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Regulation of testicular function in men: implications for male hormonal contraceptive development☆

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Abstract

In the adult male, the testes produce both sperm and testosterone. The function of the testicles is directed by the central nervous system and pituitary gland. Precise regulation of testicular function is conferred by an elegant feedback loop in which the secretion of pituitary gonadotropins is stimulated by gonadotropin hormone-releasing hormone (GnRH) from the hypothalamus and modulated by testicular hormones. Testosterone and its metabolites estradiol and dihydrotestosterone (DHT) as well as inhibin B inhibit the secretion of the gonadotropins both directly at the pituitary and centrally at the level of the hypothalamus. In the testes, LH stimulates testosterone synthesis and FSH promotes spermatogenesis, but the exact details of gonadotropin action are incompletely understood. A primary goal of research into understanding the hormonal regulation of testicular function is the development of reversible, safe and effective male hormonal contraceptives. The administration of exogenous testosterone suppresses pituitary gonadotropins and hence spermatogenesis in most, but not all, men. The addition of a second agent such as a progestin or a GnRH antagonist yields more complete gonadotropin suppression; such combination regimens effectively suppress spermatogenesis in almost all men and may soon bring the promise of hormonal male contraception to fruition.

Keywords: Spermatogenesis; Testosterone; FSH; LH; Contraception; Male

1. Introduction

The testicle is responsible for both the production of sperm and the synthesis of testosterone in the adult male. Control of both functions is guided by the central nervous system in a classic endocrine feedback loop with follicle stimulating hormone (FSH) and luteinizing hormone (LH) as the key hormonal signals. LH acts on Leydig cells in the testicular interstitium to promote the synthesis of testosterone (T), while FSH affects the Sertoli cells thereby facilitating spermatogenesis. FSH and LH secretion from the anterior pituitary is regulated by hormonal signals from both the hypothalamus and the testes including: T, estradiol (E2), dihydrotestosterone (DHT) and inhibin B. This paper will discuss our current understanding of the endocrine regulation of testicular function, focusing on the central role of FSH and LH, and will then examine efforts to use this knowledge to create a safe and effective form of reversible hormonal contraception for men.

2. Endocrine regulation of testicular function

Secretion of LH and FSH from the anterior pituitary is controlled by gonadotropin hormone-releasing hormone (GnRH). GnRH is a decapeptide that is synthesized in the hypothalamus and carried by the hypothalamico–hypophysial portal system to the anterior pituitary. Binding of GnRH to receptors on pituitary gonadotropes leads to the release of both FSH and LH. GnRH is secreted in pulses that can occur as frequently as every hour or as infrequently as once a day. Direct measurement of GnRH in the hypothalamico–hypophysial portal blood of sheep has demonstrated that a GnRH pulse precedes each elevation of serum LH [1]. Testicular hormones decrease gonadotropin release both by decreasing GnRH production and by decreasing the sensitivity of the pituitary to GnRH stimulation. For example, administration of exogenous T leads to a marked slowing in GnRH pulse frequency in men [2], and inhibits LH and FSH release by a direct pituitary effect [3]. The regulation of GnRH release at the hypothalamus is

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also mediated in part by aromatization of T to E2. In men with hypogonadotropic hypogonadism treated with pulsatile GnRH to initiate gonadotropin secretion, T and E2 infusions decrease secretion of LH and FSH markedly, while infusion of DHT does not [4]. In normal men, however, infusions of both DHT and E2 decrease serum FSH [5,6], demonstrating that differences in development may affect feedback inhibition of gonadotropin release. Inhibin B is the major protein hormone product of the testes [7]. Inhibin B is produced in the Sertoli cells under the stimulatory influence of FSH [8], and acts to inhibit FSH secretion from the pituitary.

The only known effects of LH and FSH are in the testes. LH stimulates testosterone synthesis from Leydig cells while FSH acts on the Sertoli and germ cells to stimulate spermatogenesis. LH promotes spermatogenesis indirectly by increasing intratesticular testosterone [9]. FSH and LH both act through classic protein hormone receptor mechanisms, involving a G-protein associated transmembrane receptor [10]. LH directly stimulates the synthesis of a steroidogenic acute regulatory (StAR) protein, which accelerates the transfer of cholesterol from the outer to the inner mitochondrial membrane, the first step in steroid hormone biosynthesis.

FSH is the main stimulator of seminiferous tubule growth during development, and since the tubules account for 80% of the volume of the testis, FSH is the major determinant of adult testicular size. FSH binds to Sertoli cells and probably to spermatogonial membranes in the testis, and is important in the initiation of spermatogenesis during puberty. Adult men, however, can maintain sperm production despite very low levels of FSH when LH levels are normal, although sperm concentrations are reduced. In this setting, subsequent normalization of FSH levels leads to quantitatively normal sperm production [11].

