Chapter 11
What are the roles of androgens and FSH in the hormonal regulation of sperm production?

Robert I. McLachlan and Liza O'Donnell

Overview

Spermatogenesis is the process of sperm development and features mitotic and meiotic divisions, elaborate cytodifferentiation and changing inter- cellular interactions. Sperm are produced within the seminiferous tubules from puberty onward, and spermatogenesis is supported by the somatic Sertoli cells which provide structural and nutritional support. Sperm production is driven by the interplay of autocrine, paracrine and endocrine factors. Endocrine systems regulate both the initiation (neonatal development and puberty) and maintenance of spermatogenesis via a classic negative feedback system (Fig. 1) involving elements of the hypothalamic-pituitary-testis (HPT) axis. Sperm production is dependent on the pituitary gonadotropins, LH and FSH, that are secreted in response to hypothalamic gonadotropin-releasing hormone (GnRH). LH acts on LH receptors (LH-R) in Leydig cells to simulate steroidogenesis and testosterone secretion. Testosterone acts on androgen receptors (AR) in the testicular somatic cells to stimulate sperm production, and also feeds back on the hypothalamus and pituitary to regulate GnRH secretion. FSH acts on receptors (FSH-R) within Sertoli cells to support optimal spermatogenesis, and to produce inhibin B that has a negative feedback effect on pituitary FSH secretion. Interestingly, LH-R and FSH-R share the same chromosomal location, suggesting a common ancestry. The physiology of these key endocrine regulators of spermatogenesis are outlined here and are illustrated by approaches to hormonal contraception and the treatment of infertility.

Androgen action and the androgen receptor (AR)

Androgens are essential for the initiation and maintenance of spermatogenesis (Chapter 3). Androgens act on AR in somatic cells to support spermatogenesis, but germ cells lack AR. Many androgen actions on germ cell development are thought to be mediated via AR in Sertoli cells; however, an action on AR within the peritubular myoid cells surrounding the tubules (Fig. 1) is also required for normal sperm production. In mice lacking AR in Sertoli cells, spermatogenesis does not proceed beyond the early meiotic prophase, indicating that the completion of meiosis depends on androgen action. Reduced androgen levels in the testis are associated with defective meiosis, spermiogenesis, germ cell survival and reduced sperm release, highlighting that androgen action supports multiple aspects of spermatogenesis. Androgen action promotes the pubertal maturation of Sertoli cells and maintains specialized tight junctions between Sertoli cells (Fig. 1) that are necessary for meiotic and post-meiotic germ cell development. Androgen action via AR is also important for the development and function of the adult Leydig cell population which, in turn, is required for normal testosterone synthesis.

Testosterone, or its 5α-reduced metabolite dihydrotestosterone (DHT), binds to cytosolic AR which then dimerize, translocate to the nucleus and bind to androgen response elements in the promoters of androgen-responsive genes to modulate gene transcription, the so-called genomic or "classic" pathway of action. Androgens can also elicit responses via the non-genomic or "non-classic" pathway where AR bound ligand migrates to the plasma membrane to initiate specific intracellular signalling pathways. Studies in mice indicate that both pathways co-operate, and are required in Sertoli cells to support normal spermatogenesis.

FSH and its Receptor (FSH-R)

FSH-R is expressed only in Sertoli cells. FSH action on this receptor initiates signal transduction events including cAMP stimulation and Ca^{++} release leading to intracellular signalling cascades, such as protein kinase-A and C dependent pathways. Studies in mice show that FSH is particularly important for the proliferation and development of the adult Sertoli cell population which in turn determines optimal sperm output. Although sperm production can occur without FSH action in mice, rats and perhaps man, optimal germ cell survival and the production of normal sperm numbers requires FSH action.

