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Review Article

Update on male reproductive endocrinology

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Abstract: Practitioners of male reproductive and sexual medicine must have an intimate understanding of the physiology of male reproductive endocrinology, as such a knowledge is the cornerstone on which hormonal treatments are based. In this review, we highlight what is known about male reproductive endocrine physiology and the various control mechanisms for the system. We also discuss the limitations of our current understanding of the reproductive physiology. We hope that this review is helpful for male reproductive medicine practitioners in understanding the principles on which hormonal treatments are based.

Keywords: Testosterone; follicle stimulating hormone; luteinizing hormone; estradiol

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Introduction

While only a cursory understanding of the hypothalamic-pituitary-gonadal (HPG) axis is needed in general urological practice, practitioners of male sexual and reproductive medicine must have a thorough and deep understanding of the HPG axis and how alterations in this system can affect the physiology and pathophysiology of both spermatogenesis and testosterone production. The goal of our review is to highlight what is known about the endocrine system's role in spermatogenesis and to discuss how derangements in this system can impair fertility.

Overview of the hypothalamic pituitary gonadal (HPG) axis

The hypothalamic pituitary gonadal axis is comprised of the hypothalamus, the pituitary gland (both anterior and posterior portions) and the testes. The hypothalamus secretes gonadotrophin releasing hormone (GnRH) in a pulsatile fashion, which enters the hypophyseal portal system in order to reach the anterior pituitary gland. This stimulates the anterior pituitary gland to secrete two hormones vital for reproduction, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as well as adrenocorticotropin, growth hormone, prolactin, and thyroid-stimulating hormone(TSH) whose roles in reproduction at normal physiologic levels are poorly understood (1). LH and FSH act on cells in the testes including Leydig, Sertoli and germ cells. Leydig cells are the testosterone producing cells in the testicle, while Sertoli cells produce inhibin B. Both hormones feedback onto the anterior pituitary and the hypothalamus. Testosterone, once released into the peripheral circulation may be converted to estradiol by the enzyme aromatase, which can have effects on fertility. While elegant in its simple design, derangements in any of these steps can have tremendous impact on male fertility.

Hypothalamic physiology—GnRH signaling

The discovery of peptide hormone signals from the

hypothalamus to the anterior pituitary was a Nobel prize winning discovery made by Roger Guillemin and Andrew Schally (2). Among these hormones, GnRH plays the most critical role in both male and female reproduction. GnRH is a short peptide hormone secreted by neurons that originate in the nasal placode. GnRH is secreted by neuronal endings directly into the hypophyseal circulation and binds to GnRH receptors located on pituitary gonadotrope cells in the anterior pituitary (3). GnRH activity is low in childhood and pulsatile secretion begins at puberty. This pulsatile secretion is key to normal reproductive functioning as early studies in animals and humans have shown that the pulsatility of GnRH secretion is essential in maintaining FSH and LH secretion (4-6). In fact, it is differing pulses in GnRH that lead to gonadotrope expression of LH over FSH, or vice versa, with LH synthesis being induced by fast GnRH pulses (>1 pulse per hour) and FSH by slower pulse frequencies (<1 pulse per 2–3 hours) (7). It is this knowledge of GnRH pulsations necessary to maintain LH and FSH secretion that may pave the way for "sperm safe" therapeutic approaches to the treatment of testosterone deficiency syndrome.

FSH and LH

The critical role of the LH and follicle stimulating hormones (FSH) in mainting spermatogenesis (LH/FSH) and testosterone production (LH) is best illustrated by the condition of hypogonadotropic hypogonadism (HH). While Kallman's syndrome (KS) is the prototypical form of HH, there is a continuum of disease of pubertal arrest, and not all patients with pubertal arrest will have olfactory defects like in KS. Men with this class of conditions typically have a defect in GnRH signaling leading to deficits in FSH and LH. FSH and LH signaling is essential for spermatogenesis to occur and, as a result, these patients are azoospermic. It has been shown that treatment of these patients with either pulsatile GnRH delivered by a pump or exogenous gonadotropin therapy combining human chorionic gonadotropin (hCG) (an LH analog) and FSH can lead the return of sperm in the ejaculate (8). However, though there often is return of sperm to the ejaculate and natural pregnancy is possible, these FSH and LH deficient patients may require a prolonged period of therapy with an average time to first return of sperm to the ejaculate of 11.3 months and a time to maximum sperm concentration of 24.9 months. Additionally, many of these couples will need assisted reproductive techniques to achieve pregnancy (9,10). Finally, it has been shown that GnRH administered in a pulsatile manner can initiate and maintain spermatogenesis in patients with hypogonadotropic hypogonadism to a similar degree than FSH and LH supplementation (11). Whether patients with partial or total pubertal arrest respond better to GnRH based treatments is an area of interest, though it seems that those with later arrest in puberty seem to do better with hCG and FSH injections (9).

