## HYPOTHALAMUS

### Introduction

The hypothalamus is a very small, but extremely important part of the diencephalon that is involved in the mediation of <u>endocrine</u>, <u>autonomic</u> and <u>behavioral</u> functions. The hypothalamus: (1) controls the release of 8 major hormones by the hypophysis, and is involved in (2) temperature regulation, (3) control of food and water intake, (4) sexual behavior and reproduction, (5) control of daily cycles in physiological state and behavior, and (6) mediation of emotional responses.

A large number of nuclei and fiber tracts have been described in the hypothalamus. Some of these are ill-defined and have no known function, while others have been studied in detail both anatomically and physiologically. This handout will attempt to focus your attention on the significant and interesting aspects of the structure and function of the hypothalamus.

The hypothalamus is the ventral-most part of the diencephalon. As seen in <u>Fig. 2 of the thalamus</u> <u>handout</u>, the hypothalamus is on either side of the third ventricle, with the hypothalamic sulcus delineating its dorsal border. The ventral aspect of the hypothalamus is exposed on the base of the brain (Fig. 1). <u>It extends from the rostral limit of the optic chiasm to the caudal limit of the mammillary bodies</u>.

Three rostral to caudal regions are distinguished in the hypothalamus that correspond to three prominent features on its ventral surface: 1) The <u>supraoptic</u> or <u>anterior</u> region at the level of the optic chiasm, 2) the <u>tuberal</u> or <u>middle</u> region at the level of the <u>tuber cinereum</u> (also known as the <u>median eminence</u>—the bulge from which the infundibulum extends to the hypophysis), and 3) the <u>mammillary</u> or <u>posterior</u> region at the level of the mammillary bodies (Fig. 1)

### Important components of the 3 rostral to caudal regions of the hypothalamus are as follows:

Supraoptic Region. In the supraoptic region (above the optic chiasm) there are a number of named nuclei, the most prominent being the supraoptic and paraventricular (Fig. 2A). Neither of these two nuclei is large, but each is easily recognized because it is made up of relatively large, deeply staining cells. The cells in these two nuclei secrete vasopressin (ADH, antidiuretic hormone), oxytocin, and CRH (corticotropin releasing hormone). ADH and oxytocin are transported down the axons from cells in the supraoptic and paraventricular nuclei through the infundibulum to the neurohypophysis (posterior pituitary), where they are released into the blood stream (Fig. 3A). This pathway is termed the supraopticohypophysial tract. Damage to the anterior hypothalamus blocks the production of ADH, resulting in diabetes insipidus, which is characterized by rapid water loss from the kidneys. CRH is released by the paraventricular and taken up by the portal system where it has its action on the anterior lobe of the pituitary. A recent, interesting development is the finding of a direct projection from the eye to the suprachiasmatic nucleus of the supraoptic hypothalamic region (Fig. 2A). The hypothalamus is thought to contain the "biological clock" that regulates certain body functions that vary at different times of the day (e.g., body temperature, hormone secretion, hunger) or those that vary over a period of many days (e.g., menstrual cycle). This projection from the retina to the suprachiasmatic nucleus is thought to supply the clock with day-night information needed for synchronizing diurnal (daily) rhythms (also known as circadian rhythms). Lesions of the hypothalamus often disrupt the state of the sleep-waking cycle.



FIG. 1: Ventral surface of the hypothalamus. Dashed lines indicate levels from which cross sections in figure 2A, 2B and 2C were taken.



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Corpus collosum Caudate Fornix (body) ateral ventricle (body) LD Internal capsule (posterior ĖΜ Posterior limb) IML Claustrum MD nucleus Ref Fornix Putamen Mammillary Globus pallidus Optic tract Subthalamic body nucleus Zona Mammilary . Cerebral incerta body peduncle `Amygdala 🕽 Substantia Hippocampus nigra Caudate Thalamic (tail) fasciculus Figure 2C Thalamic Level 14 Cross section through the mammillary region

### **Tuberal Region**

The tuberal region (at the level of the tuber cinereum) is commonly divided into medial and lateral parts by a plane passing through the <u>fornix</u> (Fig. 2B). The fornix, which will be covered in the olfactory-limbic lecture (you may want to look ahead to Fig. 6 of that handout), is a fiber tract that originates in the hippocampus within the temporal lobe and courses rostrally along a C-shaped course next to the lateral ventricle, then plunges into the hypothalamus where it terminates within the mammillary bodies.

