

Review

A short evolutionary history of FSH-stimulated spermatogenesis

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ABSTRACT

It is well established in various experimental models that luteinizing hormone (LH) stimulated testosterone (T) production of Leydig cells is the key endocrine stimulus of spermatogenesis. The role of the other gonadotrophin, follicle-stimulating hormone (FSH), is as yet somewhat unclear given that several clinical conditions and experimental models, including men with inactivating *FSH receptor (R)* mutation and male *Fshb* and *Fshr* knockout mice, maintain fairly normal spermatogenesis and fertility. Furthermore, FSH treatment of male infertility has produced at best modest results. On the other hand, there are animal species (e.g. teleost fishes and the Djungarian hamster) where spermatogenesis is primarily FSH-dependent. The purpose of this article is to briefly review the gonadotrophin dependence of spermatogenesis in several model species and examine how it has shifted during evolution from FSH to LH dominance. The information may provide new insight into the role of FSH treatment of male infertility.

Key words: Evolution, Follicle-stimulating hormone, Gonadotrophin, Luteinizing hormone, Pituitary gland, Spermatogenesis, Testis

INTRODUCTION

The adult testis has two functions: the production of sex steroids, in particular testosterone (T), and spermatogenesis. Two pituitary gonadotrophic hormones, follicle-stimulating hormone (FSH) and luteinizing

hormone (LH), are the pivotal endocrine regulators of these testicular functions. LH stimulates T production by Leydig cells of testicular interstitial tissue. T, on the one hand, is secreted into the circulation where it exerts its extragonadal sexual (potency, libido) and anabolic (muscle strength, bone density) actions. On the other hand, T has an intratesticular paracrine role in the maintenance of spermatogenesis, which occurs indirectly through stimulation of Sertoli cells present in the seminiferous tubules adjacent to germ cells. The Sertoli cells then send T-dependent paracrine stimuli to spermatogenic cells. Sertoli cells are also the target of FSH, and thus T and FSH regulate spermatogenesis in a similar indirect paracrine fashion.

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Received: 27-08-2015, Accepted: 05-10-2015

While it is textbook knowledge that LH-stimulated T production is quintessential for the maintenance of qualitatively and quantitatively complete spermatogenesis, the specific role of FSH is not to date so clearly delineated. FSH apparently synergizes with T in the regulation of Sertoli cell function, but there are several examples from a variety of mammalian species showing that spermatogenesis can be initiated and maintained with T alone and that sufficient, though quantitatively suppressed, spermatogenesis is possible without FSH. Moreover, considerable species differences exist with respect to the role of FSH in spermatogenesis in comparison with the almost universal dominance of LH/T action.

The purpose of this review is to reflect on the role of FSH in the LH/T-dominated maintenance of spermatogenesis. Evidence will be presented that the involvement of the two gonadotrophins has taken different directions in the course of evolution. We first briefly review the hormonal regulation of spermatogenesis in the standard experimental models, i.e. the laboratory rat and mouse, and humans. Thereafter, some evolutionary milestones in this regulatory process, as well as notable exceptions, are described. This information may help us better understand the pathogenesis of spermatogenic failure in humans and offer novel strategies for the FSH treatment of male infertility.

ROLE OF LH AND T

Rodents

Much of the experimental work on spermatogenesis has been carried out in the two commonest rodent models, the rat and mouse. They can be discussed together because the role of gonadotrophins in the regulation of their spermatogenesis is very similar. Earlier studies were mainly conducted on rats, but the most recent research, in particular genetic manipulation experiments, has been carried out on mice. Rats and mice have demonstrated that T is essential for spermatogenesis but is relatively independent of FSH.

Rat spermatogenesis can be initiated by T treatment alone in animals made gonadotrophin-deficient by immunization against GnRH¹ or FSH^{2,3} or when treated with GnRH antagonist.³ Numerous more recent

studies have demonstrated the same LH/T dominance in mouse spermatogenesis (see below).

