering



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 51.02

Distinct regions of the hypothalamus mediate heat dissipation and heat conservation (2)

- The posterior hypothalamus mediates heat conservation.
- Lesions cause:
  - Hypothermia if an animal is placed in a cold environment.
- Microstimulation causes:
  - Shivering
  - Constriction of blood vessels in the skin



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 51.02

Endocrine responses to temperature change

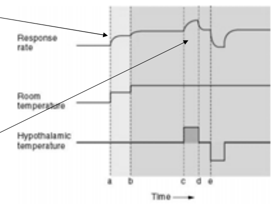
- Long-term exposure to cold can lead to increased hypothalamic secretion of thyrotropin-releasing hormone.
- This results in increased release of thyroxine, which in turns increases body heat by increasing tissue metabolism.

Behavioral responses to temperature change

- Rats can be trained to press a button for cool air if placed in a hot environment. After training, if in a cool environment, the rat will not push the button.
- If you warm the anterior hypothalamus locally by perfusing it with warm water locally, the rat will push the button for cool air, even though it is already in a cool environment.

The hypothalamus integrates peripheral and central temperature information

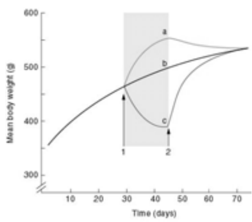
- Increases in room temperature lead to an increased in button pushing (response rate) to receive cool air.
- Increases and decreases in hypothalamic temperature also modulate response rate in a predictable manner.
- The behavioral response rate appears to sum inputs from the periphery and the hypothalamus.



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 51.03

Feeding behavior can also resemble a servo-control mechanism

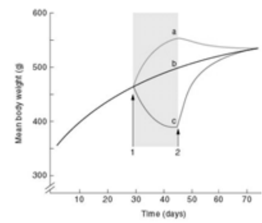
- Animals tend to adjust their food intake to achieve a normal body weight.
- Curve b = control rats on a normal diet.
- Curve a = rats force fed for 15 days.
- Curve c = rats on a restricted diet for 15 days.
- All rats returned to their normal body weight after either force feeding or restriction.



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 51.04

Feeding behavior can also resemble a servo-control mechanism (2)

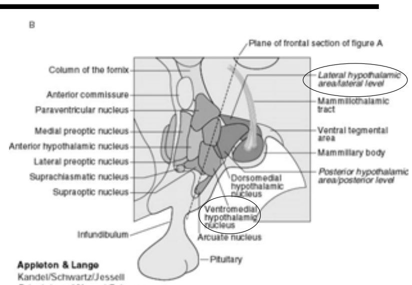
- These data demonstrate a biological set point for weight control.
- But…in humans, we know that:
  - Weight set point can vary by individual.
  - Weight set point can vary depending upon a variety of factors, including stress, taste, emotions, social factors, convenience, exercise and other environmental and genetic factors.



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 51.04

How does the hypothalamus contribute to the control of food intake?

- Early studies of the hypothalamus demonstrated that lesions of the ventromedial hypothalamus produced hyperphagia and obesity.
- Lesions of the lateral hypothalamus produced aphagia, leading to starvation. Stimulation produced the opposite effect of these lesions.
- These findings lead to the theory that the hypothalamus contains a "feeding center" and a "satiety center".



Appleton & Lange
Kandel/Schwartz/Jessell
Principles of Neural Science
Fig. 49.11b

How does the hypothalamus contribute to the control of food intake? (2)

- But…subsequent work provided the insight that the results from lesion studies may have been due to damage of fibers of passage rather than due to loss of cell bodies in distinct parts of the hypothalamus.
- In particular, hypothalamus lesions may damage fibers of:
  - the trigeminal system which affect sensory processing important for feeding
  - Dopaminergic neurons projecting from the substantia nigra to the striatum, as wells as those that project from the ventral tegmental area to innervate parts of the limbic system. Dopaminergic neurons are thought to be important for reward processing and arousal, and therefore may affect feeding behavior.

How does the hypothalamus contribute to the control of food intake? (3)

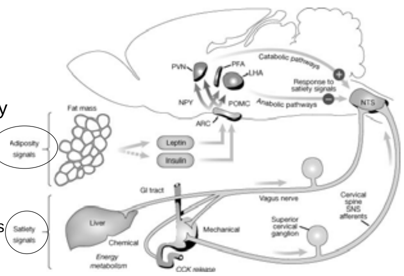
- The modern view of energy homeostasis now proposes that discrete neuronal pathways generate integrated responses to afferent input related to energy storage. The hypothalamus plays a prominent role in this integration.
- The hypothalamus is sensitive to adiposity signals supplied by the hormones leptin and insulin, secreted by fat cells and the pancrease respectively.
- Insulin and leptin both modulate neural activity in the arcuate nucleus of the hypothalamus, which transduces afferent hormonal signals into a neural response.
- Leptin may also play a role in establishing a biological set point for body weight by modifying the strength and number of synapses onto arcuate neurons and by inducing projections from the arcuate nucleus to the PVN during development.

A model for energy homeostasis

- Adiposity signals modulate anabolic and catabolic pathways in the CNS.
- These pathways control food intake and energy expenditure by influencing behavior, autonomic activity, and metabolic rate.
- Satiety signals terminate feeding, and energy balance and fat storage mechanisms control the amounts of leptin and insulin circulating in the blood (adiposity signals).

