Hypothalamus

Objectives

a. Develop your understanding of the organization and internal relationships of the hypothalamus and autonomic nervous system (ANS), their major input/output connections and their role in homeostatic mechanisms.

b. Recognize selected diseases that characteristically involve hypothalamic and/or ANS components.

c. As an elective exercise, on your own time, look at the "Marathon Man" case, and answer the various questions the case poses.

The following material is quoted or paraphrased (but rearranged from):

- Syllabus nervous system (1997), Harvard School of medicine, Boston
- Kandel, Schwartz & Jessell, 3rd Ed. (Chapters 47 & 48, Irving Kupfermann, author),

Images in the syllabus and in the powerpoint presentation are taken partly from:

I. General Concepts

The main function of the hypothalamus is maintaining the body's status quo, homeostasis. Factors such as blood pressure, body temperature, fluid and electrolyte balance, and body weight are held to a precise value called the set-point. Although this set-point can migrate over time, from day to day it is remarkably constant.

To achieve this task, the hypothalamus must receive inputs about the state of the body, and must be able to initiate compensatory changes if anything drifts out of whack. In so doing, the hypothalamus through its connections receives information from the internal environment and operates directly on the internal environment, regulating vital functions such as temperature, heart rate, blood pressure, blood osmolality, water and food intake, sexual behavior and emotions. The hypothalamus receives inputs from various sources.

II. Afferences

a. Nucleus of the solitary tract - this nucleus collects all of the visceral sensory information from the vagus and relays it to the hypothalamus and other targets. Information includes blood pressure and gut distension.

b. Reticular formation - this catchall nucleus in the brainstem receives a variety of inputs from the spinal cord. Among them is information about skin temperature, which is relayed to the hypothalamus.

c. Retina - some fibers from the optic nerve go directly to a small nucleus within the hypothalamus called the suprachiasmatic nucleus. This nucleus regulates circadian rhythms, and couples the rhythms to the light/dark cycles.

d. Limbic and olfactory systems - structures such as the amygdala, the hippocampus, and the olfactory cortex project to the hypothalamus, and probably help to regulate behaviors such as eating and reproduction.

e. Circumventricular organs - these nuclei are located along the ventricles, and are unique in the brain in that they lack a blood-brain barrier. This allows them to monitor substances in the blood that would normally be shielded from neural tissue. Examples are the organum vasculosum lamina terminalis (OVLT), which is sensitive to changes in osmolarity, and the area postrema, which is sensitive to toxins in the blood and can induce vomiting. Both of these projects to the hypothalamus.

The OVLT is involved in osmoregulation and fluid balance through osmoreceptor cells that express the transient receptor potential vanilloid (TRPV) 1 gene, and respond to circulating levels of angiotensin II and relaxin.

The subfornical organ (SFO) has an important role in coordination of fluid balance with blood pressure and drinking behavior, especially during hemorrhage and hypovolemia. The rich vasculature of the SFO allows circulating angiotensin II to stimulate intrinsic neurons via angiotensin type 1 receptors. Through direct projections to the paraventricular nucleus, supraoptic nucleus and accessory magnocellular cell groups of the hypothalamus, SFO neurons induce release of vasopressin from the posterior pituitary, activate paraventricular nucleus neurons that descend to sympathetic centers of the spinal cord that regulate vasoconstriction, and possibly favor the release of vasoactive peptides like VIP from a number of neural sites related to fluid and blood pressure balance.
Once the hypothalamus is aware of a problem, how does it fix it? The hypothalamus acts through three major output systems.

III. EFFERENCES

a. Endocrine system
The hypothalamus controls endocrine function by means of peptidergic neurons

- Directly, by secretion of neuroendocrine products into the general circulation via the vasculature of the posterior lobe of the pituitary gland (neurohypophysis).
- Indirectly, by secretion of regulating peptide hormones into the local portal venous system of the median eminence, which drains into the vessels of the anterior pituitary.

The nerve cells that secrete these peptides are called neurosecretory neurons, in that as nerve cells they receive and transmit electrical information and as endocrine cells they release their secretory products into a local or systemic circulation.

b. Autonomic nervous system
The hypothalamus acts as coordinator of the autonomic nervous system. The hypothalamus integrates various inputs to ensure a well-organized, coherent, and appropriate set of autonomic and somatic responses. Its cells are inferred to possess a wide range of receptors for neuroactive hormones and cytokines that mediate eating, drinking, sexual and other behaviors.

The hypothalamus has major caudal outputs to the brainstem (parasympathetic nuclei), intermediolateral cell column of the spinal cord (sympathetic preganglionic cells), and indirectly or directly to the sacral part of the parasympathetic system. These major outputs are carried in several (bidirectional) fiber systems, the median forebrain bundle, the mammillotegmental tract and the dorsal longitudinal fasciculus. These are both ordinary connections as well as specific peptidergic projections to distant sites, such as the locus coeruleus and dorsal vagal nucleus of the brainstem, the intermediolateral cell column of the spinal cord, the periaqueductal gray, and various forebrain sites.

c. Limbic system and its connections, including the neural substrates for motivation and drive. The hypothalamus influences, and is in turn influenced by the rest of the cerebral hemisphere through the limbic system.

