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Anatomy and Function of the Hypothalamus

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Abstract

The hypothalamus is a small but important area of the brain formed by various nucleus and nervous fibers. Through its neuronal connections, it is involved in many complex functions of the organism such as vegetative system control, homeostasis of the organism, thermoregulation, and also in adjusting the emotional behavior. The hypothalamus is involved in different daily activities like eating or drinking, in the control of the body's temperature and energy maintenance, and in the process of memorizing. It also modulates the endocrine system through its connections with the pituitary gland. Precise anatomical description along with a correct characterization of the component structures is essential for understanding its functions.

Keywords: anatomy, structure, function

1. Embryological development of the hypothalamus

At the end of the fourth week of embryological development, the neural tube is organized in primary vesicles: the forebrain vesicle or prosencephalon, the midbrain vesicle or mesencephalon, and the hindbrain vesicle, also called rhombencephalon. Prosencephalon further divides into two secondary vesicles, the telencephalon that will form the cerebral hemispheres and the diencephalon which gives rise to the diencephalon. Mesencephalon forms the midbrain, structure involved in the processes of vision and hearing. The hindbrain vesicle or rhombencephalon divides in metencephalon, which further forms the pons and the cerebellum and the myelencephalon that forms the medulla.

Embryological concepts regarding the development of the hypothalamic region are over 100 years old. Since Herrick [1] first proposed the columnar model of the forebrain organization,

the anatomical description was accepted *per se* and very few research papers have questioned its validity.

The columnar morphologic model is based on the division of the forebrain in functional longitudinal units, placing the telencephalon in the most rostral region and the diencephalon caudally, in between the telencephalon and the midbrain, while the hypothalamus is formed from the ventral most part of the diencephalic vesicle [2].

In the last decades, mapping of the genes involved in hypothalamic development allowed the identification of a disparity between the morphological, classic boundaries of this region and the molecular ones. According to Puelles' Prosomeric model [3], the initially proposed longitudinal axis of the brain is bent due to the first mesencephalic flexure of the embryo. This condition puts the diencephalon rostrally between the telencephalon cranially and the midbrain caudally and sets the hypothalamus independent from the diencephalon as a distinct posterior part of the forebrain [2, 3].

An important role in hypothalamic development is assigned also to the presence of specific signaling centers (Wingless-Int protein family–Wnt, Hedgehogs family–Hh, and Bone morphogenetic family–FgF) that modulates cell proliferation and neurulation [4].

2. Definition and localization

The hypothalamus is a small, central region of the human brain formed by nervous fibers and a conglomerate of nuclear bodies with various functions. The hypothalamus is considered to be a link structure between the nervous and the endocrine system, its main function being to maintain the homeostasis of the body.

The hypothalamus is located under the thalamus from which it is separated by the hypothalamic sulcus of Monro. The sulcus is located at the lateral wall of the third ventricle and extends anteroposteriorly from the interventricular foramen of Monro (that assures the communication between the third, diencephalic ventricle and the frontal horn of each lateral ventricle) up to the level of Sylvius cerebral aqueduct. The hypothalamus is limited anteriorly by the *lamina terminalis*, a gray matter layer of triangular aspect extended above the chiasma optique, in between the two anterior horns of the fornix. *Lamina terminalis* also forms the anterior wall of the third ventricle and contains the organum vasculosum, a circumventricular structure characterized by the absence of blood–brain barrier and thus highly sensitive to osmotic variations of the blood [5]. The superior wall of the hypothalamic region participates in the formation of the inferolateral wall of the third ventricle of the brain and has close relations with the white matter structure that surrounds it, called the fornix. The fornix is a C-shaped white cerebral structure that connects various parts from the brain (hypothalamic nuclei with hippocampal region, thalamic nuclei with hypothalamus's mammillary bodies). Even if its function is not clearly understood, its relation with memory is known, and recent studies are testing its deep brain stimulation as a treatment in advanced Alzheimer's disease [6]. Posteriorly, the hypothalamus extends up to the periaqueductal gray substance and the tegmentum of the superior part of the brainstem.