Mutations in gonadotropin and gonadotropin receptor genes provide unique insight into the roles of gonadotropins in the development and function of the male reproductive axis. Mutations in FSH and LH are of the loss-of-function type, whereas both loss and gain-of-function mutations have been described in the receptor genes. Mutation of the β-subunit of LH leads to an absence of Leydig cells, azoospermia and a lack of spontaneous puberty [12]. An azoospermic male with a mutation in the FSH-β gene and a pre-pubescent phenotype has been described [13]; however, this individual also suffered from a disturbance of Leydig cell function, since his testosterone level was low, and his LH level elevated.

Inactivating LH receptor mutations in genetic males cause congenital pseudohermaphrodism with severe Leydig cell hypoplasia [14,15]. The contrast with LH-β mutations [12] implies that either the LH receptor itself or constitutively produced T has a role in male fetal sexual differentiation. Inactivating mutations in the FSH receptor result only in oligozoospermia with reduced testicular size and normal fertility [16], similar to the phenotypes observed in FSH-β and FSH-receptor knockout mice [17,18]. This finding implies that the presence of FSH is not an absolute requirement for the pubertal initiation and maintenance of spermatogenesis or fertility, a conclusion identical to that ascertained in the FSH and LH depletion experiments in man described above.

Gain-of-function mutations of the LH and FSH receptors have also been described. Activating mutations in LH result in gonadotropin-independent precocious puberty [19] due to testosterone production. A single case of an activating FSH-receptor mutation has been described [20]. This individual had been hypophysectomized due to a pituitary adenoma and was treated with T to prevent hypogonadism, yet had persistently normal spermatogenesis despite undetectable gonadotropin levels.

3. Male hormonal contraceptive development

Because of the shortcomings of existing methods of male contraception, efforts have been made to develop hormonal contraceptives for men similar to those used by women. A hormonal male contraceptive has the potential to be safe, easy to use and reversible. Exogenously administered T functions as a contraceptive by suppressing the secretion of LH and FSH. Low levels of LH and FSH then deprive the testis of the signals required for spermatogenesis; leading to markedly decreased sperm counts in most men. Sperm counts return to normal after the cessation of T administration. In surveys, both men and women in a variety of countries indicate that such a male contraceptive would be useful and appealing [21,22].

Hormonal contraceptive regimens use injectable T esters such as T enanthate (TE) administered by intramuscular injection on a weekly to fortnightly basis. The World Health Organization (WHO) has conducted two multicenter trials of TE for male contraception [23,24]. In the first, sixty percent of 271 subjects achieved azoospermia on a regimen of 200 mg TE weekly and an additional 30% became severely oligozoospermic (sperm concentration of less than 3 million sperm/ml) [23]. The second WHO study enrolled 399 men of whom 98% became severely oligozoospermic or azoospermic. In terms of contraceptive efficacy, there were no pregnancies fathered by the men who became azoospermic, and in men who became severely oligospermic, fertility was reduced to 8.1 pregnancies per 100-person years [24]. This equals a failure rate of 3.5%, which compares favorably to the 10–15% failure rate of condoms, the only other reversible male contraceptive. Sperm counts in all men returned to normal after the cessation of testosterone injections. One notable finding in these studies was that Asian men were more easily suppressed to azoospermia than men of non-Asian ancestry; the reason for this is unknown. Side effects were minor; however, the need for weekly intramuscular injections led to many dropouts and has kept this regimen from being widely adopted or marketed for male contraception.

As a result, longer-acting T esters are currently being studied. Testosterone undecanoate (TU) is a very long-chain ester that results in normal serum T levels for at least 6 weeks in

hypogonadal men [25–27]. Recently, contraceptive trials using TU have been conducted in China and Germany [28–30]. In the Chinese study, subjects received monthly injections of 500 or 1000 mg TU alone. Eleven of 12 in the 500 mg group and 12/12 in the 1000 mg group became azoospermic, with the 1000 mg group achieving azoospermia more quickly [28]. Based on these results, TU is currently being tested in a large-scale efficacy trial in China.

Because testosterone-only regimens fail to completely suppress sperm production in all men, compounds that aid in the suppression of pituitary gonadotropins such as GnRH analogues and progestins are being studied in combination with testosterone to optimize its contraceptive efficacy. The combination of testosterone with GnRH agonists has proven disappointing [31], but research into the use of GnRH antagonists as contraceptives remains promising. GnRH antagonists potently suppress FSH and LH production within hours of administration, and the degree of gonadotropin inhibition is more complete than that produced by agonists.

Three human trials have been conducted using the GnRH antagonist "Nal–Glu" with testosterone. The first two trials showed promise, with 7 of 8 subjects in one study achieving azoospermia by 6–10 weeks of treatment [32,33]. A third trial, however, demonstrated no difference in azoospermia when compared to TE alone [34]. Acyline is a newer GnRH antagonist that can suppress gonadotropin levels for several weeks after a single administration [35]. GnRH antagonists such as Acyline, as well as Cetrorelix and Abarelix are obvious choices for future testing in male contraceptive trials.

