Chapter 2
What is the relationship among the various endocrine components of the male reproductive system?

Hypothalamic-pituitary-testicular axis-feedback loops

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The hypothalamic-pituitary-testicular unit is an integrated system that assures the adequate and appropriate secretion of male hormones and the production of sufficient sperm for the propagation of the species. Each anatomical site is integrated with the others in a classic endocrine-feedback manner, with ample local paracrine and intracrine modulation required for its most effective function. (Fig. 1)

Hypothalamic regulation of gonadotropin-releasing hormone

Hypothalamus

The hypothalamus is the principal integrative unit responsible for the normal pulsatile secretion of gonadotropin releasing hormone (GnRH) that is delivered through the hypothalamic-hypophyseal portal blood system to the pituitary gland.

The secretion of GnRH is regulated in the hypothalamus mainly by kisspeptin-neurokinin B-dynorphin (KNDy) neurons in the infundibular nucleus in the hypothalamus. Kisspeptin stimulates GnRH secretion directly, whereas neurokinin B stimulates kisspeptin neurons that, in turn, leads to GnRH secretion. In contrast, dynorphin has inhibitory effects on kisspeptin signaling. GnRH negative feedback from circulating levels of testosterone or its metabolic products (i.e., estradiol and dihydrotestosterone) in men inhibit the pulse frequency and secreation of GnRH. (Fig. 2)

The pulsatile release of GnRH provides the signals for the timing of the release of LH and FSH, which under normal circumstances occurs approximately every 60–90 minutes. The local effectors of

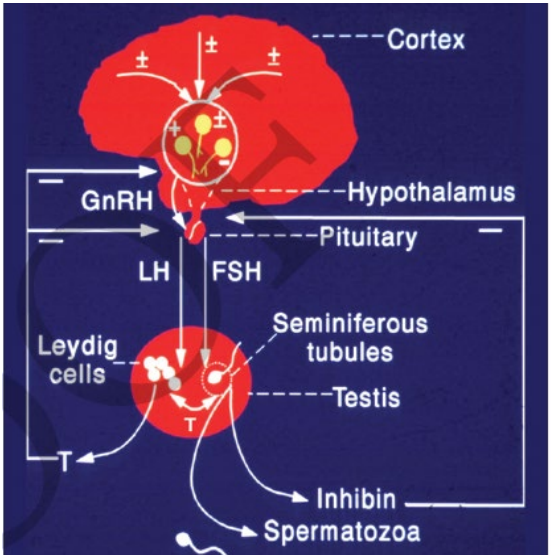

Figure 1. Schematic representation of the components of the hypothalamic-pituitary- testicular axis and of its feedback regulators.

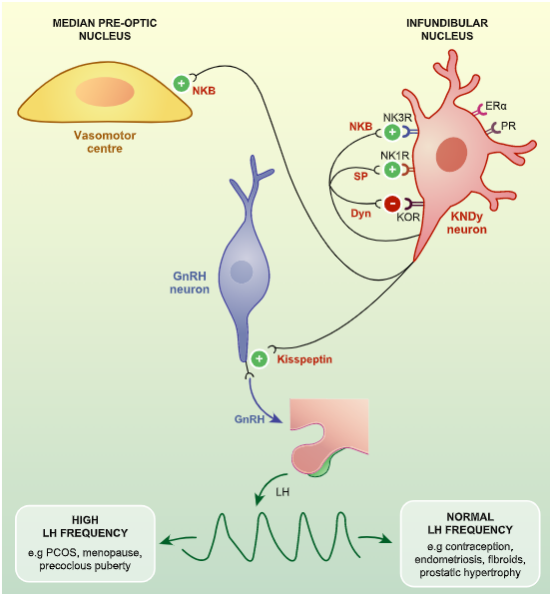

Figure 2. Hypothalamic regulation of GnRH (source: Anderson RA, Millar RP, Journal of Neuroendocrinol (2021). DOI: 10.1111/jne.13081)

GnRH synthesis and release include a number of neuropeptides, opioids, catecholamines, indolamines, nitric oxide and excitatory amino acids, γ-aminobutyric acid (GABA), dopamine, neuropeptide Y, vasoactive intestinal peptide (VIP), corticotropin-releasing hormone (CRH), and kisspeptin.

Pituitary

GnRH acts by binding to the GnRH receptors on the surface of the pituitary LH and FSH secreting cells. The normal pulsatile secretion of LH and FSH is principally driven by the pulses of GnRH from the hypothalamus. Regulation of LH and FSH levels is the result of a closed loop feedback inhibition of the hypothalamic-pituitary component by the secretory products of the Leydig cells, estradiol and dihydrotestosterone, and by inhibin secreted by the Sertoli cells. Thus, if serum testosterone is elevated, LH and FSH will be inhibited; if testosterone is low due to a primary defect in Leydig cell secretion, LH and FSH will be increased.