Before puberty, T is essential for male genital differentiation and growth, including testicular descent and Sertoli cell differentiation. The main steps of rodent spermatogenesis that are under T regulation are meiosis and postmeiotic spermiogenesis. T seems to have no role in spermatogonial proliferation and maturation,^{4,5} but it supports spermatocyte and spermatid survival in immature rats,⁶ probably by antiapoptotic mechanisms (summarized by Ruwampura et al⁷). *Androgen receptor (AR)* knockout mice have clearly demonstrated that spermatogenesis does not proceed to complete meiosis without indirect T action through Sertoli cells.^{8,9}

Male *Lhb* and *Lhr* knockout mice are azoospermic,¹⁰⁻¹² indicating that LH stimulated T production is indispensable for spermatogenesis. However, old *Lhr* knockout (LuRKO) mice do show low levels of qualitatively complete spermatogenesis, apparently due to the residual LH independent T production of the immature Leydig cells present in LuRKO testes.¹³ This steroidogenesis is either constitutive or stimulated by paracrine Sertoli cell factors. Because treatment with the antiandrogen flutamide blocks the progression from round to elongating spermatids in old LuRKO mice, the process is clearly shown to be dependent on T stimulation. Although LuRKO mice have elevated FSH levels, due to reduced feedback inhibition of testicular inhibin, the flutamide effect demonstrates that FSH is not able to compensate for the lack of T action in this model.

Numerous studies have demonstrated that FSH alone is not able to rescue full spermatogenesis in gonadotrophin-deficient animals, except for a small increase in the number of spermatogonia and premeiotic spermatocytes;⁷ however, androgen action is absolutely necessary for the completion of meiosis, progression from round to elongating spermatids and spermiogenesis.¹⁴⁻¹⁶

Although Leydig cells produce numerous nonsteroidal paracrine factors, most of the evidence indicates that T is the important mediator of LH effects on spermatogenesis, occurring through paracrine effects of Sertoli cell derived factors. The best evidence for the role of Leydig cell factors other than T in spermatogenesis

genesis comes from comparison of T and LH [using the LH agonist human chorionic gonadotrophin (hCG)] treatments in gonadotrophin-deficient *hpg* mice.¹⁷ Whereas no difference was found in the production of mature sperm, the number of spermatogonia was larger after hCG treatment. Hence, some Leydig cell factor(s) other than T can promote the proliferation and/or survival of spermatogonia. However, high-dose T supplementation seems to fully restore the number of mature spermatids in LuRKO^{18,19} and *hpg*¹⁶ mice. Furthermore, transcriptome analysis of testes of wild-type LuRKO and T-treated LuRKO mice showed that most of the defects in gene expression in the absence of LH action were corrected by T treatment.²⁰

Another potential Leydig cell factor stimulating spermatogenesis could be insulin-like factor 3 (INSL3), though it has been shown to be dispensable for mouse spermatogenesis.²¹ However, recent studies have shown that INSL3 can promote spermatogonial differentiation in zebrafish testis,^{22,23} providing another example of evolutionary divergence in the hormonal regulation of gametogenesis. The spermatogenic effect of INSL3 thus seems to have been lost in mammals during evolution.

Humans and other primates

The overall LH/T effects on spermatogenesis appear to be rather similar in most mammalian species, thus no major differences exist between rodents and primates in this respect. In humans and monkeys, as in rodents, T is important for the distal part of spermatogenesis, i.e. the conversion of round to elongating spermatids and spermiation.^{15,24} As in rodents, T also acts as an antiapoptotic survival factor for spermatocytes and spermatids.²⁵

ROLE OF FSH

Rodents

The first actions of FSH on testicular function start in rodents postnatally when Sertoli cells acquire *Fshr* expression.²⁶ FSH stimulates Sertoli cell proliferation prepubertally and determines their finite number, which then determines the size of the testes and the quantity of spermatogenesis.²⁷ Further evidence for this role of FSH has been obtained from *Fshr* and *Fshb* knockout mice, which have somewhat reduced

testis size in the face of otherwise roughly normal spermatogenesis and fertility.²⁸⁻³⁰ Hence, FSH action per se is not necessary for the initiation of spermatogenesis and maintenance of fertility in mice. The main role of FSH is, in synergy with T, to maximize the quantity of sperm production.