The medial part of the tuberal region (between the fornix and third ventricle) contains 2 important nuclei; the lateral part, which is more loosely organized, is termed the <u>lateral hypothalamic area</u> (<u>LHA</u>). The medial forebrain bundle, which is described below, courses through the LHA.

The largest and most prominent of the nuclei in the medial part of the tuberal region is the ventromedial nucleus. One important function that has been attributed to the ventromedial nucleus is control of eating. Bilateral lesions of the ventromedial nucleus in animals and probably humans as well, result in overeating (hyperphagia) and extreme obesity (Fig. 4) as well as a chronically irritable mood and increase in aggressive behavior (termed hypothalamic rage). By contrast, bilateral lesions in the lateral hypothalamic area result in anorexia (lack of appetite). Animals with lesions in this area may die of starvation. As a result of these lesion studies (along with supporting stimulation studies), the ventromedial nucleus has been referred to as a satiety center and the lateral hypothalamic area as a feeding center. It has been postulated that these opposing centers define a "set point" for body weight: the set point theory of weight control. According to this theory, when body weight goes below the set point, the lateral hypothalamus is activated and appetite is increased; when body weight goes above the set point, the ventromedial nucleus is activated and appetite is decreased. This theory was questioned in the past, but recent evidence has been obtained that supports an integrative role of the ventromedial nucleus and lateral hypothalamic area in body weight control: their neurons respond to glucose, free fatty acid and insulin levels in a manner consistent with the set point theory, and activity levels in the two nuclei display a strict reciprocal relationship that is appropriately correlated with the level of hunger or satiety.





A second nucleus of great importance in the tuberal region is the <u>arcuate nucleus</u> (also known as the infundibular or periventricular nucleus). This nucleus apparently contains many of the neurons that control the endocrine functions of the <u>adenohypophysis</u> (although cells with this role are also found in other nuclei of the tuberal region as well as in the supraoptic region and preoptic area). These neurons do not directly release hormones from their endings like neurons in the supraoptic region, but rather secrete <u>releasing or release-inhibiting</u> factors (also termed releasing hormones) that regulate release of hormones by the adenohypophysis (Fig. 3B). Releasing factors are secreted from terminals of these neurons in the median eminence and infundibulum where they enter the portal system of vessels which carries them into the adenohypophysis. Hormones under control of this system include: growth hormone, ACTH, thyrotropin, the gonadotropins (FSH and LH), and prolactin. Consideration of the functional roles of these hormones is beyond the scope of this course.



FIG. 4: Hypothalamic control of appetite. (After Netter, Ciba Clinical Symposia.)

### Mammillary Region

The mammillary part of the hypothalamus consists of the <u>posterior hypothalamic nucleus</u> and the prominent <u>mammillary nuclei</u>. The posterior nucleus is a large, ill-defined group of cells that may play a role in thermoregulation (see below). The mammillary nuclei are considered to be part of the hypothalamus on anatomical grounds, but, unlike the other hypothalamic nuclei, they do not appear to be closely related to autonomic and endocrine functions. Instead, the mammillary nuclei are believed to play a role in memory, and will be discussed during the limbic system lecture. For now, just associate the mammillary nuclei with memory.

<u>Summary of hypothalamic fiber tracts</u>: There are four major fiber systems in the hypothalamus, all of which are bi-directional. The two largest and most clearly defined tracts carry fibers to and from the mammillary nuclei: the <u>fornix</u> (Figs. 6 & 9; also see Fig. 6 in Olfactory Pathways and Limbic System handout) carries fibers to these nuclei from the hippocampal formation (to be described in the limbic system lecture), and the <u>mammillothalamic tract</u> contains fibers running to and from the anterior nuclear group of the thalamus (Figs. 5 and 9). The <u>stria terminalis</u> (Fig. 6) is an afferent pathway to the hypothalamus from the amygdala (also to be described in the limbic system lecture). The <u>medial forebrain</u> bundle (Figs. 6, 9) is an ill-defined bundle of unmyelinated and thinly myelinated axons which courses through the lateral hypothalamic area. This bundle contains a very large number of different ascending and descending components (50 were distinguished in a recent paper). These include fibers ascending from the monoamine cell groups in the brainstem, descending fibers from the olfactory cortex that may play a role in appetite control, and descending fibers from other basal forebrain structures. It has been implicated in controlling many physiological functions like sleep, and behavioral traits like depression and pleasure.