Progestins decrease gonadotropin levels in men and combinations of progestins and testosterone for male contraception has been extensively tested. Recent studies have focused on newer compounds, such as the potent oral progestin, levonorgestrel (LNG). A trial of LNG (500 mg orally daily) with TE (100 mg IM/week), showed the LNG–TE combination was superior to TE alone in terms of azoospermia (67% vs. 33%) by 6 months [36]. In addition, 94% achieved either severe oligozoospermia or azoospermia in the LNG–TE group compared to 61% of the TE-alone group. Drawbacks to the LNG–TE regimen included greater weight gain and decreases in HDL-cholesterol when compared to the TE-alone group. Subsequently, lower doses of LNG have been demonstrated to be as effective at achieving azoospermia with less weight gain and smaller reductions of HDL-cholesterol [37]. Other progestins, such as desogestrel (DSG), have been tested in male contraceptive regimens. When combined with 50 and 100 mg doses of weekly TE, 18 of 23 subjects became azoospermic after 24 weeks and all but one suppressed to less than 3 million sperm per milliliter [38]. Another study has shown that 100 mg of TE weekly with 150 μg DSG daily was more effective than TE/LNG at suppressing sperm counts without causing more weight gain or larger drops in HDL-cholesterol than have been seen with LNG/TE [39]. The long-acting androgen TU has been combined with the progestin norethisterone enanthate (NETE) in two trials from Germany [29,30]. In the first TU alone led to azoospermia in 7 of 14 volunteers, but the combination of TU and NETE led to azoospermia in 13 of 14 [29]. The second trial confirmed this high rate of azoospermia and demonstrated that the norethisterone was just as effective when administered orally [30]. Lastly, a combination of depot testosterone and subcutaneous implants containing the progestin etonogestrel resulted in azoospermia in 75% of the study subjects and sperm concentrations of less than 0.1 million sperm per milliliter in 13 of 14 [40]. These promising results have encouraged a pharmaceutical company to sponsor a multicenter Phase II trial of these implants and an androgen for hormonal contraception.

Progestins with anti-androgenic effects such as cyproterone acetate (CPA) have also been tested as potential male contraceptives. In trials of this compound, CPA at administered orally daily in combination with 100 mg TE IM weekly had resulted in rates of azoospermia above 90% [41,42]. Subsequently, CPA has been combined with oral testosterone undecanoate-in a fully oral male contraceptive regimen [43]; however sperm suppression was less complete than seen with injected TU. Alterations in these regimens will hopefully lead to more complete spermatogenic suppression and the eventual availability of a true "male pill".

Transdermal T patches have been in use for the treatment of male hypogonadism for the last several years, but they have only recently been tested for male contraception. A study combining 5.4 mg of T daily delivered via transdermal patch with the progestin levonorgestrel was recently described [44]. This combination was disappointing resulting in azoospermia in only two of eleven men, with counts below 3 million sperm per milliliter. in three others. This low success rate was probably due to the insufficient doses of T delivered by the patch. In another study combining T patches with the progestin desogestrel [45], 24% of participants withdrew from the study because of skin irritation. The only reported use of an androgen gel combined a DHT gel with the progestin levonorgestrel [46]. Contraceptive efficacy was poor with no individuals reaching azoospermia. In addition, the gel was found to be uncomfortable by the majority of subjects; however, newer T gels may be useful in future contraceptive research.

As there are no apparent differences in gonadotropin levels among most men in male contraceptive trials who suppress to azoospermia and those who do not [47,48], it remains a mystery why some men fail to suppress their sperm counts completely despite extremely low levels of gonadotropins. It has been suggested that this difference may be due to greater 5α reductase-II activity in the testes of patients who failed to suppress to azoospermia on 200 mg weekly TE [49]. This would result in higher intratesticular DHT levels that could help to maintain spermatogenesis. Two recent studies, however, have demonstrated that the co-administration of testosterone and a type II 5α-reductase inhibitor (finasteride) did not enhance suppression of spermatogenesis any more than T alone [50] or T plus the

progestin desogestrel [51]. In support of this theory, however, recent analysis of the intratesticular hormone environment during male contraception has shown that the DHT concentration is preserved [52]. Newer inhibitors of 5α-reductase, such as dutasteride, which inhibits both isozymes of the enzyme [53], may be useful in future male contraceptive trials.

Recent research in cynomolgus monkeys implies that suppression of FSH may be more important than low levels of intratesticular T in the inhibition of spermatogenesis in male contraceptive regimens [54]. Indeed, a recent highly sensitive gonadotropin assay has detected FSH immunoreactivity in men on hormonal contraceptive regimens [55], which may imply that residual FSH activity could be present, allowing for spermatogenesis to persist. Lastly, the addition of E2 to T has been shown to enhance T-induced suppression of spermatogenesis [56]. Since E2 is the major source of feedback inhibition of FSH in men at the pituitary [57], enhancing estrogen signal may be crucial in improving rates of azoospermia in future male contraceptive trials. Certainly, further investigation is needed to better understand the innate differences that allow some men to continue to produce sperm in the extremely low gonadotropin environment created by current male contraceptive regimens.

4. Conclusions

Testicular function is regulated by an endocrine feedback loop with many unique features; however, full understanding of gonadotropin control and function has yet to be achieved. Greater knowledge of control of testicular function is essential for improvements in the treatment hypogonadism and in efforts to develop a safe, effective and reversible hormonal contraceptive for men.

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