Only on the inferior surface of the brain, the hypothalamus can be visualized from the optic chiasm and the anterior perforated substance anteriorly to the posterior cerebral peduncles of the midbrain and the mammillary bodies, dorsally (**Figure 1**). The mammillary bodies are small, round white-matter structures that belong to the limbic system. They are involved in memory due to their connections with the hippocampal region and also in maintaining the sense of direction [7]. The hypothalamus is limited laterally by the optic tracts in their direction toward the lateral geniculate bodies, an important relay of the optical pathway. Inside the delimited area on the exterior surface of the brain, a small prominence, called tuber cinereum or infundibulum connects the hypothalamus with the posterior lobe of the underneath pituitary gland. The pituitary or the hypophyseal gland is located at the base of the brain, in a depression of the sphenoid bone called the sella turcica.

2.1. The hypothalamus—hypophyseal complex

The pituitary gland is a three-lobe structure: anterior, posterior and intermediate lobe, with different embryological origin.

The anterior lobe, pars anterior, or adenohypophysis is derived from the anterior wall of Rathke's pouch, an ectodermal structure that also forms the primitive oral cavity and the pharynx [8]. The anterior gland contains a heterogeneous cellularity that synthesized and secreted hormones in the blood stream: the majority of the cells are somatotrope cells that produced the human growth hormone (hGH) or somatotropin hormone (STH), a peptide that promotes growth in childhood. The production of the somatotropic hormone is under the control of the hypothalamic growth-releasing hormone (GRH) produced by the arcuate nucleus. The next hormones produced in high quantity by the anterior gland of the hypophysis are the corticotrope ones (adrenocorticotrophic hormone—ACTH, melanocyte-stimulating hormone—MSH, and beta-endorphins). This group of hormones is under the control of the hypothalamic corticotropin-releasing hormones (CRHs) derived from the paraventricular nuclei. In smaller percentages, the adenohypophysis has population of cells that produced

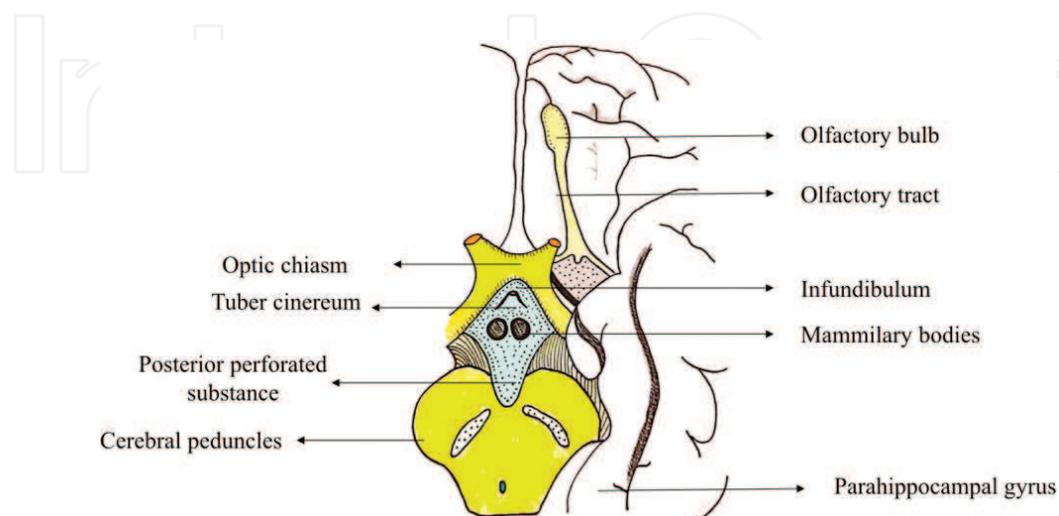


Figure 1. Inferior surface of the brain with hypothalamic visualization at this level.