In adult rat testis, FSH impacts on gonocyte maturation, acts as an antiapoptotic survival factor for spermatogonia, spermatocytes and spermatids and supports meiosis and spermiogenesis by regulating the adhesion complexes between germ and Sertoli cells (reviewed by Ruwanpura et al⁷). The findings that FSH treatment increases the numbers of all cell types up to round spermatids may be explained by increased supply of spermatogonia and 'passive' increase in subsequent downstream maturational steps, including the meiotic reduction of late pachytene spermatocytes to round spermatids. However, spermatid elongation was not restored by FSH, indicating the need for additional factor(s), most critically T, as described above.³¹

There is also some evidence of FSH support of spermatocyte survival and of meiosis, but as the sperm mature the role of T becomes more prominent. Sertoli cell-specific *AR* knockout mice have shown that FSH alone can support mitosis and meiosis during the first spermatogenic wave, but androgen action is absolutely necessary for the completion of meiosis, spermiogenesis and fertility in adult life.^{8,9}

Humans and other primates

The individual role of FSH in human spermatogenesis is still largely unexplored, although many similarities exist between rodents and man. One example comes from men with inactivating *FSHR* mutation who are subfertile with reduced testis size, but not azoospermic.³² Likewise, male *Fshr* and *Fshb* knockout mice are fertile with somewhat suppressed, though qualitatively normal, spermatogenesis (see above). This indicates that, as in rats and mice, human spermatogenesis is mainly LH/T-dependent and FSH is able to synergize with T to assure qualitatively and quantitatively normal spermatogenesis, which however is not an absolute prerequisite for fertility.

Another example of the less crucial role on FSH in human spermatogenesis comes from the classical

study where gonadotrophin-suppressed men were treated with hCG, i.e. LH-stimulated T production was achieved in the absence of FSH.³³ Near-complete restoration of spermatogenesis was observed, again indicating that the absence of FSH action had only limited suppressive effect on spermatogenesis.

Studies in men with inactivating *FSHB* or *FSHR* mutations have yielded controversial results. While the five men described with an inactivating *FSHR* mutation all have at least some level of spermatogenesis, two of them having sired two children each,³² the three men with inactivating *FSHB* mutation³⁴⁻³⁶ were all azoospermic. Of these men two were found in cohorts of azoospermic men, so it is not proven that the *FSHB* mutation detected was the cause of their phenotype. Only one of the men was detected as a brother of a woman homozygous for the same mutation and with no other abnormality. It is clear that the mutation data for or against the compulsory role of FSH in the onset and maintenance of spermatogenesis in humans are insufficient to allow final conclusions.

In monkeys, the role of FSH in spermatogenesis has long been under debate.³⁷ While there are studies showing that immunization of monkeys for FSH or *FSHR* brings about azoospermia,^{38,39} the bulk of evidence shows that the FSH dependence of monkey spermatogenesis is very similar to that of other mammalian species, i.e. FSH is not essential, although it synergizes with T to maximize sperm output.

The overall impression from the existing literature, albeit all findings do not agree, is that the two important roles of FSH in spermatogenesis in rodents and man are to regulate the finite number of Sertoli cells before puberty and to act as a survival factor of premeiotic germ cells. Rather than being a mitogen, FSH is a survival factor constraining apoptosis.

Combined action of FSH and T

Besides its support of proliferation and development of spermatogonia, FSH synergizes with T to support spermiation, i.e. the release of spermatids from Sertoli cells.¹⁵ In general terms, although there is plenty of synergy between FSH and T in the regulation of spermatogenesis, the proximal pre-meiotic stages of this process are more FSH-responsive and the post-meiotic maturation is critically T-dependent.

Much of this regulation entails the maintenance of balance between cell division and death (apoptosis) where FSH and T act as survival factors.⁷ The FSH and T effects in the spermatogenic process converge in complementary, synergistic and permissive modes at specific phases of the process to maximize its efficacy (reviewed by^{7,40,41}). One such effect is the regulation of the intrinsic and extrinsic apoptotic pathways of spermatogenic cells.⁷ Synergism is also observed in spermatocyte development and spermiation.⁴¹

FSH and T cooperation is also indicated by findings that lower doses of either hormone is effective when the other one is present.⁴²⁻⁴⁴ This view has led to the speculation that T and FSH may have common postreceptor pathways of action,⁴⁵ evidence for which is still lacking, especially since the main signaling pathway evoked by *FSHR* activation, i.e. protein kinase A-cyclic AMP, is not stimulated by T. However, there are additional signaling systems, like MAP kinase and CREB, where FSH and T actions can converge.⁴⁶

It seems that the role of FSH in mammalian spermatogenesis is less important, since there are many models where spermatogenesis and fertility are maintained at sufficient levels without FSH action. One can therefore question the necessity and meaning of such a weak stimulus of spermatogenesis. Current knowledge of the evolution of the two-gonadotrophin system could offer an explanation, as will be discussed below.