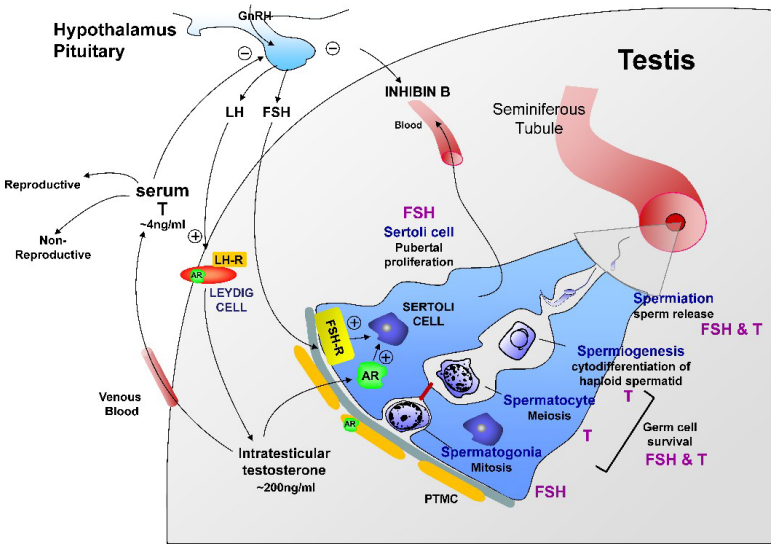

Figure 1. The regulation of spermatogenesis by androgen and FSH. FSH; follicle stimulating hormone, LH; luteinizing hormone, GnRH; gonadotropin-releasing hormone, LH-R; LH receptor, FSH-R; FSH receptor, AR; androgen receptor, PTMC; peritubular myoid cells. Note the location of FSH- R and AR in Sertoli cells that transduce these effects to complete spermatogenesis, and the expression of AR in Leydig cells and PTMCs. Inter-Sertoli cell junctions are denoted by the red line. The 4 phases of spermatogenesis are shown (mitosis, meiosis, spermiogenesis, and release of sperm into the lumen [spermiation]). The principal hormone (FSH or T) regulating each phase is indicated (although evidence for combined action exists in many models). Note also that testicular testosterone levels are exceedingly high relative to those in serum, and that serum T effects androgenic actions on other reproductive and non-reproductive tissues and provides negative feedback on pituitary gonadotropin secretion. Inhibin B exerts inhibitory effects only on FSH release.

The dependence of human spermatogenesis on androgen and FSH

FSH and testosterone support the initiation of spermatogenesis and both are needed for quantitatively normal spermatogenesis in men. The requirement for these hormones in human spermatogenesis is the physiological principle behind male hormonal contraception

wherein exogenous testosterone (with or without progestin) administration reduces pituitary LH and FSH secretion rendering the majority of men (reversibly) azoospermic. This requirement is also the basis of combined gonadotropin therapy to restore fertility in hypogonadotropic hypogonadism (HH) that may result from a deficiency of hypothalamic GnRH drive or pituitary gonadotropin secretion (see Fig. 1). In congenital HH where the testes have not been exposed to FSH or androgens, germ cells do not proceed beyond the spermatogonial stage. In HH acquired after puberty (where pubertal testis development is normal), the testes exhibit spermatogenic regression and markedly reduced sperm counts (oligo/azoospermia). In situations of partial HH, reduced sperm output may permit fertility but complete HH is associated with the cessation of spermatogenesis and infertility.

Testicular androgen physiology

Both the initiation of spermatogenesis at puberty, and its maintenance during adulthood, requires androgen action. Due to its production by Leydig cells in the testicular interstitium (Fig. 1), testosterone is present in high concentration in the testis (>50 fold that in serum). In adults, spermatogenesis can proceed when testicular testosterone levels are lower than normal, but the initiation of pubertal spermatogenesis requires higher levels of androgen support.

Interesting observations regarding androgen regulation of human testicular function include:

- In men engaging in performance-enhancing androgen abuse, serum androgen levels are greatly elevated and spermatogenesis is severely regressed in line with gonadotropin suppression; thus even very high serum levels of exogenous androgens are not able to maintain spermatogenesis.
- The ability of androgens alone to initiate human spermatogenesis is evidenced by the appearance of seminiferous tubules with germ cell differentiation adjacent to androgen secreting Leydig cell tumors in pre- pubertal boys
- During testosterone (±progestin) administration for the purpose of hormonal contraception, LH levels are profoundly suppressed, yet residual intra- testicular testosterone (iTT) levels remain ~ two-fold higher than normal adult serum levels (Chapter 30). While most men given this treatment become azoospermic or severely oligospermic, ~5% of men demonstrate that spermatogenesis is not adequately suppressed for contraceptive efficacy.