thyrotropes, gonadotropes, and lactotropes. Thyrotropes respond to signals from the hypothalamic thyrotropin-releasing hormone (TRH) produced in the paraventricular nuclei and further synthesize the hormone responsible for thyroid hormones production—thyroid stimulating hormone (TSH). Luteinizing hormones (LHs) and follicle stimulating hormones (FSHs) are secreted by gonadotrope cells of the gland under the influence of pulsatile secretion of gonadotropin-releasing hormone (GRH) produced in hypothalamus preoptic area. The secretion of prolactin (PRL) from the lactotropes is stimulated by hypothalamic thyrotropin-releasing hormone (TRH) and inhibited by the dopamine [9].

Hypothalamic hormones reach the adenohypophysis through a vascular system. Hypothalamus exerts its effects over the anterior part of the gland through the hypothalamo-hypophyseal portal system, a special vascular system formed by fenestrated capillaries. The proximal vascular structure of the portal system is the anterior hypophyseal artery, branch from the ophthalmic segment of the internal carotid artery [9]. Through it, hypothalamic hormones are transported to the primary plexus, located near the infundibulum of the hypothalamus. From this region, hormones are drained into the second vascular venous plexus of the hypothalamo-hypophyseal portal system that surrounds the adenohypophysis [9]. This vascular system allows hormones to diffuse through the wall, inside of the gland. The hypophyseal vein further drains the blood into the venous sinuses of the dura mater and from here in the venous system of the body.

The posterior wall of Rathke's pouch forms the intermediate lobe of the gland [8]. It is absent or of small size in adults. In children, it is the part of the gland responsible for skin pigmentation through the secretion of the melanocyte stimulating hormone (MSH) or "intermedins" [9]. Pars intermedia also produces corticotrophin-like intermediate lobe peptide (CLIP) and adrenocorticotrophic hormone (ACTH) [9].

The posterior lobe of the gland, pars distalis or neurohypophysis derives from the neuroectoderm [9]. It is an inferior extension of the hypothalamus and is mainly from its neural fibers. The connection between the hypothalamus and the posterior lobe of the gland forms the infundibular stalk. Through this complex, hormones synthesized in the hypothalamus nuclei are transported and deposited in the posterior gland where they are stored in presynaptic vesicles and then released into the blood stream. The supraoptic nuclei of the hypothalamus are responsible for the secretion of antidiuretic hormone (ADH) or vasopressin, the hormone involved in maintaining the water balance in organism and thus in preventing dehydration. The paraventricular nuclei produce oxytocin, a hormone released during labor, in the presence of uterine contractions.

The hypothalamus intervenes along with the pituitary gland the majority of the endocrine and metabolic functions of the body through a double-sense transport of hormones between the two structures.

3. Structure of the hypothalamus

The hypothalamus is divided by the anterior horns of the fornix in a lateral, medial, and periventricular (median) region and by a coronal plane passing through the infundibulum in

an anterior and posterior region. The anterior region is also referred to as the prechiasmatic region, due to its location above the chiasma optic, while the posterior region is called the mammillary region. The infundibular region is situated between the previous two regions.

From a structural point of view, the hypothalamus is formed by gray matter conglomeration of neurons that organize in nuclei and also by white-matter substance formed by myelinated nervous fibers.

The anterior region of the hypothalamus is located above the optic chiasm and is referred to as the supraoptic area. It contains the following nucleus: supraoptic, preoptic and medial preoptic, the suprachiasmatic and the anterior hypothalamic nucleus, alongside with the paraventricular one (**Figure 2**). The supraoptic nucleus produces vasopressin or the antidiuretic hormone (ADH) that is stored in the posterior lobe of the pituitary gland and is responsible for blood pressure control and water balance of the organism. The preoptic region alongside with the anterior hypothalamic nucleus is involved in cooling (thermoregulation) of the body through the sweating process. The preoptic nucleus is also involved in the habit of eating and in reproduction while the medial preoptic region is involved in cardiovascular control as a response to stress [10]. The suprachiasmatic nucleus is situated above the optic chiasm and is involved in the circadian rhythm. The paraventricular nucleus (named after its location near the third diencephalic ventricle) represents an important autonomic center of the brain involved in stress and metabolism control [11].

