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A Study On Endocrinology Of The Male Reproductive System

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ABSTRACT

The testes synthesize two important products: testosterone, needed for the development and maintenance of many physiological functions; and sperm, needed for male fertility. The synthesis of both products is regulated by endocrine hormones produced in the hypothalamus and pituitary and locally within the testis. Testosterone is indispensable for sperm production, however, both testosterone and Follicle Stimulating Hormone (FSH) are needed for optimal testicular development and maximal sperm production. Sperm are produced via the extraordinarily complex and dynamic process of spermatogenesis that requires co-operation between multiple testicular cell types. While it has long been known that testosterone and FSH regulate spermatogenesis, years of research have shed light on many of the intricate mechanisms by which spermatogonial stem cells develop into highly specialized, motile spermatozoa. Spermatogenesis involves the concerted interactions of endocrine hormones, but also many paracrine and growth factors, tightly co-ordinated gene, and protein expression programs as well as epigenetic modifiers of the genome and different non-coding RNA species. This chapter provides a comprehensive overview of the fascinating process of spermatogenesis and its regulation and emphasizes the endocrine regulation of testicular somatic cells and germ cells.

Keywords: LH, FSH, Endocrine Hormones, Testosterone

1. INTRODUCTION

The secretion of hypothalamic gonadotropin-releasing hormone (GnRH) stimulates production of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the pituitary. LH is transported in the blood stream to the testes, where it stimulates Leydig cells to produce testosterone: this can act as an androgen (via interaction with androgen receptors) but can also be aromatized to produce estrogens. The testes, in turn, feedback on the hypothalamus and the pituitary via testosterone and inhibin secretion, in a negative feedback loop to limit GnRH and gonodotropin production. Both androgens and FSH act on receptors within the supporting somatic cells, the Sertoli cells, to stimulate various functions needed for optimal sperm production. Spermatogenesis is the process by which immature male germ cells divide, undergo meiosis and differentiate into highly specialized haploid spermatozoa. Optimal spermatogenesis requires the action of both testosterone (via androgen receptors) and FSH. Spermatogenesis takes place within the seminiferous tubules of the testis. These tubules form long convoluted loops that pass into the mediastinum of the testis and join an anastomosing network of tubules called the rete testis. Spermatozoa exit the testes via the rete and enter the efferent ductules prior to their passage through, and final maturation in, the epididymis. The seminiferous tubules are

comprised of the seminiferous epithelium: the somatic Sertoli cells andthe developing male germ cells at various stages of development. Surrounding the seminiferous epithelium is a layer of basement membrane and layers of modified myofibroblastic cells termedperitubular myoid cells. The interstitial space between the tubules contains blood and lymphaticvessels, immune cells including macrophages and lymphocytes, and the steroidogenic Leydig cells.

Male germ cell development relies absolutely on the structural and nutritional support of the somatic Sertoli cells. Sertoli cells are large columnar cells, with their base residing on basementmembrane on the outside of the seminiferous tubules, and their apical processes surrounding germ cells as they develop into spermatozoa. Androgens (and estrogens) and FSH act on receptors within Sertoli cells: germ cells lack both androgen and FSH receptors, therefore thesehormones act directly on Sertoli cells to support spermatogenesis. Sertoli cells regulate the internal environment of the seminiferous tubule by secreting paracrine factors and expressing cell surface receptors needed for germ cell development. Sertoli cells form intercellular tight junctions at their base: these occluding junctions prevent the diffusion of substances from the interstitium into the tubules and create a specialized milieu required for germ cell development.These junctions are a major component of the so-called 'blood-testis-barrier', wherein the passage of substances from the circulation is prevented from entering the inner part of the seminiferous tubules. The most immature germ cells, including germline stem cells, reside near the basement membrane of the seminiferous tubules and thus have free access to factors from the interstitium, however germ cells undergoing meiosis and haploid cell differentiation develop"above" the blood-testis-barrier and thus are entirely reliant on the Sertoli cell microenvironment. The seminiferous tubules are also an immune-privileged environment. Meiotic and post-meiotic germ cells develop after the establishment of immune tolerance, and could thus be recognized as "foreign" by the immune system, therefore the seminiferous tubules,via a number of different mechanisms including the blood-testis-barrier, actively excludeimmune cells and factors from entering the seminiferous tubules and being exposed to meiotic and haploid germ cells.