Some men may exhibit higher levels of the enzyme that converts testosterone to the more potent androgen dihydrotestosterone, which could preserve some level of androgen activity in the testis. However, the reason why some men fail to achieve adequate sperm count suppression remains unknown.

- A fundamental question arises as to the mechanism of androgen action within the testis: how does one understand the relationship between androgen levels and AR receptor function given that the dissociation constant of the testicular AR is 3 x 10-9M suggesting it is always fully saturated by the very high levels of androgen in the normal testis? What co-factors modulate androgen action in this unique setting? Why are the levels adequate for the full expression of androgen action in non-gonadal tissues so clearly inadequate for spermatogenesis?

The role of FSH in human spermatogenesis

Based on studies in rodents, it is likely that a major, independent role of FSH in establishing the spermatogenic potential of the testis is by promoting Sertoli cell proliferation and development of the functionally competent, adult Sertoli cell population (Chapter 3). This is evident in human spermatogenesis by the fact that FSH administration is frequently required to establish spermatogenesis in congenital HH. Also, the time to spermatogenic induction is shorter in the second round of treatment after a successful first course, pointing to a permanent effect of FSH on Sertoli cell maturation necessary for spermatogenesis. In rodents, spermatogonial development is particularly reliant on FSH, but in humans this requirement is less well understood.

Case reports of rare men with mutations in the FSH gene (FSHβ) or the FSH-R reveal some inconsistencies in the spermatogenic phenotypes: men with FSH-R mutations have moderately elevated FSH levels and variably severe reductions in sperm counts, whereas men with an inactivating FSHβ mutation are azoospermic. This latter observation contrasts with data in mice lacking FSHβ where fertility is preserved. This observation suggests that human spermatogenesis may be more reliant on FSH to establish / maintain spermatogenesis.

Co-operation between androgen and FSH is required for normal spermatogenesis

There is abundant evidence that both hormones are required for quantitatively normal spermatogenesis and that they co-operate, particularly within Sertoli cells, to support multiple aspects of Sertoli and germ cell development. Spermatogenesis can proceed without FSH (at least in rodents), but due to its role in supporting peri-pubertal Sertoli cell proliferation and germ cell survival, the testes are smaller and sperm count is reduced in the absence of FSH.

The requirement for androgens and FSH in human spermatogenesis is evidenced by studies in men undergoing hormonal contraception (exogenous testosterone ± progestin therapy). Contraception-induced gonadotropin suppression in normal men inhibits spermatogenesis, due to an inhibition of spermatogonial maturation, accelerated germ cell apoptosis during meiosis and spermiogenesis, and the failure of sperm to be released by Sertoli cells at the end of spermatogenesis. Studies in men show that either LH or FSH can support these aspects of spermatogenesis during gonadotropin suppression, highlighting their ability to co-operate.

Androgens and FSH have individual, overlapping and synergistic effects on spermatogenesis, and the threshold of action of one hormone is lower when the other hormone is present. For example, a patient with a mutated form of LH exhibited very low testosterone production, very few Leydig cells, but high FSH and the presence of spermatogenesis in his testes, highlighting the remarkable co-operation between androgens and FSH in supporting fertility. In men with experimental gonadotropin suppression, sperm production was restored to 50% of baseline values by either FSH or human chorionic gonadotropin [hCG] (as an LH substitute), whereas only combined hCG plus FSH treatment led to quantitative restoration.

In men with HH, the restoration of endogenous gonadotropin secretion or exogenous gonadotropin replacement therapy (usually using hCG as an LH substitute and human FSH) will induce/restore spermatogenesis in most cases; however, this may take many months given that it takes more than two months for human spermatogonia to develop into spermatozoa. In the case of severe congenital HH, where the Sertoli cell population has not been able to mature, several years of gonadotropin therapy may be required to stimulate fertility.

Conclusion

Androgen and FSH act on receptors within the testes to support somatic cell function and to stimulate spermatogenesis. Androgen action is essential for the production of sperm, and FSH action is required for the development of the functionally normal Sertoli cell population during puberty. Both hormones co-operate and synergize to ensure optimal spermatogenesis and fertility.

Suggested reading

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