The central part as the hypothalamus is located above tuber cinereum and is named the tuberal area. It is composed of two parts, anterior and lateral, and contains the following nucleus: dorsomedial, ventromedial, paraventricular, supraoptic, and arcuate (**Figure 2**). The ventromedial area is involved in controlling the habits of eating and the feeling of satiety [12]. The arcuate or infundibular nucleus is responsible for orexigenic peptides secretion: ghrelin, orexin, or neuropeptide Y [11].

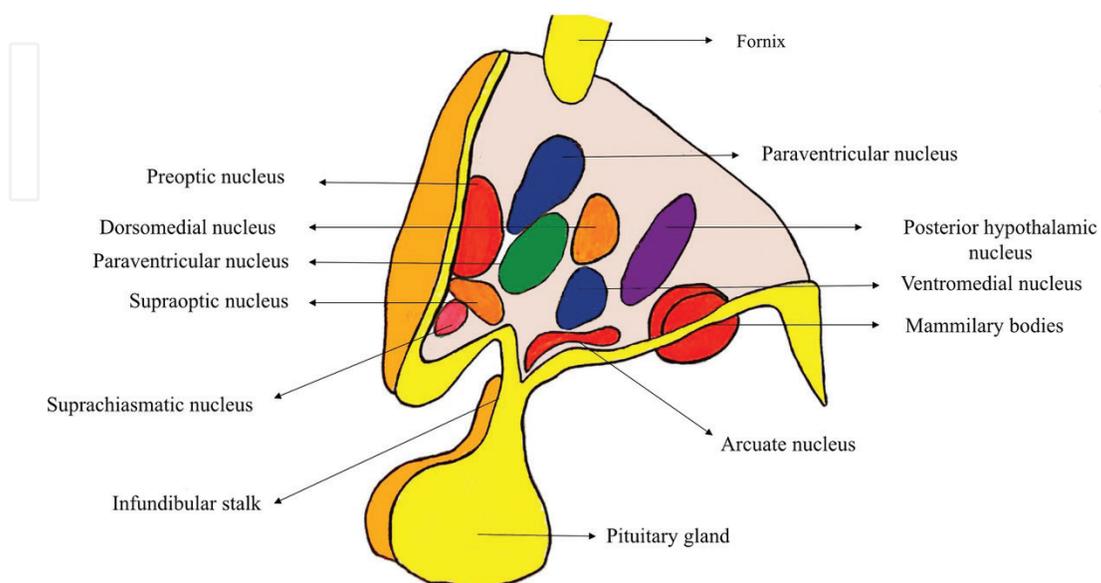


Figure 2. Schematic representation of hypothalamic nuclei (sagittal section).

The posterior region is formed by a medial and, respectively, lateral area. The medial region contains the mammillary nucleus alongside with the posterior hypothalamic nucleus, the supramammillary and the tuberomammillary ones. The nucleus of the lateral region contains the hypocretins (orexin) peptides that control feeding behavior, thermoregulation, gastrointestinal motility [13], and cardiovascular regulation and are also involved in sleep regulation [14]. Lesions of the lateral region lead to the refusal to feed or aphagia. The posterior part of the hypothalamus is involved overall in energy balance, blood pressure, memory, and learning. The posterior hypothalamic nucleus has a major role in controlling the body temperature [12]. The tuberomammillary nucleus is involved in memory due to their connection with the hippocampus and Papez memory circuit [9].

4. Connections of the hypothalamus

The hypothalamus is a small region of the brain connected with numerous, various cerebral structures that allows it to intervene in many regulatory processes of the organism. It has an important role in the optimal, normal functioning of the body, and it controls the endocrine system, the metabolism, and it is involved in stress control and in other different actions that modulates a person's behavior. More, the hypothalamus is involved in the homeostasis of the organism in terms of body temperature, blood pressure, fluid balance, and body weight.