SPECIES DIFFERENCES: EVOLUTIONARY ASPECTS

Concerning the building blocks of gonadotrophin function, i.e. the expression of growth factors with cysteine knot structural signature, such as TGF β and glycoprotein hormones (GPHs), including gonadotrophins, their genes are found in the genome of almost all metazoan (multicellular animals) with the exception of very primitive forms like the sea anemone and sponge.⁴⁷ Likewise, leucine-rich repeat-containing G protein-coupled receptors (GPCRs), akin to gonadotrophin receptors in higher species, have been detected in basal metazoans.^{47,48} It is therefore possible that gonadotrophin action-like regulation of reproduction is a very archaic early evolutionary event,

present in the most primitive metazoans. Whether gonadotrophin regulation of spermatogenesis starts with FSH and/or LH action is crucially dependent on the divergence of the two gonadotrophins and their receptors during evolution.

Lower animal species

The most ancestral form of GPHs is thyrostimulin whose homologues can be detected both in vertebrates and invertebrates, including the fly, nematode and sea urchin,^{49,50} but not in basal animals such as the sea anemone.⁴⁷ It has α and β subunits like all GPHs, which have arisen through gene duplication of a single ancestral gene.⁵¹ These subunits have given rise, through another whole-genome duplication, to another GPH, which is first detected as the single gonadotrophin in the most primitive ancestral agnathan (jawless) vertebrates.⁵²⁻⁵⁴ Hagfish (or the slime eel) and lampreys are the two remaining members of this group and considered the most primitive vertebrates known, living or extinct. Their single pituitary GPH has no specific LH- or FSH-like function. The next evolutionary step includes retention of thyrostimulin in vertebrates and the divergence of hagfish GTHb to Lhb, Fshb and Tshb during additional whole-genome duplications. The first duplication product was akin to Lhb, after which the common ancestor of Fshb and Tshb formed during the next duplication.⁵¹ As a result of this, most jawed teleost fishes have two gonadotrophins, Lh and Fsh, akin to those in mammals.⁵⁵ However, the biological actions of the two primitive fish gonadotrophins are not as well-defined as in mammals.

Two glycoprotein hormone receptors, again results of gene duplication and functional diversification, are first encountered in the lamprey, but it has not been possible to classify them unequivocally as being specific for Lh, Fsh or Tsh.⁵⁶ Their overall structure is surprisingly close to their mammalian counterparts. Interestingly, despite the two gonadotrophin receptors, the lamprey has only one gonadotrophin. It is therefore understandable that the two lamprey gonadotrophin receptors cannot have Lhr- or Fshr-like specificity because these two ligands only evolve later. It therefore seems that the coevolution of the two-gonadotrophin system is driven by the evolution of receptors, which is followed by that of the cognate ligands.

Teleost fish are the first evolutionary stage that clearly has two gonadotrophins and their cognate receptors with partially acquired specificity. Although there are exceptions, the general pattern in fishes is that Fshr is responsive to both Fsh and Lh, whereas Lhr only responds to Lh.⁵⁵ Besides functional promiscuity, in addition the sites of expression of fish gonadotrophin receptors are more relaxed than will be the case with higher vertebrates. Taking into account the earlier appearance of Lh (see above), the fact that Lh can activate both Lhr and Fshr and that the gonadotrophin-responsive gonadal cells initially expressed both gonadotrophin receptors, it is enigmatic why evolution took the path of introducing the two-gonadotrophin system for gonadal regulation. The Lh/Lhr system might have been sufficient, as is implied by the minor role of Fsh in male mammalian fertility (see above). The two gonadotrophins were mainly created for the needs of ovarian function.

Zebrafish

It appears that teleost fishes, including the model species zebrafish, are halfway through in the evolution of the specific two-gonadotrophin regulatory system of gonadal function. As described before, lampreys and hagfish have one gonadotrophin and two non-specific gonadotrophin receptors. Teleost fishes have acquired two specific gonadotrophins, but their cognate receptors still possess some degree of promiscuity: Fshr responds to both Fsh and Lh, whereas only Lhr is specific for the cognate ligand.⁵⁷ Another divergence from the mammalian system is that Fshr and Lhr are expressed in fishes both in Leydig and Sertoli cells.^{58,59}