The number of Sertoli cells determines the ultimate spermatogenic output of the testes. In humans, Sertoli cells proliferate during the fetal and early neonatal periods and again prior to puberty. At puberty, Sertoli cells cease proliferation and attain a mature, terminally differentiatedphenotype that is able to support spermatogenesis. Disturbances to Sertoli cell proliferation during these times can result in smaller testes with lower sperm production. Conversely,disturbances to the cessation of proliferation can result in larger testes with more Sertoli cells and greater sperm output. It seems likely that the failure of many men with congenital hypogonadotropic hypogonadism (HH) to achieve normal testicular size and sperm output, whentreated by gonadotropic stimulation, may result from deficient Sertoli cell proliferation during fetal and prepubertal life. The action of both androgens and FSH on Sertoli cells is necessary for the ability of Sertoli cells to support full spermatogenesis. In addition, the expression of many genes and paracrine factors within Sertoli cells is necessary for spermatogenesis.

Spermatogenesis relies on the ability of Leydig cells to produce testosterone under the influenceof LH. Fetal Leydig cells appear following gonadal sex differentiation (gestational weeks 7-8 inhumans) and, under the stimulation of placental human chorionic gonadotropin (hCG), results inthe production of testosterone during gestation. In humans, fetal cells decrease in number towards term and are lost from the interstitium at about twelve months of age. The adult population of Leydig cells in humans arises from the division and differentiation of mesenchymalprecursor cells under the influence of LH at puberty. Factors secreted by Sertoli cells and peritubular myoid cells are also necessary for Leydig cell development and steroidogenesis. Optimal Leydig cell steroidogenesis also relies on a normal

complement of macrophages withinthe testicular interstitium as well as on the presence of androgen receptors in peritubular myoid cells, presumably because these cells secrete factors necessary for Leydig cell development andfunction.

2. General Anatomy of the Male Reproductive System

The testis lies within the scrotum and is covered on all surfaces, except its posterior border, by aserous membrane called the tunica vaginalis. This structure forms a closed cavity representing the remnants of the process vaginalis into which the testis descends during fetal development. Along its posterior border, the testis is loosely linked to the epididymis which at its lower pole gives rise to the vas deferens.

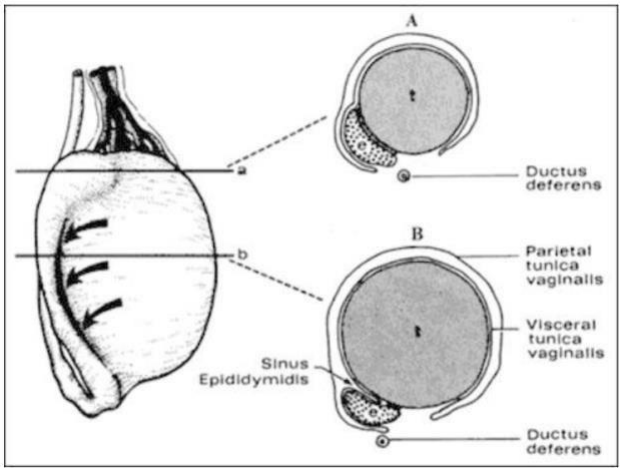


Figure 1: The relationships of the tunica vaginalis to the testis and epididymis are illustrated from the lateral view and two cross-sections at the level of the head and mid- body of the epididymis. The large arrows indicate the sinus of the epididymis posteriorly.

The testis is covered by a thick fibrous connective tissue capsule called the tunica albuginea. From this structure, thin imperfect septa run in a posterior direction to join a fibrous thickeningof the posterior part of the tunica albuginea called the mediastinum of the testis. The testis is thusincompletely divided into a series of lobules. Within these lobules, the seminiferous tubules form loops, the terminal ends of which extend asstraight tubular extensions, called tubulin recti, which pass into the mediastinum of the testis and join an anastomosing network of tubules called the rete testis.