The connections of the hypothalamus are made with the following structures.

4.1. The midbrain

The ascending reticular activating system represents a structure composed by neural fibers passing from the reticular formation of the midbrain, through the thalamus, reaching the cerebral cortex [15]. The system is responsible for concentration, attention, and for maintaining the awakening state. Through it, the reticular formation is connected with the hypothalamic nuclei: the lateral mammillary bodies [12], the tuberomammillary nuclei, and the periventricular ones. The periventricular nuclei receive information about the general visceral sensibility [16] while the two others mediate behavior and are involved in consciousness [17]. Information from the solitary tract nucleus passing from the reticular substance of the midbrain can also reach the hypothalamus. The nucleus of the solitary tract is connected with the hypothalamus through either the solitarohypothalamic tract or through colaterales from the solitariothalamic tract.

4.2. The thalamus

The anterior hypothalamus has connections with the intralaminar nucleus and the nucleus of the median line. Recent studies described that lesions of the intralaminar group of nucleus can lead to Parkinson's disease [18] or even schizophrenia [19]. The mamillothalamic fascicle of Vicq d'Azyr connects both the medial and lateral mammillary nuclei with the anterior part of the thalamus [20]; its destruction in case of a cerebral hemorrhage is associated with memory loss [17, 20].

4.3. The amygdala

The amygdala represents a conglomerate of perykarions located in the temporal lobe. Efferent fibers from this region project directly to hypothalamus or neural fibers can detach from the amygdala-thalamic fascicle and reach the anterior hypothalamus [12]. It is involved in body's response to fear and rewards but also in memory [21]. Direct connections of amygdala with the hypothalamus are either through the ventral amygdalofugal pathway or through the stria terminalis.

4.4. The hippocampal region

The hippocampus is a curved-shaped cerebral structure located in the temporal lobe. It is formed by the dentate gyrus and different regions called Cornus Ammonis (CA): CA1, CA2, CA3, and CA4 [22]. CA1 and CA3 are connected with the infundibular and the ventromedial nuclei of the hypothalamus [22].

According to a recent study [23] CA2 area lighted that also CA2 area, a small region in the hippocampus composed from pyramidal neurons, is involved in memory and learning through its connections with the supramammillary nuclei of the hypothalamus.

4.5. The olfactory bulb

Fibers from the olfactory bulb reach the periamygdalian region (the entorhinal and periamygdaloid cortex) and then the lateral hypothalamus through either the amygdalian or the accumbens nucleus [12].

4.6. The retina

Visual information from the retinal neuroepithelium through the lateral geniculate body of the mesencephalon and then the superior colliculus reach the suprachiasmatic and supraoptic nuclei of the hypothalamus and are involved in circadian rhythm [12]. The hypothalamus can receive direct fibers from the retina through a retinohypothalamic tract that reach the suprachiasmatic nuclei. The connections are involved in the circadian rhythm.

4.7. Cerebral cortex

There is a double sense connection between the cerebral cortex and the hypothalamus. The hypothalamus projects on the surface of the cortex diffuse, in a poorly defined area over the cortex and transmits information that maintain the cortical tonus while from the gray matter of the cerebral cortex, neural fibers projects over the hypothalamus and triggers visceral response according to the affective state (sweating in case of fear, intestinal manifestations in case of stress). Neural fibers from the lateral hypothalamus project in the prefrontal cortex while the frontal lobe also has efferent for all the hypothalamic regions [24]. Through these connections, the autonomic control is assured in the organism. More, from the paraorbital gyrus, fibers project into the paraventricular and ventromedial nuclei.

