7. HYPOTHALAMUS
PITUITARY AXIS

HYPOTHALAMUS

The hypothalamus is located at the base of the brain, dorsal to the sphenoid bone, ventral to the thalamus, anterior to the mammillary bodies and posterior to the optic chiasm. It has a weight of about 1/300 of the brain. The pituitary or hypophysis is situated below the hypothalamus within a depression of the sphenoid bone called the sella turcica. The pituitary weighs only about 0.5 g in humans. Figure 7-1 represents a generic distribution of the main structure of the brain while figure 7-2 shows two pictures of the same area.

Nomenclature

The nomenclature for the different areas of the hypothalamus and the hypophysis can be, at times, a bit confusing.

Many of the structures can be referred to by different names depending upon the terminology used. Each of these two parallel nomenclatures refers to areas encompassing slightly different structures. It is, therefore, recommended to refer to the precise structure to avoid misunderstanding.

Figure 7-1. Main components of the CNS

Figure 7-2. Longitudinal cut showing the location of the diencephalon

Figure 7-3. Main structures of the hypothalamus and the hypophysis
The basic structures of the hypothalamus and hypophysis are depicted in figure 7-3 and the allocation of these to their main areas is shown in figures 7-4 and 7-5.

The hypothalamus serves as the main regulator or processing centre, for all internal and external information gathered throughout the organism. The primary purpose is to ensure that the organism functions within certain ranges of endocrine concentrations which permit the maintenance of homeostatic conditions. Receptors and sensory terminals convey a multiplicity of information regarding the internal and external environment. This information is processed by the hypothalamus and the appropriate response is then formulated and carried out (Fig. 7-6).

Functional anatomy

Although there are many different nuclei in the hypothalamus, there are three distinct functional areas of interest in the hypophysis (Fig. 7-3).

The pars nervosa is associated with the posterior pituitary and the neurohypophysis. The pars intermedia will be considered independently. The pars distalis is clearly identified with the anterior pituitary and the adenohypophysis (Fig. 7-7).
Neurons in the different nuclei of the hypothalamus produce hormones or neurohormones which reach different areas of the hypophysis. These hormones could be releasing hormones or inhibitor factors which will mediate the release of other hormones by the hypophysis. In some cases the hypothalamus produces the final hormone which will exert biological effects in the body (Fig. 7-8).

**Pars nervosa**

Neurons from the hypothalamus synthesize hormones which travel through the hypothalamic-hypophyseal neural tract (H.H.N.T.). They are released in the pars nervosa; from there they reach the systemic circulation where they exert their effect in different tissues of the body. i.e. Oxytocin, antidiuretic hormone.

**Pars Intermedia**

Similar neurons to those mentioned above produce releasing and inhibitory substances, i.e. Melanocyte Inhibitory Factor (MIF) and Melanocyte Releasing Factor (MRF). These factors diffuse from the pars nervosa to the pars intermedia to regulate the secretion of the melanocyte stimulating hormone (MSH) which then moves into the systemic circulation to reach its target cells throughout the organism.

**Pars distalis**

Different types of neurons from the several hypothalamic centres produce a variety of inhibitory and stimulatory factors, which are released into a specific microcirculatory system called the portal system. This network of vessels starts in the base of the hypothalamus and extends into the pars distalis of the hypophysis, where it irrigates all cells (Fig. 7-3). Through the portal system the inhibitory and stimulatory hormones reach the pars distalis where they promote or reduce the production and/or release of several hormones which control most physiological processes in the organism, i.e. thyroid activity, adrenal function, reproduction, lactation and growth (Fig. 7-8).

**Endocrinological relationships**

In the following section, there will be a very succinct review of the endocrine relationship between some of the centres of the hypothalamus, the associated structures and/or cells in the hypophysis, as well as, the target tissue in the body. This will include only a general explanation of the regulatory systems in place. The details of each system will be discussed in further sections of the course.

