Physiology of the Hypothalamic Pituitary Gonadal Axis in the Male

Patricia Freitas Corradi, MD[a], Renato B. Corradi, MD[b], Loren Wissner Greene, MD, MA[c,*]

KEYWORDS

• Testosterone • Gonadotropin • Hypogonadism • Primary hypogonadism
• Secondary hypogonadism • Hypogonadotropic hypogonadism

KEY POINTS

- Testosterone synthesis and male fertility are controlled by a negative feedback mechanism between the hypothalamus, the pituitary, and the testis.
- Congenital or acquired conditions leading to a failure of hormone synthesis or action at any level of the hypothalamic-pituitary-gonadal axis result in the clinical syndrome of hypogonadism.
- Medications and contemporary diseases are major causes of impairment of male reproductive function. Novel therapies may improve spermatogenesis along with elevating testosterone levels in men.

INTRODUCTION

Reproductive function changes markedly during life in humans. Impeccable coordination of the hypothalamic-pituitary-gonadal axis is required for normal testicular function in the male, including normal testosterone production and male fertility. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus stimulates the biosynthesis of pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) that, in turn, sustain intragonadal testosterone production and spermatogenesis. A negative feedback mechanism, controlled by sufficient levels of testosterone, is responsible for decreasing both hypothalamic GnRH secretion into the portal circulation and gonadotropin release from the pituitary into the bloodstream.

Congenital or acquired conditions leading to a failure of hormone synthesis or action at any level of the axis result in the clinical syndrome of hypogonadism. Hypogonadism may be caused either by a primary testicular disease or by a secondary (or central) cause (eg, a hypothalamic or pituitary disorder). In the setting of acquired hypogonadism, comorbidities and use of medications are common causes of low testosterone and must be ruled out before making the diagnosis.

Despite the cause, end organ replacement therapy with natural testosterone is recommended for chronic use but with the understood general caveat that this treatment does not improve fertility. If medications that stimulate hypothalamic or pituitary function are successful, these agents may be used for several-month intervals to enhance spermatogenesis; however, their long-term use needs further investigation. In addition, novel therapeutic agents have been proposed to stimulate both testosterone and spermatogenesis. The understanding of hypothalamic-pituitary-gonadal axis physiology is the first step for the correct diagnosis

[a] Division of Endocrinology, New York University School of Medicine, 650 First Avenue, 7th Floor, New York, NY 10016, USA; [b] Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 417 E 68th Street, New York, NY 10065, USA; [c] Bioethics and Medical Ethics, New York University School of Medicine, 650 First Avenue, 7th Floor, New York, NY 10016, USA
* Corresponding author.
E-mail address: loren.greene@nyumc.org

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and treatment of hypogonadism, a frequent condition affecting quality of life and causing other comorbidities including osteoporosis in men.

This article reviews the physiology of the brain-hypothalamic-pituitary-gonadal axis, to correlate it to disorders that can induce male hypogonadism, and discusses available and potential future treatment modalities.

ANATOMIC OVERVIEW OF THE HYPOTHALAMUS AND PITUITARY

The hypothalamus lies at the base of the brain, below the thalamus and the third ventricle, just above the optic chiasm and pituitary gland. It synthesizes and secretes certain neurohormones, often called *releasing hormones* or *hypothalamic hormones*, and these in turn stimulate or inhibit the secretion of pituitary hormones. The neurovascular link between hypothalamus and pituitary gland is the pituitary stalk, which comprises mainly neural and vascular components.

The pituitary gland, also known as the *hypophysis*, is located immediately beneath the hypothalamus, resting in a depression of the base of the skull called the *sella turcica* (Turkish saddle). The pituitary gland is entirely ectodermal in origin but is composed of 2 functionally distinct structures that differ in embryologic development and anatomy: the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary). The adenohypophysis develops from an upward invagination of oral ectoderm named *Rathke's pouch*, whereas the neurohypophysis derives from a downward extension of neural ectoderm, the infundibulum.[1] Because the pituitary is just below the crossing of the visual nerves at the optic chiasm, pituitary tumors enlarging superiorly may affect superior temporal vision selectively.

The adenohypophysis is the manufacturer of an array of peptide hormones—gonadotropins (FSH and LH), adrenocorticotropin, growth hormone, prolactin, and thyroid-stimulating hormone (TSH)—and makes up roughly 80% of the pituitary gland. The release of these pituitary hormones is mediated by hypothalamic neurohormones that reach the adenohypophysis via a portal venous system.

Unlike the adenohypophysis, the neurohypophysis is not glandular and does not synthesize hormones. It stores and releases oxytocin and vasopressin, which are synthesized by neurosecretory cells of the hypothalamus. The neurohypophysis comprises axons of hypothalamic neurons; the neurohypophysis is, therefore, considered an extension of the hypothalamus.

CONTROL OF HYPOTHALAMIC SECRETION

In recent years, kisspeptin, a 54-amino-acid peptide, encoded by the KiSS-1 gene, was identified. Kisspeptin activates the G protein–coupled receptor (GPR54) of the hypothalamus. During pregnancy, kisspeptin levels increase 7000 times. Human placenta secretes varying lengths of the peptide, but the C-terminal 10-amino-acid portion is sufficient to activate GnRH receptors in the fetus, initiating function of the hypothalamic-pituitary-gonadal axis. Kisspeptin also provides the major trigger for puberty. In rat studies, chronic infusion of kisspeptin triggers precocious puberty and enables pubertal development in undernourished animals.[2]

NORMAL HYPOTHALAMIC REGULATION OF GONADOTROPINS

Secretion of pituitary gonadotropic hormones is regulated by the hypothalamic decapeptide hormone, GnRH, which binds to a membrane receptor on pituitary gonadotrophs, stimulating synthesis and secretion of both FSH and LH, the 2 pituitary gonadotropic hormones (**Fig. 1**).

Animal studies found that, in GnRH-deficient mice, pretreatment with GnRH led to both an increase in the gonadotropin content of the pituitary gland and[3] an induction of the expression of pituitary GnRH receptors.[4] Under certain physiologic conditions, GnRH receptor number varies and usually directly correlates with the gonadotropin secretory capacity of pituitary gonadotrophs.

Besides the number of GnRH receptors, pulsatile regimens of GnRH are required for the precision of pituitary gonadotropin signaling.[5] GnRH pulsatility seems to be an intrinsic function of hypothalamic cells, dependent on calcium, with communication similar to nerve synapse conduction.[6] Studies find a sequential response of gonadotropin secretion after exogenous GnRH administration in GnRH-deficient mice; there is an immediate and persistent increase in plasma FSH concentrations during the period of GnRH injections, whereas LH secretion requires a more prolonged and pulsatile GnRH therapy before LH is detected in the circulation.[7] Furthermore, these important data indicate that FSH continues to be synthesized and stored even in the absence of sustained GnRH administration, but continued GnRH stimulation is required for LH synthesis.

FOLLICLE-STIMULATING HORMONE, LUTEINIZING HORMONE, AND TESTICULAR FUNCTION

FSH and LH are heterodimers with structural similarities; each consists of α and β peptide