<u>Functions of the Hypothalamus:</u> Many of the functions of the hypothalamus are of a homeostatic nature (maintenance of constant body states). Several of these have already been described in conjunction with the description of the nuclei involved. Such functions require the integration of activity in many different body systems. A good example is temperature regulation (see Fig. 7 but do not learn this figure). When body temperature increases, neurons in the anterior part of the hypothalamus turn on mechanisms for heat dissipation that include sweating and dilation of blood vessels in the skin. When body temperature decreases, neurons in the posterior part of the hypothalamus are responsible for heat production through shivering, vasoconstriction in the skin, and blockage of perspiration. Lesions in the anterior part can result in hypothermia (increase in body temperature) and lesions in the caudal part can result in hypothermia when the environmental temperature is low.

A recent, very significant finding is a direct projection from the hypothalamus to the <u>preganglionic sympathetic neurons in the lateral horn</u> (intermediolateral cell column) of the spinal cord and to the preganglionic <u>parasympathetic neurons in the dorsal motor nucleus of the vagus</u>. (*Recall from Dr. Harting's lecture that Horner's syndrome can result from interruption of the pathway from the hypothalamus to the lateral horn as it passes thru the brain stem.*) The cells of origin for these projections are located in many different parts of the hypothalamus. The hypothalamus has long been known as the "head ganglion" of the autonomic nervous system, but had been assumed to mediate its effects through multisynaptic pathways.

In addition to autonomic and endocrine functions, the hypothalamus is also involved in the control of emotional expression. As described above, bilateral lesions including the ventromedial nucleus of the hypothalamus in animals have long been known to produce expressions of rage (see Fig. 8 but do not learn this figure). Stimulation of various other hypothalamic nuclei produces a variety of other emotions including pleasure and fear.



### Fig. 5

Mid-sagittal section through the thalamus, hypothalamus and colliculi to show the mammillothalamic tract.



# Fig. 6

Diagrammatic representation of the major afferent pathways to the hypothalamus including the fornix, the medial forebrain bundle and the stria terminalis.



Fig. 7 Temperature regulation (after Netter)



Fig. 8 Neurogenic and hormonal pathways in the rage reaction.

It is important to bear in mind, however, that many other areas of the brain, especially those collectively termed the limbic system (following lecture), are involved in the control of emotions.

Another aspect of hypothalamic function that is interesting to consider is that it may be the site where, in many cases, emotional factors influence body functions. It is well known that many functions that are under autonomic or hormonal control are influenced to a large degree by emotions. For example, emotional factors can influence or block menstruation, lactation, or sexual function. Since the hypothalamus is concerned with control of emotions, and regulation of both hormone release and the autonomic nervous system, it is thought to be involved in the mediation of such effects.

### Neurotransmitters in the Hypothalamus

The hypothalamus has been referred to as a "pharmacological museum" (Goodman and Gilman, '55) by virtue of the plethora of neurotransmitters that it contains. Some of these neurotransmitters are found in the terminals of axons that originate from neurons outside the hypothalamus, but most are synthesized within the hypothalamus itself. The list of putative neurotransmitters includes the "classical" transmitters ACh, GABA, glutamate, serotonin, dopamine, and norepinephrine as well as literally dozens of peptides that have been identified in recent years.

While the overwhelming number of transmitters may create headaches for scientists and students, their presence offers hope for pharmacological intervention in the large number of different medical problems that are thought to involve the hypothalamus.

SUMMARY

# A. Major hypothalamic nuclear groups and nuclei:



**B.** Fiber tracts:



Fig. 9 Summary diagram of major fiber tracts of the hypothalamus (excluding supraopticohypophyseal).

### POINTS TO CONCENTRATE ON WHEN STUDYING:

- 1) Spatial relationships to surrounding brain structures. Don't forget that the optic chiasm overlies the hypothalamus and therefore that visual disturbances (especially bitemporal hemianopsia, to be discussed in the vision lectures, can accompany pathology of the hypothalamus or hypophysis.
- 2) Know the location of each important nucleus or area with respect to the hypothalamic subdivisions (supraoptic, tuberal, etc.). This is, of course, helpful in diagnosis of lesions.
- 3) Functions: I consider all of the information in the handout with regard to functions as essential. However, you will not be tested on hormones since this material is covered in other courses. Read the section, "Functions of the Hypothalamus" very carefully.
- 4) Don't worry about details in the "Neurotransmitters in the hypothalamus" section of the handout. Just read it for concepts.