This review will follow the reverse sequence of the summary presented in figure 7-8.
Posterior pituitary

Neurohypophysis is innervated from the supraoptic nuclei (SON) and paraventricular nuclei (PVN) through the H.H.N.T.. Some of these neurons produce Ot while others produce ADH (also known as vasopressin).

Both, Ot and ADH, are produced in the body of the neurons located in the hypothalamus. The hormones are stored in Herring bodies together with neurophysins, and transported through the axon. The releasing stimulus is an action potential which results as a consequence of an input received from somewhere in the body and processed in the hypothalamus. Several types of receptors can send the releasing signal.

Oxytocin. Tactile receptors in the udder, uterus, cervix and external genitalia send information to the hypothalamus, specifically to the SON and PVN where a decision to release Ot is made (Fig. 7-9). This can also be triggered by a Pavlovian response to a conditioned stimulus, such as viewing or hearing milking equipment, however this only occurs when it is close to milking time.

Antidiuretic hormone. Osmo and baroreceptors located throughout the body can sense an increase in viscosity of the blood or a decrease in blood pressure, respectively. As a result, these receptors send information to the hypothalamus where cells located in the SON and PVN are capable of releasing ADH. The hormone is released into circulation from the pars nervosa of the hypophysis. The consequence of the action of ADH is a reduction in the elimination of water by the kidneys, thus, attempting to maintain blood pressure and reduce the viscosity of the plasma (Fig. 7-10).

Osmoreceptors are located in the hypothalamus, liver, mouth, throat, and stomach; the baroreceptors can be found in the wall of vessels, liver, and atrium.

Pars intermedia

The pars intermedia is embryonically derived from tissue of the anterior pituitary, but it is physically more attached to the posterior lobe. It is especially prominent in species living in arid regions. It contains melanotropes which make MSH. MSH stimulates chromatocytes to produce melanin which in turn affects fur coloration. Some ACTH and endorphins are also produced in this area.

Pars distalis

Connected by portal vessels from the hypothalamus, the pars distalis contains a variety of specific cells capable of synthesizing a large number of hormones. Hormonal secretion, by these cells within the pars distalis is mainly controlled by stimulatory or inhibitor factors produced in the hypothalamus and secreted into the portal system.

The following is a list of the most important secretory cells found in the pars distalis. Also listed are their products and the releasing factor which is responsible for its stimulation.
or inhibition. Details of the biosynthetic and regulatory mechanisms will be discussed in the sections associated with the respective biological function of each hormone.

**Corticotropes.** Receive stimulation from the corticotrophin releasing hormone (CRH), which is released into the portal system as a consequence of emotional distress, physical stress or low glucocorticoid concentration in circulation. CRH promotes 100% elevation in cAMP within corticotropes, which in turn secretes adrenocorticotropic hormone (ACTH). ACTH reaches the adrenal gland where it stimulates glucocorticoid production (Fig. 7-11).

There are negative feedback mechanisms at all levels of the synthetic pathway. CRH exerts negative feedback on the hypothalamus to regulate its own production. ACTH acts on corticotropes, through an ultra-short negative feedback mechanism to reduce ACTH production, and also acts on the hypothalamus, through a short negative feedback to reduce the production of CRH. Glucocorticoids from the adrenal gland, feedback on the adrenal to control its own production. They also act on the corticotropes of the pars distalis and on the hypothalamus to further regulate production of ACTH and CRH, respectively.

**Thyrotropes.** Stimulated by the hypothalamic thyrotropin releasing hormone, thyrotropes produce a thyroid stimulating hormone, which travels to the thyroid to stimulate secretion of T$_4$ and T$_3$ (Fig. 7-12).

TRH and TSH exert a negative feedback on the neurons of the hypothalamus. Thyroid hormones feedback on the thyroid, on the thyrotropes and on neurons of the hypothalamus to regulate TH, TSH and TRH respectively.