- Higher cortical centers communicate with the hypothalamus via the limbic system. This allows thought, perception, and emotion to influence hypothalamic regulation. To variable degrees, conversely, the forebrain connects the hypothalamus with the outer world, so that appropriate endocrine and autonomic concomitants of emotion are expressed in response to internal conditions. The hypothalamus
does have at least one direct input from the brain's perceptual apparatus for exterior events, namely from the retina.

- **Limbic system inputs** to the hypothalamus include: the *fornix* which connect the *mammillary bodies* of the posterior hypothalamus with the *hippocampal formation* (specifically the *subiculum*) which, in turn, receives input (via the perforant path) from the *entorhinal cortex*. (The entorhinal cortex and the subiculum both receive neocortical input as well.)

- **Hypothalamic outputs** to the limbic system and other forebrain structures include:

  1. The *mammillothalamic tract* (from the mammillary bodies to the anterior nuclear group) from which projections are sent to the *cingulate gyrus*.
  2. The *fornix* (to the hippocampal formation)
  3. The *stria terminalis* (to the amygdala, septal rim, etc.)
  4. Others, including intrinsic circuits such as the ventrolateral preoptic hypothalamic to tuberomammillary pathway involved in sleep and arousal.

Output to limbic system
IV. Internal organisation

Using phylogenetic and cytoarchitectonic criteria, a number of nuclear groups and fiber tracts are recognized in the vertebrate hypothalamus.

<table>
<thead>
<tr>
<th>Region</th>
<th>Area</th>
<th>Nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>Medial</td>
<td>Medial preoptic nucleus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supraoptic nucleus (SO)</td>
</tr>
<tr>
<td></td>
<td>Medial</td>
<td>Paraventricular nucleus (PV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior hypothalamic nucleus (AH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suprachiasmatic nucleus (SC)</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>Lateral preoptic nucleus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Part of supraoptic nucleus (SO)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral nucleus (LT)</td>
</tr>
<tr>
<td>Tuberal</td>
<td>Medial</td>
<td>Dorsomedial hypothalamic nucleus (DM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventromedial nucleus (VM)</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>Arcuate nucleus (AR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periventricular nucleus (PeV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral tuberal nuclei (LTN)</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>Lateral nucleus (LT)</td>
</tr>
<tr>
<td>Posterior</td>
<td>Medial</td>
<td>Mammillary nuclei (part of mammillary bodies)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(MB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior nucleus (PN)</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>Lateral nucleus (LT)</td>
</tr>
</tbody>
</table>

These nuclei are organized into three major regions including the lateral, medial and periventricular hypothalamus, each having distinct morphological and functional features. In the mammalian hypothalamus, the anterior column of the fornix that extends rostro-caudally through the substance of the hypothalamus to end in the mammillary bodies, and the mammillothalamic tract that projects from the mammillary bodies upward to the thalamus, create an anatomical boundary that divides the hypothalamus into medial and lateral subdivisions. Contained within the medial subdivision is the periventricular subdivision, a 5-6 cell layer thick nuclear group surrounding the third ventricle.

The periventricular subdivisions of the mammalian hypothalamus contain a high density of neuronal cell bodies organized into nuclear groups. It is crucial for the regulation of the anterior and posterior pituitary gland.

The medial hypothalamus also contains nuclear groups that serve as relay centers for highly differentiated neural information coming from the limbic system and autonomic sensory centers in the brainstem involved in initiation phases of specific homeostatic behaviors such as thirst, hunger, thermoregulation, the sleep-wake cycle, and reproductive behavior.

The lateral hypothalamus occupies the largest portion of the hypothalamus by volume. However, it has relatively fewer neurons compared to the medial hypothalamus, and only a limited number of nuclear groups intercalated within a massive fiber system, the medial forebrain bundle (MFB). It is through this fiber system that information from the medial forebrain (amygdala, hippocampus, septum, olfactory system) and the brainstem is carried to the medial and periventricular hypothalamic subdivisions, delegating an important role to the lateral hypothalamus to influence
homeostatic control systems elaborated by the medial hypothalamus.

Each of the three hypothalamic subdivisions can be further divided along the rostro-caudal axis into the:

a) anterior or chiasmatic region, extending between the lamina terminalis and the anterior limit of the infundibular recess;

b) median or tuberal region, extending between the infundibular recess and the surface of the anterior column of the fornix; and

c) posterior or mammillary region, extending between the anterior column of the fornix and the caudal limit of the mammillary bodies.

In a flattened horizontal plane, which we will need in a later stage of our discussion, the nuclei can be seen to occupy approximately these regions.

Single hypothalamic nuclei are parcellated in regions with different connections and functions. The best example is the paraventricular nucleus, which consists of at least 3 different subsets of neurons: magnocellular to the posterior pituitary gland, parvocellular to the median eminence and further neurons which project to the spinal cord.