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Chapter

Endocrine Functions of the Testes

Emojevwe Victor, Igiehon Osarugue, Oyovwi Mega Obukohwo, Nwangwa Eze Kingsley and Naiho Alexander Obidike

Abstract

The testes, also known as the male gonads are found in the scrotal sacs. In addition to their spermatogenic functions, they also secrete steroids and protein hormones. The steroid hormones are the androgens, testosterone and dihydrotestosterone as well as estrogen, while the protein hormones are inhibins, activins, and anti-Mullerian hormone (AMH). This chapter therefore discusses the role of the testis in the production and functions of the testicular androgens as well as testicular protein hormones.

Keywords: testicular functions, anti-Mullerian hormone (AMH), testosterone, inhibin, activin

1. Introduction

The testes, also known as the male gonads, are male reproductive organs located in the scrotal sacs and basically responsible for spermatogenesis [1]. However, various studies have shown that in addition to the spermatogenic functions, the testes also secrete steroid and protein hormones, a role known as the endocrine functions of the testis. The testis produces androgens such as testosterone (T), dihydrotestosterone and estrogen which are the most typical steroids, and also releases proteins called inhibins, activins, and anti-Mullerian hormone (AMH)/Mullerian-inhibiting substance (MIS) [1]. Collectively these hormones maintain the health of the testes and ensure its proper functioning regarding sperm production and delivery. In the following sessions, the androgens and the testicular protein hormones are discussed in detail.

2. The androgens

Androgens are required for the development and maintenance of specific reproductive tissues in men, such as the testis, prostate, epididymis, seminal vesicle, and penis, as well as other male characteristics such as increased muscle strength, hair growth, and so on. To maintain a sufficient androgen concentration, androgen development rates must be balanced against excretion rates and metabolic clearance [2]. The actions of the androgens are influenced by the steroid concentration that can penetrate target cells, the degree of metabolic conversion within the cells, interactions with receptor proteins, and, finally, the action of androgen receptors at the genomic level. These hormones regulate the development of the male reproductive system, as well as the development of "masculine" physical characteristics such as beards and a deep voice, as well as sexual activities [3].

It is worth noting that the testis' secretion of androgens begins even before birth. For example, the testes begin generating testosterone during the first or second part of pregnancy, depending on the species of the animal. The presence of human chorionic gonadotropin at the 7th week of intrauterine life (IUL) brings about some hormonal biosynthesis activities in the testis, leading to early expression of testosterone, which further leads to more activation of the testicular hormonal function utero. In other words, male genitalia development (and brain masculinization) require high amounts of androgens, which are produced by fetal Leydig cells [4]. However, due to the fact that placental hormones are eliminated after delivery, the pituitary-gonadal axis undergoes significant alterations, and the newborn male enters a new phase of gonadal endocrine activity which eventually leads to the death of the fetal Leydig cells. With the death of these cells, androgen production decreases, reaching a trough at postpartum. With the formation of mature Leydig cells from stem cells, testosterone levels eventually rise to high levels. Furthermore, there is also a definite sex difference in this regard, since quantitatively significant ovarian steroid production does not begin until puberty in humans. The synthesis of androgens and protein hormones such as anti-Mullerian hormone by the fetal testis, which is addressed later in this chapter, certainly plays a role in the establishment of male genital differentiation. Female differentiation, on the other hand, occurs more independently, regardless of ovarian hormone output. The androgens are very important in male reproduction [5]. Therefore, the following sessions will be devoted to explaining the physio-chemistry of the testicular androgens (testosterone, dihydrotestosterone).

3. Testosterone

This is the most common form of androgen produced by the testes. It is responsible for the growth of male genitals and sperm production. Testicles in a healthy male can produce about 6 milligrams of testosterone each day. It is synthesized and secreted by the Leydig cells of the testis. These cells do not contain 210-hydroxylase or 110-hydroxylase and so do not synthesize glucocorticoids or mineralocorticoids like the adrenal cortex, which also secrete testosterone [6]. Luteinizing hormone, in conjunction with adrenocorticotropic hormone produced by the adrenal cortex, increases testosterone synthesis by stimulating cholesterol *desmolase,* which in turn helps in steroidogenesis [7].

The prostate contains 5a-reductase which converts testosterone to its active form, dehydrotestosterone [7]. The testicular synthesis of testosterone is controlled by the activities of the hypothalamic-pituitary control mechanism. In this system, the arcuate nuclei of the hypothalamus secrete gonadotropic releasing hormone (GnRH) into the hypothalamic-hypophysial portal blood which stimulates the anterior pituitary to secrete Follicle stimulating hormone (FSH) and luteinizing hormone (LH). The luteinizing hormone is then transported to the testis where it stimulates the Leydig cells to produce testosterone [8]. This action is regulated by the presence of D-aspartic acid that is present in the pituitary gland and the testes and has a role in the regulation and release of LH and testosterone (T). In other words, luteinizing hormone acts on the Leydig cells to promote testosterone secretion, while testosterone acts as an intratesticular paracrine mechanism to reinforce the spermatogenic effects of FSH on the Sertoli cells as well as the germ cells [9].