Axons from the spinal cord can project in the hypothalamic region using the path of the spinothalamic tract. They carry out pain and temperature information. The hypothalamus exerts its effects within two projections: the spinothalamic tract reaching the lateral horn of the spinal cord of T1-L2 segments regulates the sympathetic autonomic response; the mammillotegmental tract and the dorsal longitudinal fasciculus carry out information from the posterior region of the hypothalamus while the anterior one connects with the thalamus (mammillothalamic tract) and the above fornix.

5. Functions of the hypothalamus

The hypothalamus is involved in different daily activities like eating or drinking, in the control of the body's temperature and energy maintenance, and in the process of memorizing and in stress control. It also modulates the endocrine system through its connections with the pituitary gland.

5.1. Thermoregulation

Thermoregulation is the process that allows maintenance of the body's temperature within normal ranges. In case of high body temperature, the hypothalamus responds through thermoregulatory heat loss behavior (either sweating or vasodilatation). If the body needs to be warm up, hypothalamus can determine heat production behavior (vasoconstriction, thermogenesis—heat production from muscles, brain or other organs, including the thyroid gland) [25].

They are of the hypothalamus responsible for controlling this process is the anterior one, more specific the preoptic nucleus.

5.2. Regulation of food intake

The hypothalamus controls appetite and food intake through the ventromedial, dorsomedial, paraventricular, and lateral hypothalamus nucleus. The ventromedial nucleus is referred to as the appetite-suppressing or anorexigenic center. Destruction of this nucleus leads to hyperpolyphagia, obesity, and to an aggressive behavior.

Contrary, the appetite-increasing or orexigenic center is considered to be the lateral hypothalamic nucleus that can lead to aphagia and cachexy in case of its destruction and to hyperphagia or polyphagia in case of its stimulation.

Appetite control is modulated by the leptin hormone released by the fatty cells that binds to specific hypothalamic receptors.

5.3. Regulation of body water content

Water control in the living organism is assured by the hypothalamus through the antidiuretic hormone (ADH) secretion. In cases of blood volume loss and dehydration, the ADH hormone

is secreted from the supraoptic nucleus—that have osmoreceptor cells—and released in the circulation. The peptide is directed toward the specific receptor from kidneys and decreases the urine production with subsequent water retention in the organism.

5.4. Center for autonomic nervous system

The hypothalamus regulates both sympathetic and parasympathetic systems. The anterior region of the thalamus has an excitatory effect over the sympathetic system while the posterior and lateral ones have an excitatory effect over the parasympathetic system.

5.5. Endocrine control

The endocrine control is realized through the pituitary gland or the hypophysis situated below the tuberal region of the hypothalamus. The hypothalamus is connected with the posterior lobe of the gland through the hypothalamo-hypophyseal tract. Along these fibers, the AHD and oxytocin hormones are transported into the neurohypophysis where they are stocked in vesicles.

Hormones secretion in the body is regulated by the hypothalamus through the releasing and inhibitor factors: thyrotropin-releasing, gonadotropin-releasing, corticotrophin-releasing, somatostatin, and dopamine. These hormones are involved in the process of growth, in the reproduction, in the metabolism of the body, and also can assure the homeostasis of the body.

5.6. Reproduction

The reproduction function of an organism is assured by the hypothalamic-pituitary-gonadal axis. The gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus stimulates the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the anterior subdivision of the pituitary gland. Action of these two hormones on the gonads determines the estrogen and testosterone production.

Behavior in males and females is influenced as well by the sex steroids. The neurons in the preoptic are involved in the male sexual behavior while the ones from the tuberal regional exert their properties in females [26].

5.7. The circadian rhythm

The photosensible suprachiasmatic nucleus is involved, along with its connections with the pituitary gland, in the circadian rhythm. The suprachiasmatic nucleus receives electro-chemical information from the stimulated retina. The circadian rhythm represents the endogenous clock of an organism that is involved in the well-being of the body due to keeping within normal limits the major functions.

Despite its reduced size, the hypothalamus represents an important, integrative region of the brain with complex functions and multiple connections with essential cerebral structures.

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