Recent studies on gonadotrophin and gonadotrophin receptor knockouts in zebrafish using the TALE technique⁶⁰⁻⁶² have elucidated the marked special features of gonadotrophin action that diverge from mammals. Neither *lhb* nor *lhr* knockouts affected testicular histology, fertilization rate or sperm motility in male fishes, indicating that Lh signaling, unlike in mammals, is not important for the fertility of the male zebrafish. This would indicate the importance of Fsh action for male zebrafish fertility. Nevertheless, *fshb*- and *fshr*-deficient male zebrafish were fertile, with only some delay in sexual maturation. The promiscuity of Fshr to Lh and Fsh stimulation

and the coexpression of both gonadotrophin receptors in Leydig and Sertoli cells provide an explanation for these apparently surprising findings. Double *lhb/fshb* knockout males showed delayed sexual maturation but were finally fertile. Infertility with azoospermia was only found in *lhr/fshr* double knockout males.

The studies show that unlike in mammals, Lh action is not needed for zebrafish spermatogenesis and is more dependent on Fshr activation. However, in the absence of Fsh, Lh can activate Fshr, and in the absence of Fshr its effect is compensated for by Lh action because both gonadotrophin receptors are expressed in Leydig and Sertoli cells. Finally, the mild phenotype of combined *lhb/fshb* deletion can be explained by the fact that non-liganded gonadotrophin receptors may have a low level of constitutive activity which is able to maintain a low level of Lhr/Fshr activity sufficient to maintain partial spermatogenesis. A similar difference is observed in male mice where the testicular phenotype is more severe in *Fshr* than *Fshb* knockout⁶³ apparently for the same reason.

When we now consider the evolution of gonadotrophin maintenance of spermatogenesis, it seems that the specialization of LH and FSH action has occurred gradually and taken a different course in various species. First, jawless fishes have one gonadotrophin and two non-specific gonadotrophin receptors. Thereafter, the two gonadotrophins appear in bony fishes, which show a relaxed specificity in ligand-receptor interaction. Usually only LHR is specific for the cognate hormone and FSH is the dominant gonadotrophin in spermatogenesis. The situation will be the opposite in mammals, but with some remarkable exceptions.

The Djungarian hamster

The Djungarian hamster (*Phodopus sungorus*), a seasonally breeding rodent, forms a peculiar exception in the mode of hormonal control of spermatogenesis amongst mammalian species. Hypophysectomized males or those gonadotrophin-suppressed during short days (photoinhibited) respond to FSH treatment with full recovery of spermatogenesis without simultaneous stimulation of Leydig cell steroidogenesis.⁶⁴⁻⁶⁶ In contrast, LH alone has a marginal effect on spermatogenesis even though it restores testicular T production to control level. It seems therefore that FSH alone, and without additive or synergistic action of T, is

able to drive the whole spermatogenic process in this species. Remarkably, no effect of FSH on Leydig cell function, including stimulation of T production, could be detected. Furthermore, T synergized with FSH in the maintenance of spermatogenesis in the Djungarian hamster because sperm production, and in particular the number of elongating spermatids, was higher in the combined treatment than with FSH alone.⁶⁴ This finding emphasizes the role of T in the maturation step from round to elongating spermatids, also considered crucial in rodents.

Further studies in photoinhibited and antiandrogen (flutamide) treated animals demonstrated that FSH treatment in these conditions was able to increase Sertoli cell and spermatogonial numbers and to advance the premeiotic phases of spermatogenesis.⁶⁷ The conditions used were not appropriate to study whether FSH would have increased the numbers of postmeiotic germ cells, which leaves the question open whether FSH in the absence of T is able to advance later stages of spermatogenesis. Because a low level of T production is possible in the photoinhibited hamster testis in the absence of LH stimulation, the current evidence is not sufficient to conclude whether postmeiotic maturation of hamster sperm is possible with FSH stimulation alone. The least we can conclude about the Djungarian hamster is that its spermatogenesis is predominantly dependent on FSH with a possible supporting role of T, which is the opposite to other mammalian species.

PHARMACOLOGICAL AND GENETIC AMPLIFICATION OF FSH ACTION: EFFECTS ON SPERMATOGENESIS

The efficacy of FSH therapy in the treatment of oligozoospermia remains a contentious issue.⁶⁸⁻⁷⁰ The results are variable, although there are some promising new leads indicating that specific genetic polymorphisms in *FSHb* and *FSHR* may cause functional FSH deficiency, in which case FSH therapy may improve spermatogenesis.⁷¹⁻⁷³ To be effective, FSH therapy will therefore require stratification of men according to genotype into FSH-responsive and non-responsive individuals.