FSH is also regulated by other Sertoli cell products; inhibin is a suppressor of FSH. If Sertoli cells are dysfunctional, spermatogenesis may be hindered and an elevated FSH may be a marker for such injury. Some patients with infertility will have reduced inhibin and isolated elevations of serum FSH. Prolactin is a potent inhibitor of GnRH secretion, thus explaining its role in inhibiting LH and testosterone secretion in the clinical condition of hyperprolactinemia.

Testes

LH and FSH circulate in the systemic blood either firmly bound to a binding protein, sex hormone binding globulin (SHBG), loosely bound by albumin or unbound (free testosterone). LH acts on surface receptors of the Leydig cells of the testes to stimulate steroidogenesis resulting in high levels of testosterone in the interstitial space and secretion of testosterone into the blood stream (Chapters 3, 4). The high levels of testosterone in the interstitial space act on the Sertoli cells in the seminiferous tubules to stimulate spermatogenesis. (Fig. 3) FSH also acts on the Sertoli cells and is required for efficient maturation of sperm that are then released into the lumen of the tubules and eventual transport with seminal fluid to the epididymis and ejaculation through the urethra.

Testosterone and its metabolites, estradiol and dihydrotestosterone, travel in the blood stream to many tissues and act on tissue receptors creating the hormonal milieu required for male sexual development and functions associated with maleness. (Fig. 4). The

testes, through their production of steroid and peptide secretory substances, provide the regulatory feedback control of the hypothalamic and pituitary components of the axis.

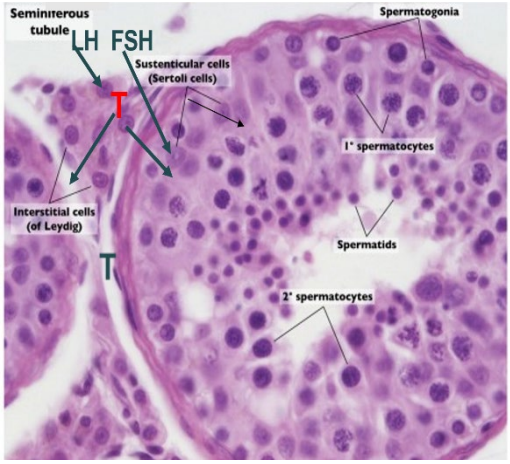

Figure 3. LH action on Leydig Cell and FSH and testosterone action on Sertoli cells.

Integration of the hypothalamic -pituitary system.

The hypothalamus through its complex neuronal network creates the pulsatile release of GnRH and the subsequent stimulation of pituitary gonadotrophs to secrete LH and FSH into the bloodstream to regulate the Leydig cells to release high levels of testosterone necessary for regulation of spermatogenesis and secretion of testosterone into the blood stream. Testosterone and its metabolites bind to cell surface and nuclear tissue receptors for end organ androgenic and estrogenic biologic actions. Regulation of the system occurs at every level, but the closed feedback effects of the steroid hormones are necessary to keep the sex steroids at physiologic levels. If there is a primary defect in hypothalamic GnRH secretion or pituitary secretion of LH and FSH then impaired steroidogenesis and spermatogenesis can occur and low levels of testosterone, LH, and FSH are measured in the blood (central hypogonadotropic hypogonadism). If the primary defect is at the testes level, then

testosterone is low and their negative feedback is reduced, GnRH, LH, and FSH increase in an effort to normalize the system. Low serum T and high levels of LH and FSH are measured in the blood (primary gonadal deficiency). (Fig. 4)

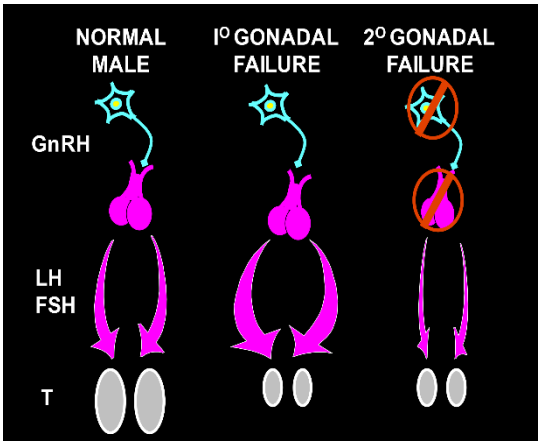

Figure 4. Primary and Secondary Hypogonadism

Suggested reading

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