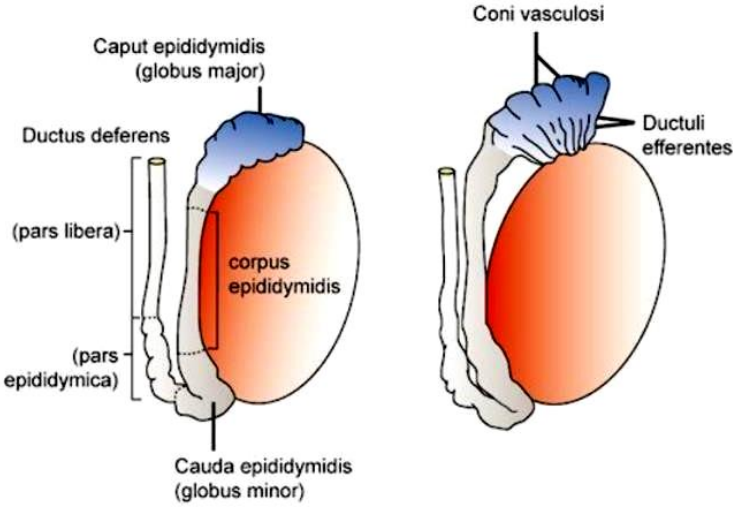


Figure 2: The arrangement of the efferent ducts and the subdivisions of the epididymisand vas are shown.

From the rete testis, in the human,a series of six to twelve fine efferent ducts join to form the duct of the epididymis. This duct, approximately 5-6m long in the human, is extensively coiled and forms the structure of the epididymis that can be divided into the head, body, and tail of the epididymis. At its distal pole,the tail of the epididymis gives rise to the vas deferens.

An Overview of Spermatogenesis

Spermatogenesis is the process by which precursor germ cells termed spermatogonia undergo acomplex series of divisions to give rise to spermatozoa. This process takes place within the seminiferous epithelium, a complex structure composed of germ cells and radially-oriented supporting somatic cells called Sertoli cells. The latter cells extend from the basement membraneof the seminiferous tubules to reach the lumen. The cytoplasmic profiles of the Sertoli cells are extremely complex as this cell extends a series of processes that surround the adjacent germ cellsin an arboreal pattern.

Spermatogonial Renewal and Differentiation

Spermatogonia are precursor male germ cells that reside near the basement membrane of the seminiferous epithelium. Spermatogonial stem cells (SSC) divide to renew the stem cell population and to provide spermatogonia that are committed to the spermatogenic differentiation pathway. Adult mouse and human SSC are pluripotent and have the ability to differentiate into derivatives of all three germ layers.

In general, two main types of spermatogonia, known as Type A and B, can be identified in mammalian testes on the basis of nuclear morphology. Type A spermatogonia exhibit fine pale-staining nuclear chromatin and are considered to include the SSC pool, the undifferentiated spermatogonia (Aundiff) pool, and spermatogonia which have become committed to differentiation (Adiff). The Cundiff pool is comprised of the SSC, single A spermatogonia (As), and interconnected cysts of either 2 (known as A paired, or Apr) or more (aligned or Aal) undifferentiated spermatogonia that remain connected by intercellular bridges. Once per cycle, the Cundiff cells transform into Adiff cells, which are then designated A1, A2, etc. Rediff spermatogonia ultimately divide to produce type B spermatogonia. Type B spermatogonia

show coarse chromatin collections close to the nuclear membrane and represent the more differentiated spermatogonia that are committed to entry into meiosis.