Given patients with HH will require years of costly FSH/hCG or GnRH injections, there has been research to investigate if hCG injection alone is sufficient to maintain spermatogenesis. The evidence is limited, with one study that looked at men with idiopathic HH who had been treated with a combination of FSH and hCG until sperm was seen back in their ejaculate. The authors were able to demonstrate that after spermatogenesis was induced, hCG could maintain a degree of spermatogenesis in most patients without the need for further FSH supplementation (12). Thus, these experiments show that although FSH is not essential for maintenance of spermatogenesis, it does have a critical role in the establishment of spermatogenesis, and experiments in humans where FSH and LH is suppressed by exogenous testosterone reveal that optimal FSH levels are necessary to achieve quantitatively normal spermatogenesis (13). Along these lines hCG monotherapy alone has been found to be useful in other scenarios such as maintaining testicular size and spermatogenesis in men using exogenous testosterone (14) and improving outcomes of testicular sperm retrieval in men with Kleinfelters and other forms of non-obstructive azoospermia (15,16). The theoretical mechanism by how hCG/LH maintains spermatogenesis is described later in this review as it involves regulation of intra-testicular testosterone.

For the clinician using hCG and FSH to induce spermatogenesis, the clinical question is how to determine the optimal dose and timing based on normal physiology. One can start by looking back at studies that show that there is a linear relationship between GnRH secretion and resultant LH production (17). Unfortunately, some studies on LH and FSH pulsatility suggest great variation among subjects in terms of secretory dose and pulsatility when measured in short time intervals. In fact it is even debated whether there are FSH pulses (5,18-20). Small-scale studies on hCG (or recombinant LH) may imply that low dose hCG divided into several doses (300 IU over 5 days) may be more effective at producing an optimal testosterone to estradiol ratio compared to a single larger dose (1,500 IU ×1 dose) (21). In contrast, one study shows that

hCG induces a biphasic response in testosterone production resulting in a peak at 2–4 hours and a higher one at 48 to 72 hours after one administration of hCG (22). This finding would indicate that every third or fourth day dosing would be ideal. Guidance on FSH dosing is even more elusive as the clinically useful outcome, spermatogenesis, is typically checked at 2.5 to 3 months intervals making it difficult to study multiple FSH doses and regimens. Therefore, the optimal dosing regimen for either hormone remains elusive and is likely patient specific.

Testosterone

The LH produced by the pituitary gland eventually reaches the testicle inducing the production of testosterone from Leydig cells by stimulating the conversion of cholesterol into testosterone (23). Testosterone deficiency syndrome (TDS) can be characterized by a serologic laboratory value, generally total testosterone, below a certain pre-defined cutoff and symptoms such as decrease or loss of muscle strength, libido, memory, vitality, alterations in mood, and erectile dysfunction (ED) (24). Although this condition is typically considered exclusively in older men, symptoms of TDS, along with ED, are prevalent in patients being treated for male factor infertility, affecting up to one third of these patients (25,26). However, although there is a strong association between certain symptoms of TDS such as libido/sexual function with serologic markers such as total testosterone (27), this association has not been found to correlate with the TDS symptoms found in patients being treated for infertility (28). In fact, it is surmised that most of the sexual dysfunction symptoms typical of TDS in this population are of a psychogenic component (29). The role of testosterone's contribution in ED found in infertile men is also controversial because it is not clear how much testosterone contributes to ED in older men, particularly those with co-morbid conditions (30). Despite the weak association of testosterone with sexual dysfunction in infertile men, testosterone remains an essential laboratory in the workup of an infertile patient given its role in spermatogenesis.

The vital role of testosterone in human spermatogenesis is partially elucidated by previously cited studies where it has been shown that spermatogenesis could be stimulated with the LH analog hCG in patients who had active spermatogenesis prior to pituitary suppression (13,31). More intimate knowledge of the intra-testicular hormonal milieu was deciphered through the development of a percutaneous approach to test intra-testicular hormones in humans (32). These studies led to the finding that intra-testicular testosterone was roughly ten times higher than circulating testosterone and that its inhibition was associated with significant declines in spermatogenesis. These findings led to the concept that preservation of intra-testicular testosterone is necessary for spermatogenesis and clinically translates into a potential cutoff in circulating testosterone below which deficits in intra-testicular testosterone (ITT) are suspected. It is apparent that intratesticular testosterone levels similar to normal circulating serum testosterone concentrations are insufficient to support normal spermatogenesis, but besides that observation, no studies in humans exists that defines a cutoff of intratesticular or serum testosterone that is necessary to maintain spermatogenesis adequate enough to maintain normal male fertility potential (32).