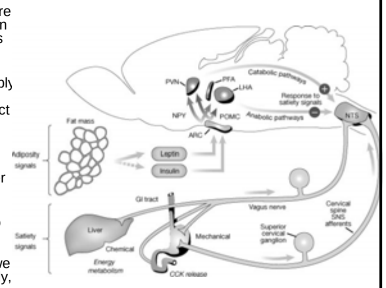
A model for energy homeostasis

- Two sets of signals are important for modulating food intake in response to body adiposity and food intake:
  - Satiety signals
    - Short-term control
  - Adiposity signals
    - Long-term control



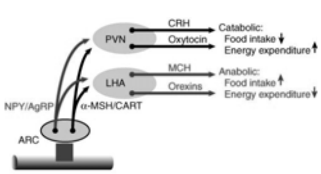
How do satiety signals control meal size?

- Meal size tends to be more biologically controlled than meal timing, that depends on numerous emotional and social factors.
- Satiety signals are probably initially processed by the nucleus of the solitary tract (NTS), which receives afferent input from the vagus nerve and from afferents passing into the spinal cord from the upper gastrointestinal tract.
- Adiposity signals can modulate the response to satiety signals, either indirectly through the hypothalamic pathways we have discussed, or directly, since the NTS does have some leptin receptors.



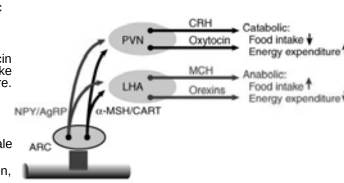
Hypothalamic neuropeptides that influence caloric homeostasis

- Two adiposity signals, insulin and leptin, are produced in the periphery and travel through the blood-brain barrier to influence neurons in the arcuate nucleus.
- Some arcuate neurons synthesize and release neuropeptide Y (NPY) and agouti-related protein (AgRP) and are inhibited by adiposity signals.
- Other arcuate neurons synthesize and release α-melanocyte-stimulating hormone (α–MSH) and cocaine-amphetamine-related transcript (CART) and are stimulated by adiposity signals.

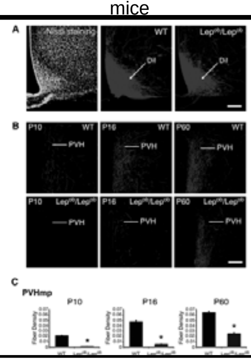


Hypothalamic neuropeptides that influence caloric homeostasis (2)

- NPY/AgRP neurons inhibit the paraventricular nucleus (PVN) and stimulate the lateral hypothalamic area (LHA). α-MSH/CART neurons do the opposite.
- The PVN has a net catabolic action, releasing CRH and oxytocin and thereby decreasing food intake and increasing energy expenditure. Plasma levels of oxytocin, which we previously discussed with reference to the milk let-down reflex, have also been correlated with food intake in male and female rats.
- The LHA has a net anabolic action, releasing two additional neuropeptides, orexin A and melanin-concentrating hormone (MCH), both of which stimulate food intake.



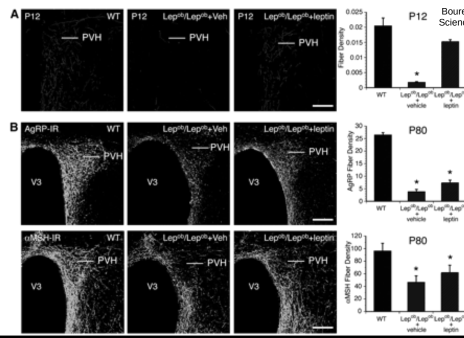
Leptin deficiency disrupts the normal developmental pattern of projections from the arcuate nucleus to PVN in mice



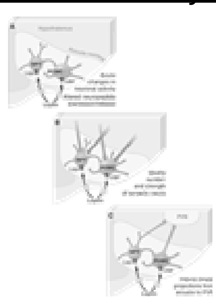
Bouret et al., (2004)
Science 304:108-110

Leptin treatment during development can rescue projections from the arcuate nucleus to PVN

Bouret et al., (2004)
Science 304:108-110



Effects of leptin on hypothalamic neurocircuitry



Summary of Hypothalamus Lecture

- Reviewed basic hypothalamus anatomy.
- Reviewed basic hypothalamic function:
  - Hormonal and neural inputs and outputs
  - Control of autonomic, endocrine, and behavior to maintain homeostasis
- Temperature regulation is an excellent example of a servo-control mechanism operating in the hypothalamus. The hypothalamus is sensitive both to hypothalamic and peripheral temperature, and it mediates changes in autonomic, endocrine and behavioral responses in order to maintain homeostasis.
- Feeding behavior is a less good example of a servo-control system, in part because of variable biological set points depending upon numerous factors. Nonetheless, feeding behavior appears to be influenced by short-term satiety signals, and long-term adiposity signals. Adiposity signals influence catabolic and anabolic pathways in the hypothalamus that can control a variety of autonomic, endocrine, and behavioral functions to maintain homeostasis. Emerging evidence implicates leptin as playing an important role in modulating the neurocircuity of the hypothalamus to influence feeding behavior.
- Fever and obesity are two major clinical conditions that are mediated by these neural pathways.