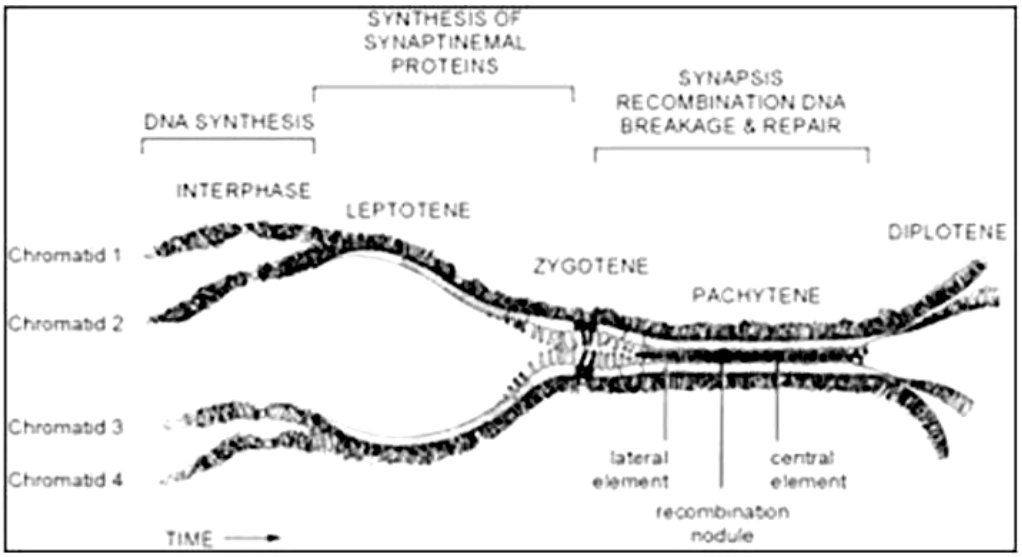
Recent studies have focused on dissecting the molecular properties of the various A spermatogonial subtypes to identify the SSC population of the testis. Studies have also investigated their clonal behavior as they divide and differentiate. The pioneering technique of spermatogonial transplantation is used to determine the regenerative capacity of a cell populationand to define subtypes with SSC potential.

Meiosis

Meiosis is the process by which gametes undergo reductive division to provide a haploid spermatid, and in which genetic diversity of the gamete is assured via the exchange of genetic material. During meiosis I, DNA synthesis is initiated, resulting in a tetraploid gamete. The exchange of genetic information is achieved during meiotic recombination, which involves the induction of DNA double-strand breaks

(DSBs) during pairing of homologous chromosomes andthe subsequent repair of DSBs using homologous chromosomes as templates. Once the exchange of genetic material is complete, the cells proceed through two successive reductive divisions to yield haploid spermatids. This process is governed by genetically programmed checkpoint systems.

Meiosis commences when Type B spermatogonia lose their contact with the basement membraneand form preleptotene primary spermatocytes. The preleptotene primary spermatocytes commence DNA synthesis and the condensation of individual chromosomes begins, resulting inthe appearance of thin filaments in the nucleus which identify the leptotene stage. At this stage,each chromosome consists of a pair of chromatids. As the cells move into the zygotene stage, there is a further thickening of these chromatids and the pairing of homologous chromosomes. The further enlargement of the nucleus and condensation of the pairs of homologous chromosomes, termed bivalents, provides the nuclear characteristics of the pachytene stage primary spermatocyte. During this stage, there is an exchange of genetic material between homologous chromosomes derived from maternal and paternal sources, thus ensuring the geneticdiversity of the gametes. The sites of exchange of genetic material are marked by the appearance of chiasmata and these become visible when the homologous chromosomes separate slightly during diplotene. The exchange of genetic material involves DNA strand breakage and subsequent repair.



The diagrammatic representation of the events occurring between homologous chromosomes during the prophase of the first meiotic division shows the period of DNA synthesis, the formation of the synaptonemal complex, and the processes involved in recombination.

