The hypothalamic–pituitary–adrenal axis (HPA axis or HTPA axis) is a complex set of direct influences and feedback interactions among three endocrine glands: the hypothalamus, the pituitary gland (a pea-shaped structure located below the thalamus), and the adrenal glands (small, conical organs on top of the kidneys).

Function

An organism’s reproductive fitness is sensitive to the environment, integrating cues of resource availability, ecological factors, and hazards within its habitat. Events that challenge the environment of an organism activate the central stress response system, which is primarily mediated by the hypothalamic–pituitary–adrenal (HPA) axis.

The regulatory functions of the HPA axis govern the cardiovascular and metabolic system, immune functions, behavior, and reproduction. Activation of the HPA axis by various stressors primarily inhibits reproductive function (Pic. 1) and is able to alter fetal development (Pic. 2), imparting a biological record of stress experienced in utero. Clinical studies and experimental data indicate that stress signaling can mediate these effects through direct actions in the brain, gonads, and embryonic tissues.

Specifically, the hypothalamic-pituitary axis directly affects the functions of the
thyroid gland, the adrenal gland, and the gonads, as well as influencing growth, milk production, and water balance. The hypothalamus is also involved in several important nonendocrine functions, such as temperature regulation, the activity of the autonomic nervous system, and control of appetite.

**Anatomy**

**Hypothalamus**

The hypothalamus in vertebrates integrates the endocrine and nervous systems. The hypothalamus is an endocrine organ located in the brain (Pic. 3). The hypothalamus in vertebrates integrates the endocrine and nervous systems. It receives input from the body and other brain areas and initiates endocrine responses to environmental changes. The hypothalamus acts as an endocrine organ, synthesizing hormones and transporting them along axons (part of nerve cell that transmits stimuli away) to the posterior pituitary gland. It synthesizes and secretes regulatory hormones that control the endocrine cells in the anterior pituitary gland. The hypothalamus contains autonomic centers that control endocrine cells in the adrenal gland.

**Pituitary**

The pituitary gland, sometimes called the hypophysis or “master gland” is located at the base of the brain in the sella turcica, a groove of the sphenoid bone of the skull. It is attached to the hypothalamus via a stalk called the pituitary stalk (or infundibulum). The anterior portion of the pituitary gland is regulated by releasing or release-inhibiting hormones produced by the hypothalamus, and the posterior pituitary receives signals via neurosecretory cells to release hormones produced by the hypothalamus. The pituitary has two distinct regions - the anterior pituitary and the posterior pituitary (Pic. 4) - which between them secrete nine different peptide or protein hormones. The posterior lobe of the pituitary gland contains axons of the hypothalamic neurons.

1. **Anterior Pituitary**

The anterior pituitary gland, or adenohypophysis, is surrounded by a capillary network that extends from the hypothalamus, down along the infundibulum, and to the anterior pituitary. This capillary network is a part of the system (hypophyseal portal) that carries substances from the hypothalamus to the anterior pituitary and hormones from the anterior pituitary into the circulatory system. A portal system carries blood from one capillary network to another; therefore, the hypophyseal portal system allows hormones produced by the hypothalamus to be carried directly to the anterior pituitary without first entering the circulatory system.
The anterior pituitary produces seven hormones: growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), melanin-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

Anterior pituitary hormones are sometimes referred to as tropic hormones, because they control the functioning of other organs. While these hormones are produced by the anterior pituitary, their production is controlled by regulatory hormones produced by the hypothalamus. These regulatory hormones can be releasing hormones or inhibiting hormones, causing more or less of the anterior pituitary hormones to be secreted. These travel from the hypothalamus through the hypophyseal portal system to the anterior pituitary where they exert their effect. Negative feedback then regulates how much of these regulatory hormones are released and how much anterior pituitary hormone is secreted.