### **PRACTICE QUESTIONS - HYPOTHALAMUS**

- 1. With which of the following does the hypothalamus have important efferent connections?
  - A. thalamus
  - B. hypophysis
  - C. brain stem
  - D. spinal cord
  - E. all of the above
- 2. Which of the following nuclei is (are) contained in the tuberal region of the hypothalamus?
  - A. ventromedial
  - B. suprachiasmatic
  - C. arcuate
  - D. mammillary
  - E. two of the above
- 3. Which of the following nuclei is (are) contained in the supraoptic region of the hypothalamus?
  - A. ventromedial
  - B. posterior
  - C. paraventricular
  - D. arcuate
  - E. mammillary

- 4. Which of the following are concerned with control of food intake?
  - A. supraoptic
  - B. posterior
  - C. mammillary
  - D. lateral hypothalamic area
  - E. arcuate

#### The following are <u>True/False</u> questions:

- 5. The structure that serves as a point of reference for dividing the hypothalamus into medial and lateral zones is the fornix. True or False?
- 6. The hypothalamus extends from the rostral limit of the optic chiasm to the caudal limit of the mammillary bodies. True or False?
- 7. The supraoptic region is at the level of the optic chiasm. True or False?
- 8. The medial forebrain bundle courses through the ventromedial nucleus. True or False?
- 9. Bilateral lesions of the lateral hypothalamic area result in hyperphagia and rage. True or False?
- 10. Lesions of the anterior hypothalamus result in a decrease in body temperature (hypothermia). True or False?
- 11. The suprachiasmatic nucleus receives a direct projection from the retina. True or False?
- 12. Diurnal or circadian rhythms are daily cycles in hormone secretion, sleep, etc. True or False?
- 13. The arcuate nucleus is where many releasing factors are secreted. True or False?



- 14. Which of the following statements is true regarding the shaded structure?
  - A. lies in the caudal hypothalamus
  - B. cells receive input from the fornix
  - C. cells project to the anterior nucleus of the thalamus via the mammillothalamic tract
  - D. lesion results in hyperthermia
  - E. three of the above are true



- 15. Which of the following statements is true regarding the shaded structure?
  - A. shaded area is the paraventricular nucleus
  - B. lesion results in hyperphagia
  - C. shaded area is the arcuate nucleus
  - D. lesion results in anorexia
  - E. lesion results in diabetes mellitus



16. Which of the following statements is true regarding the shaded structure?

- A. shaded area is the ventromedial nucleus
- B. lesion results in hyperphagia
- C. shaded area is the arcuate nucleus
- D. lesion results in anorexia
- E. lesion results in diabetes mellitus

Hypothalamus Practice questions



17. Which of the following statements is true regarding the shaded structure?

- A. shaded area contains cells that produce releasing factors
- B. shaded area is the arcuate nucleus
- C. structure lies in the rostral hypothalamus
- D. shaded area is the ventromedial nucleus
- E. two of the above are true



- 18. Which of the following statements is true regarding the shaded structure?
  - A. cells are involved in the regulation of circadian rhythm
  - B. cells are involved in the production of oxytocin
  - C. cells are involved in the production of vasopressin
  - D. cells project to the posterior lobe of the pituitary
  - E. three of the above are true

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- 19. Which of the following statements is true regarding the shaded structure?
  - A. cells are involved in the regulation of circadian rhythm
  - B. cells are involved in the production of oxytocin
  - C. cells are involved in the production of vasopressin
  - D. cells are involved in the production of corticotrophin releasing hormone (CRH)
  - E. three of the above are true



- 20. Which of the following statements is true regarding the shaded structure?
  - A. cells are involved in the regulation of circadian rhythm
  - B. cells are involved in the production of oxytocin
  - C. cells are involved in the production of vasopressin
  - D. cells are involved in the production of corticotrophin releasing hormone (CRH)
  - E. three of the above are true

Practice question answers - Hypothalamus

1. E 2. E 3. C 4. D 5. T 6. T 7. T 8. F 9. F 10. F 11. T 12. T 13. T 14. E (A,B and C) 15. B 13. B 16. D 17. E (A and B) 18. E (B, C and D) 19. E (B, C and D) 20. A