The Limbic System

3. The Hypothalamus and the Pleasure-Pain Axis

Boundaries of the Hypothalamus:
The hypothalamus is the most ventral division of the diencephalon. It is easy to point it out, but difficult to define its boundaries:

- **Superior boundary** - the hypothalamic sulcus of the IIIrd ventricle
- **Lateral boundary** - an arbitrary line drawn from the internal capsule to the basal surface of the brain
- **Rostral boundary** - another arbitrary line drawn from the anterior commissure to the optic chiasm
- **Caudal boundary** - the end of the IIIrd ventricle

Functions of the Hypothalamus:
Its functions are **endocrine, autonomic, and behavioral.**

Endocrine
In our grandparents' day, the idea was current that the pituitary gland was the "master gland" of the body. Now we know that this phrase really applies to the numerous sets of neurosecretory neurons in the hypothalamus. They synthesize some hormones directly, and control the synthesis of others by means of oligopeptide "releasing factors" or "inhibiting factors."

Sometimes this involves a three-level cascade:

- **Hypothalamus** secretes oligopeptides which control the pituitary.
- **Pituitary** in turn secretes larger amounts of higher molecular weight peptide trophic hormones which control target endocrine glands.
- **Target endocrine glands**, such as thyroid, adrenal cortex, or gonads secrete the final non-peptide hormones which modify target tissues and also feed back onto the hypothalamic and pituitary control system.

Autonomic
The hypothalamus is continuous with the **reticular formation** of the brainstem, and is connected with it by numerous afferent and efferent pathways. These pathways consist of small diameter, poorly myelinated fibers. You are not asked to memorize their names or to identify them in your photographs of myelin-stained sections. However, the concept that they exist is extremely important, for they control parts of the reticular formation which in turn control the activities of preganglionic autonomic neurons. Thus, the hypothalamus is the "brain" of the autonomic nervous system.

Behavioral
Parts of the hypothalamus seem to be "centers" for elemental visceral behaviors. Let us take, as an example, the feeding and satiety centers:

Animals with bilateral (it must be bilateral) destruction of the ventromedial nucleus will eat and eat without stopping, and become grotesquely fat. Such animals usually also have disturbed sleep patterns and an unpleasant, hostile disposition.

Animals with bilateral lesions of the part of the hypothalamus immediately lateral to the ventromedial nucleus lose all their appetite, and will starve to death in the presence of nourishing, tasty food.

Some of these "centers" for elemental visceral behavior are entirely contained within the hypothalamus.

Others, in particular the sexual centers, involve adjacent structures as well.

Blood supply of the hypothalamus is provided by deep perforating branches of the posterior cerebral arteries.

Structures adjacent to the hypothalamus: concept of the "pleasure-pain axis"

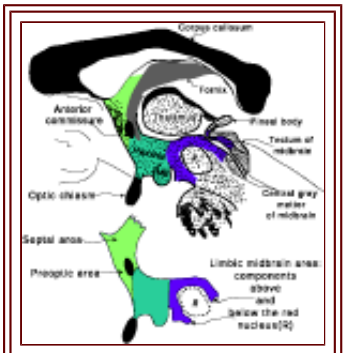
Inspection of a sagittal brain section through the hypothalamus shows continuity, rostrally, with the septal and preoptic areas of the telencephalon, and caudally, with two different parts of the midbrain reticular formation: the central or periaqueductal gray matter, and the interpeduncular or ventral tegmental area. Coronal sections add the information that the septal/preoptic areas are continuous laterally with the ventral striatum, while the central and interpeduncular gray areas of the midbrain are above and below the red nuclei, respectively. The interpeduncular gray contains the mesolimbic dopamine neurons, which as you will learn send dopamine axons to the ventral striatum.

An animal with an electrode permanently implanted in its septal area will work hard for the reward of being allowed to stimulate its own brain with an electric shock. Observing the animal shows that the stimulus is producing sexual pleasure. Obviously, the disorganized, convulsion-like activity such a shock produces in septal neurons can have only a crude resemblance to the effects of a natural stimulus; but the fact that even this crude stimulus is rewarding must be significant. Similar, though not identical results, are obtained with electrode placements in more lateral ventral forebrain areas, in lateral parts of the hypothalamus, and in the interpeduncular gray matter.

An animal with an electrode in its central gray midbrain area behaves very differently. In some locations, the artificial stimulus produces rage and fear. In others a fraction of a millimeter away, the artificial stimulus inhibits ongoing pain. This, of course, is the central midbrain pain gate which has already been discussed. Stimulation of posterior medial parts of the hypothalamus, in particular those bits closest to the fornix, also produces negative reinforcement.

Many of these observations have been directly corroborated in human patients: none of them have been contradicted.

From this kind of evidence, we learn that these areas collectively form a core of gray matter which provides the anatomical substrate for elemental experiences of appetite and satiety, pleasure and pain, reward and punishment. In this course, we call this area the "pleasure-pain axis" of the brain. You won't find that name in any textbook, but we feel that it summarizes the aggregate function of the area in a way that is easy to remember.



The "Pleasure-pain" Axis

Intrinsic Connections

Intrinsic connections i.e. connections between the "pleasure end" (septal and preoptic areas) and the "pain end" (midbrain areas) of the limbic core. One set is short distance, polysynaptic, poorly myelinated fibers running within the limbic core itself, designated the **median forebrain** bundle. Another set is a fast conducting, heavily myelinated detour around the intermediate parts of the limbic core, involving the epithalamus. Septal and preoptic areas and anterior hypothalamus send axons via the **stria medullaris thalami** to the **habenula**. This structure in turn sends axons via the **habenulo-interpeduncular tract**, also called **fasciculus retroflexus of Meynert** in some atlases, to the interpeduncular nucleus and other parts of the midbrain reticular formation. Recent work shows that this latter bundle also provides strong inhibitory input to the substantia nigra. Thus, this system may be an important avenue for the limbic system to relay information to the motor system.

INPUTS TO THE PLEASURE-PAIN AXIS	
Nature of Inputs	**Source of Inputs**
About Bodily Sensations	Spinothalamic and trigeminothalamic tracts to central gray of midbrain (pain) and to hypothalamus and septal area (pleasure)
About Chemical Sensations	
- Taste	Brainstem taste system
- Smell	Olfactory allocortex near the amygdala
- Blood chemistry and temperature	Chemosensory and thermosensory neurons within the hypothalamus
From the Reticular Formation	Various tracts originating from this all-purpose visceral structure
From Higher Forebrain Structures	(see image directly below)
- Amygdala and basal allocortex	Primarily direct ventral output from amygdala but also stria terminalis
- Hippocampal formation	Fornix
- Limbic cortex in frontal lobes	Direct frontohypothalamic pathways

Input from Major Forebrain Structures

Blood supply to the septal area is provided by the anterior cerebral artery. The more posterior parts of the pleasure-pain axis are all supplied by branches of the posterior cerebral or basilar arteries.