Another explanation for the poor outcome of the FSH treatments is that the doses used have been

too small, and to be effective they have to be pharmacological. Paradisi et al^{74,75} and Ding et al⁷⁶ have observed in placebo-controlled studies that a high dose of recombinant FSH (300 IU every other day for ≥ 4 -5 months), instead of the standard dose of 75 IU/every other day, significantly increased sperm counts and pregnancy rates.






The success of treatment with higher FSH doses may have relevance to some additional findings in the involvement of FSH in spermatogenesis. Gromoll et al reported in 1996⁷⁷ a hypophysectomized male who had normal spermatogenesis despite unmeasurable gonadotrophin levels. He was found to carry a *D567G* mutation in exon 10 of *FSHR*, which evoked marginal constitutive activity of FSHR. Replication of the same mutation in transgenic mice in the gonadotrophin-deficient *hpg* background increased the number of FSH-responsive Sertoli cells, spermatogonia and postmeiotic germ cells, but did not lead to full spermatogenic maturation. Hence, although the mouse model confirmed the constitutive biological activity of the human *D567G FSHR* mutation, it did not confirm the human finding of full spermatogenesis. Furthermore, these models were confounded by the paracrine stimulation of Leydig cell T production by the FSH-stimulated Sertoli cells, which made it difficult to decipher whether the spermatogenic effect was due to this effect or direct Sertoli cell stimulation by the mutant FSHR. Our very recent findings

(Oduwole et al, manuscript in preparation) of fully compensated spermatogenesis in another genetically modified mouse model of a strongly activating *Fshr* mutation expressed in the *Lhr*^{-/-} background suggests that the spermatogenesis in the male patient may really be due to the *FSHR* mutation and that the lack of a full phenocopy in the mouse may be due to too weak activity of the human gain-of-function *FSHR* mutation in the mouse.

Taken together, these findings suggest that very strong FSHR stimulation can compensate for the lack of androgen stimulation in spermatogenesis and that T and FSH can totally compensate for each other, provided that the level of stimulation of the remaining hormone is strong enough. Hence, there seem to be no specific stages of spermatogenesis that are exclusively T- or FSH-dependent. The dose may be critical when treating oligozoospermia with FSH and the typically used doses may have been insufficient. Finally, the currently accepted assumption that T is a '*sine qua non*' in spermatogenesis may not be true. Almost the same can be achieved with FSH, but it requires pharmacological doses.

CONCLUDING REMARKS

In this review we have made an evolutionary journey from lamprey to humans in the gonadotrophin regulation of spermatogenesis (Figure 1). The regula-

Species	Gonadotrophins	Receptors	Dominant hormone in spermatogenesis
Lamprey, Slime eel	single GPH*		?
Zebrafish	fsh lh		fsh
Rat Mouse	Fsh Lh		Lh
Djungarian hamster	Fsh Lh		Fsh
Primates	FSH LH		LH

* , gonadotrophic hormone

Figure 1. The gonadotrophins, their receptors, specificity of the interaction and dominant gonadotrophin in the regulation of spermatogenesis in the species discussed in the text. The abbreviations of the molecules are according to the Committee on Genetic Symbols and Nomenclature (1957). *Union of International Sci Biol Ser B*, Colloquia No. 30.

tion starts from the action of a single gonadotrophin on two non-specific receptors in the slime eel and lamprey, and moves to jawed fishes in which FSH is the dominant gonadotrophin in a situation where FSHR has relaxed ligand specificity to FSH and LH and where both gonadotrophin receptors are expressed in Sertoli and Leydig cells. When evolution reaches mammals, LHR and FSHR have become specific for their cognate ligands and are expressed only in Leydig or Sertoli cells, respectively. FSH can still in a paracrine fashion, through Sertoli cells, stimulate some T production, but in mammals in general LH is the driving force of spermatogenesis. The Djungarian hamster forms a remarkable exception that proves the rule, maintaining the fish-like FSH-dependent pattern of spermatogenic regulation. The real importance of FSH in the regulation of mammalian spermatogenesis still remains an enigma, since many mammalian models seem to maintain sufficient spermatogenesis in the absence of FSH. The effect of strong FSH stimulation on mammalian spermatogenesis appears to hark back to the evolutionarily earlier fish and suggests that higher than previously presumed doses of FSH may be effective in the treatment of male infertility.

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