The above mentioned gap in knowledge of what a "normal" testosterone is in patients being evaluated for infertility leads one to rely on more current studies on testosterone levels in young men. One recent study helped define testosterone ranges in young men by measuring sample testosterone levels obtained during the conduction of several large cohort studies in a central Centers for Disease Control and Prevention (CDC) lab (33). This study revealed that 303 ng/dL was the fifth percentile value among healthy non-obese patients between 19 and 39 years of age. Unfortunately without any access to semen analyses or other hormonal laboratories it is difficult to assess whether those in the fifth percentile or below had poorer semen quality. However, given these findings, it may not be unreasonable to treat certain patients with testosterone values less than 300 ng/dL and poor semen quality with agents that can increase ITT (34) Treatment strategies that may help increase ITT include the use of hCG injections or selective estrogen receptor modulators that block normal estrogen negative feedback leading to increase in endogenous FSH and LH (e.g., clomiphene citrate). It should be emphasized that trying to increase serum testosterone with exogenous testosterone will not help in this regard as it will decrease ITT by suppressing endogenous LH (as well as FSH) production due to negative feedback action on the hypothalamus and anterior pituitary. In fact, exogenous testosterone typically leads to a decline in spermatogenesis to the level of azoospermia in a majority of patients (35).

Estradiol

As testosterone is produced and released into the bloodstream it reaches peripheral tissues, particularly fat, where it undergoes metabolism into estradiol by the enzyme aromatase (36).

In a revelatory study by Finkelstein, it was shown that estradiol plays a fundamental role in body fat regulation as well as maintaining sexual desire (37). These findings are supported by observational studies correlating higher estradiol levels with improvement in libido in patients undergoing testosterone replacement (38). Studies on patients with aromatase deficiency begins to shed light on its role in fertility, particularly spermatogenesis. Case reports of this rare condition often reveal infertility due to oligospermia (39). The mechanism by which estradiol impacts spermatogenesis is likely related to its role, along with testosterone, in inhibiting LH production in the hypothalamus and pituitary (40). Thus it may be hypothesized that dysregulation of circulating estradiol may lead to altered LH pulse frequencies not ideal for spermatogenesis. The clinical utility of modifying estradiol is highlighted by the use of aromatase inhibitors in men with impaired semen parameters and an abnormal testosterone to estradiol ratio of (<10). Several groups have reported improvement in semen parameters after modifying this abnormal ratio suggesting high levels, or at least abnormal ratios, of estradiol are deleterious for spermatogenesis (41,42). The role of estradiol in testicular maturation as well as its impact on the local autocrine and paracrine hormonal milieu has also been studied, but its importance is not completely defined at this level (43).

Inhibins

While LH is regulated mostly by estradiol and testosterone, FSH negative feedback occurs through inhibin hormones, particularly inhibin B which is produced in Sertoli cells (44). Although inhibins are produced independent of FSH, it has been shown that the quantity of inhibins is modulated tightly by FSH secretion supporting their inhibitory/stimulatory relationship (45). It has been postulated that inhibin B may be a better marker of Sertoli cell mass, and therefore spermatogenesis, in patients not suffering from the histopathologic finding of maturation arrest. This is based on studies correlating inhibin B and sperm production as well as those showing lower inhibin B levels in patients with cryptorchidism with abnormal testicular histopathology and patients with varicoceles (46,47). However, unfamiliarity with clinical relevant ranges of inhibin B, the cost of obtaining the laboratory, and the lack of evidence showing its superiority to obtaining a serum FSH has potentially limited its clinical utility.

Conclusions

A properly functioning HPG axis is essential to spermatogenesis. Practitioners of male sexual and reproductive medicine must have an intimate and clear knowledge of this system and the effects of commonly used medications on the system in order to safely treat patients with impaired fertility. Partial or incomplete understanding of the system can easily lead to mistreatment and unexpected effects on spermatogenesis and libido. We have reviewed the basic physiology of the HPG axis, which is the foundation on which all hormonal manipulation in male infertility is based.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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