The diplotene stage is recognized by partial separation of the homologous pairs of chromosomesthat remain joined at their chiasmata and each is still composed of a pair of chromatids. With thedissolution of the nuclear membrane, the chromosomes align on a spindle and each member of the homologous pair moves to opposite poles of the spindle during anaphase. The resultant daughter cells are called secondary spermatocytes and contain the haploid number of chromosomes but, since each chromosome is composed of a pair of chromatids, the DNA contentis still diploid. After short interphase, which in the human represents approximately six hours, the secondary spermatocytes commence a second meiotic division. The chromatids of each chromosome move to opposite poles of the spindle, forming daughter cells that are known as round spermatids. Meiotic maturation in humans takes about 24 days to proceed from the preleptotene stage to the formation of round spermatids.

It is well known that advancing maternal age is associated with increased meiotic errors leadingto reduced gamete quality, however, whether this phenomenon occurs in males has been the subject of debate. A recent study in mice showed that advanced age was associated with increased defects in chromosome pairing, however, no increase in aneuploidy was observed at Metaphase II, suggesting that such errors were corrected during metaphase checkpoints in males.Therefore, advanced age, at least in mice, has more of an impact on gamete aneuploidy in femalescompared to males.

3. The Role of Sertoli Cells in Spermatogenesis

Sertoli cells have an intimate physical relationship with the germ cells during the process of spermatogenesis. The cytoplasmic extensions that pass between the germ cell populations surrounding the Sertoli cell provide structural support through a microfilament and microtubularnetwork present in the cytoplasm of the Sertoli cell. This architecture is not static but changes inthe tubule depending on the stage of the spermatogenic process.

Sertoli cells regulate the internal environment of the seminiferous tubule. This regulation is facilitated by specialized inter-Sertoli cell occluding-type junctions which are formed at the siteswhere processes of Sertoli cell cytoplasm from adjacent cells meet. These junctions contribute to the blood-testis barrier that regulates the entry of a variety of substances into the seminiferoustubule. These occluding junctions towards the base of Sertoli cells prevent the diffusion of substances from the interstitium into the inner part of the seminiferous tubule. Because of the location of the junctions, spermatogonia have free access to substances from the interstitium (including the vasculature), however, the germ cells “above” this junction, including meiotic and post-meiotic germ cells, have their access to factors from the interstitium restricted by the blood-testis-barrier. This effectively divides the seminiferous epithelium into a basal compartment containing spermatogonia, and an adluminal compartment containing meiotic and post-meiotic germ cells. As preleptotene spermatocytes migrate from the basement membrane of the tubule into the adluminal compartment, these tight junctions open up to allow this cellular migration totake place and reform beneath the preleptotene spermatocytes which have now left the basement membrane to form leptotene spermatocytes.

4. CONCLUSION

Male infertility due to undetectable (azoospermia) or low (oligozoospermia) numbers of sperm in the ejaculate may occur in many clinical settings. Details of the approach to the treatment of men with reduced sperm counts are reviewed elsewhere. Gonadotropic stimulation of sperm production is appropriate in men with gonadotropin deficiency, such as hypogonadotropic hypogonadism (HH) or acquired androgen deficiency, may be of limited benefit in some men with oligospermia but is of no or minimal benefit in men with non-obstructive azoospermia dueto primary testicular failure in whom gonadotropic drive is already high.

As androgens are essential for the initiation of sperm production, the induction of spermatogenesis in HH acquired after puberty is achieved by the administration of hCG (as an LH substitute), 1000-2000 IU sc 2-3 times per week. Prolonged therapy is required to produce sperm in the ejaculate, given that human spermatogenesis takes more than 2 months to producesperm from immature spermatogonia. Treatment with hCG alone may be sufficient for the induction of spermatogenesis in men with larger testes due to potential residual FSH action. However, for many men, and particularly for those with congenital HH, the co-administration ofFSH (75–150 IU sc 3 times per week) is needed for maximal stimulation of sperm output. In men with congenital HH, FSH is needed to induce Sertoli cell maturation,

whereas men with acquired HH and smaller testes benefit from the co-administration of FSH due to the well-knownsynergistic actions of FSH and androgens on spermatogenesis as described above. It is also worthnoting that in some men, treatment may need to be particularly protracted (1-2 years) to enable pubertal maturation of the testis, for example, the induction of spermatogenesis in Kallmann's syndrome.

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