2. **Posterior Pituitary**

The posterior pituitary is significantly different in structure from the anterior pituitary. It is a part of the brain, extending down from the hypothalamus, and contains mostly nerve fibers and neuroglial cells, which support axons that extend from the hypothalamus to the posterior pituitary. The posterior pituitary and the infundibulum together are referred to as the neurohypophysis.

The hormones antidiuretic hormone (ADH), also known as vasopressin, and oxytocin are produced by neurons in the hypothalamus and transported within these axons along the infundibulum to the posterior pituitary. They are released into the circulatory system via neural signaling from the hypothalamus. These hormones are considered to be posterior pituitary hormones, even though they are produced by the hypothalamus, because that is where they are released into the circulatory system. The posterior pituitary itself does not produce hormones, but instead stores hormones produced by the hypothalamus and releases them into the blood stream.

**Stress response**

In reaction to a stress-producing stimulus, the body produces a response via activation of the HPA axis. This is a necessary mechanism as it prepares the body for the well-known "fight or flight" reaction to a potentially dangerous situation. However, the stress response that is produced does not differ greatly depending on the stressor. In humans the molecules greatly responsible for the stress response are adrenaline and glucocorticoids (cortisol in humans). These hormones affect a wide spectrum of body functions, and in particular, they have an essential role in regulating energy body requirements by acting on glucose, protein, and fat metabolic pathways.
Pathological conditions

The HPA axis is a key neuroendocrine signaling system involved in physiological homeostasis and stress response. Disturbances of this system lead to severe hormonal imbalances, and the majority of such patients also present with behavioral deficits and/or mood disorders.

If there is the decreased secretion of one or more of the hormones normally produced by the pituitary gland (hypopituitarism), the most common problem is insufficiency of follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH) leading to sex hormone abnormalities. Growth hormone deficiency is more common in people with an underlying tumor than those with other causes.

Male fertility

The hypothalamus, the pituitary, and the testes form an integrated system that is responsible for the adequate secretion of male hormones and normal sperm maturation (spermatogenesis). The endocrine components of the male reproductive system are integrated in a classic endocrine feedback loop. The testes require stimulation by the pituitary gonadotropins, i.e., LH and FSH, which are secreted in response to hypothalamic gonadotropin releasing hormone (GnRH).

The effect of LH and FSH on germ cell development is mediated by the androgen and FSH receptors that are present on Leydig (producing testosterone) and Sertoli cells (help in the process of spermatogenesis), respectively. Whereas FSH acts directly on the germinal epithelium, LH stimulates the secretion of testosterone by Leydig cells. Testosterone stimulates sperm production and virilization, in addition to providing feedback to the hypothalamus and pituitary to regulate GnRH secretion. FSH stimulates Sertoli cells to support spermatogenesis and secrete inhibin B, which negatively regulates FSH secretion.

The GnRH pulse generator is the main regulator of puberty, and the production of GnRH starts early in fetal life. Hypogonadism is often discovered during evaluation of delayed puberty, but ordinary delay, which eventually results in normal pubertal development, wherein reproductive function is termed constitutional delay. It may be discovered during an infertility evaluation in either men or women.

Female fertility

Stress-induced levels of glucocorticoids have been shown to impair oocyte
competence. Heat stress can also change the follicular fluid composition, altering the environment within the oocyte.

The study correlated levels of intra-follicular glucocorticoids to oocyte maturation and successful fertilization in oocytes recovered from women undergoing in vitro fertilization (IVF). The authors reported that follicular fluid from follicles whose oocytes were not fertilized had levels of cortisol significantly higher than the levels in follicular fluid from follicles containing successfully fertilized oocytes. This suggests that high levels of glucocorticoids negatively influence the ability of an oocyte to become fertilized.

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    - An endocrine gland, about the size of a pea, whose secretions control the other endocrine glands and influence growth, metabolism, and maturation.
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  - High levels of glucocorticoids experienced in utero through stress or exogenous administration can cause effects in the organ systems of offspring.
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