**Lactotropes.** Prolactin is a hormone associated with the milk secretory capacity of the mammary gland. Production of prolactin by the lactotropes of the pars distalis is regulated by a prolactin releasing factor (PRF) and by a prolactin-inhibiting factor (PIF). PRF happens to be the same amino acid sequence as that of the molecule of TRH. To activate production of prolactin by the lactotropes, however, TRH is stimulated by impulses generated by the suckling stimulus. Lactotropes produce prolactin (Prl) in response to stimulation of the udder and other unknown receptors. Baseline prolactin is increased with sudden stress.

**Somatotropes.** Somatotropes, cells capable of producing GH, are normally in secretory mode but are regulated principally by the inhibitory influences of somatostatin (Fig. 7-13) which is produced in the hypothalamus and in many other tissues throughout the organism. A hypothalamic releasing hormone, called growth-releasing hormone (GRH), further enhances the normal secretory mode of the somatotropes (Fig. 7-13). The growth hormone does not exert the growth-promoting stimulus directly. GH acts on the liver to stimulate the production of a variety of growth promoting factors called somatomedins (SM). GH, however, is detected by the tissues throughout the body, which respond by secreting SS, which in turn participates in the regulation of further secretion of GH by the somatotropes of the hypophysis.
There are several versions of SS with different molecular weight and with different biological potency and specificity. Furthermore, SS not only influences GH but also influences other systems.

**Gonadotropes.** Gonadotropes are a population of cells stimulated by a decapeptide luteinizing releasing hormone (LRH). It is also known as the gonadotropin releasing hormone (GnRH). It is synthesized in two different centres of the hypothalamus, the tonic and the ovulatory or surge center. The gonadotropes produce LH and FSH. The tonic center is made up of neurons in the ventromedial nucleus and the arcuate nucleus, while the pre-ovulatory or surge center is made up of neurons from the preoptic nucleus, the anterior hypothalamic area, and the suprachiasmatic nucleus.

The gonadotropin releasing hormone is produced in the hypothalamus in response to olfactory, visual, tactile, thermal and psychological stimulus. GnRH exerts its action in the gonadotropes through Ca\(^{2+}\) and cAMP. Its action is terminated by internalization of the membrane receptors in the gonadotropes (Figs. 7-14, 7-15).

**Role of GnRH in the male**

In the males LRH, like GnRH, stimulates both LH and FSH. LH in turn stimulates Leydig or interstitials cells, to produce testosterone. FSH stimulates Sertoli cells to nurture sperm production. As a regulatory mechanism, Sertoli cells produce a protein, inhibin, which acts on the gonadotropes of the hypophysis to prevent further secretion of FSH (Fig. 7-14). Testosterone exerts a negative feedback at three levels: on Leydig cells to regulate testosterone production; on gonadotropes to regulate LH and FSH and; on the hypothalamus to regulate GnRH production.

**Role of GnRH in the female**

In the female, a similar cascade takes place (Fig. 7-15). GnRH from the hypothalamus stimulates
gonadotropes in the pars distalis and these in turn release both LH and FSH.

These gonadotropins stimulate follicular development and eventually trigger ovulation. As the follicles develop, they release estrogens exerting a positive feedback on the tonic centre of the hypothalamus to secrete more GnRH. Estrogen also prepares the gonadotropes in such a way that they are able to respond to a massive release of GnRH prior to ovulation. While the follicles are growing, either the still low concentration of circulatory estrogen prevents the ovulatory centre of the hypothalamus from discharging GnRH or, this centre only discharges when a given critical concentration of circulatory estrogen has been reached. When a massive release of GnRH from the ovulatory centre takes place, the already prepared gonadotropes release a large amount of LH and a modest amount of FSH. The LH released here triggers the ovulation of the Graafian follicles which are present in the ovary. Meanwhile the FSH stimulates a crop of growing follicles to slowly start developing so that they can ovulate in the next cycle, if pregnancy does not take place. After ovulation, the empty follicle becomes the corpus hemorrhagicum (CH) and eventually the corpus luteum (CL). The CL is responsible for the production of progesterone, which in turn inhibits significant production of GnRH from the tonic centre of the hypothalamus.

Figure 7-16. Summary of the main hypothalamic-hypophyseal-target tissue relationships