4. Biosynthesis of testosterone

The androgens are secreted in the testis by interstitial cells of Leydig, which account for 20% of the adult testis mass. Leydig cells are abundant in both newborn

and adult males. However, in childhood, these cells are scarce or nonexistent. As a result, androgen secretion occurs in newborns and after puberty. Its secretion begins in the seventh week of fetal life by the fetal genital ridge. Around the second to fourth month of fetal life, the testes begin to secrete testosterone. Human chorionic gonadotropins, which are secreted by the placenta during pregnancy, stimulate testosterone secretion from the testes. However, until the age of 10 to 12 years old, almost no testosterone is secreted. Following that, testosterone secretion begins, and it rapidly increases at the onset of puberty and continues for the rest of one's life. After 40 years, the secretion begins to decline and reaches near zero by the age of 90 [3].

Cholesterol, a substrate that can be synthesized from acetate de novo or taken up from plasma lipoproteins, is a precursor in the synthesis of steroids at any stage. The low density lipoprotein fraction appears to be the primary extracellular store of cholesterol in human Leydig cells [10]. Furthermore, intracellular lipid droplets containing cholesterol esters can serve as intracellular cholesterol stores. The Cytochrome P_{450} side chain cleavage enzyme of the inner mitochondrial membrane of Leydig cells hydroxylates the side chains C_{22} and C_{20} of cholesterol to convert it into pregnenolone. It is then trans-located to smooth ER for conversion to testosterone in two pathways.

4.1 Dehydroepiandrosterone pathway

In this system, cholesterol is converted to pregnenolone by cAMP. Pregnenolone is then hydrolyzed to 17α-hydroxypregnenolone by the action of 17α-hydroxylase. The end product of the hydroxylation is converted in the Leydig cells to dehydroepiandrosterone (DHEA) by the actions of 17, 20-Lyase. Two events then follow. Firstly, DHEA is converted by the action of 17-HSD to androstenediol and then to testosterone by the combined action of 3-HSD and 5-4 isomerase. Secondly, DHEA is converted to androstenedione with the help of 3-HSD and 5-4 isomerase and then to testosterone by the action of 17-HSD [11].

4.2 Progesterone pathway

In this system, most of the pregnenolone is converted to progesterone in presence of 3β-HSD and 5, 4 isomerase. The activities of 17-hydroxylase convert progesterone to 17-hydroxyprogesterone, which is then converted to androstenedione by 17, 20-Lyase, and finally to testosterone by the action of 17-OHSD.

5. Actions of testosterone

The hormone helps in the differentiation of the epididymis, vas deferens, and seminal vesicle. It is also responsible for the pubertal growth spurt and the cessation of the pubertal growth spurt (epiphyseal closure). It ensures libido, spermatogenesis in Sertoli cells (paracrine effects), deepening of the voice in males, increased muscular mass, and growth of the penis and seminal vesicles, and negative feedback control of the anterior pituitary. In order to carry out its role in spermatogenesis, testosterone is said to mediate maintenance of the blood-testis barrier (BTB) [11].

6. Degradation of testosterone

Many target tissues convert testosterone into dehydrotestosterone, the most active androgen. Some tissues, including adipose tissue, the hypothalamus, and the liver, convert testosterone to estradiol. The liver degrades the majority of

testosterone into inactive androsterone and dehydroepiandrosterone which are then conjugated and excreted in the urine [3].

7. Dihydrotestosterone

This metabolite of testosterone is considered the most active form of testosterone and it helps in the differentiation of the penis, scrotum, and prostate (including growth of the prostate), male hair pattern, and baldness, as well as sebaceous gland activity. It is believed that the mechanisms of action of dihydrotestosterone are the same as those of testosterone since it is the active form of testosterone.

8. Mechanism of action of testosterone and dihydrotestosterone (DHT)

Both DHT and testosterone have the ability to bind to the androgen receptor, but DHT has a higher affinity than unbound or unchanged testosterone. When DHT or testosterone binds to the androgen receptor, it forms a complex that undergoes structural changes. This complex then enters the nucleus of the cell and binds to specific nucleotide sequences of DNA known as hormone response elements. This binding causes changes in the transcription of various proteins mediated by specific genes, resulting in the androgenic effects of the cells [3].

8.1 Androgen insensitivity disorder

This is a condition characterized by the appearance of physical traits of a woman in a person who is genetically male. This disorder is caused by a deficiency of androgen receptors in target tissues of males, thereby leading to the absence of the desirable actions of testosterone and dihydrotestosterone. In this condition, female external genitalia are present but no internal genital tract. Serum testosterone levels are also very high in these individuals [12].

9. Estrogen

Testicular estrogen is formed from testosterone in Sertoli cells and it is also said to be necessary for spermeogenesis. This hormone is essential for modulating libido, erectile function, and spermatogenesis [13].

9.1 Testicular production of estrogens

Over 80% of plasma estradiol and 95% of plasma estrone in adult men is formed by extragonadal and extraadrenal aromatization of circulating testosterone and androstenedione under the control of the enzyme, aromatase. The testes produce the remaining percentage of estradiol and estrone. The Leydig cells produce larger amount of these while a minor quantity is also produced by Sertoli cells aromatizing androgens. The normal plasma estradiol levels in men range from 20 to 50 pg/mL (73–184 pmol/L), while the total production rate is around 50 g/d (184 nmol/d). These values may rise as men become older.

9.2 Mechanism of action of estrogen

Estrogen action is induced through interaction with specific nuclear estrogen receptors (ERs), which are ligand-inducible transcription factors that regulate

the expression of target genes following hormone binding. There are two types of ERs: estrogen receptor (ER) and the more recently discovered estrogen receptor (ER). These two ER subtypes have distinct ligand specificities and transcriptional activity, and they mediate the classic, direct, ligand-dependent pathway involving estrogen response elements in target gene promoters and protein-protein interactions with several transcription factors. The transcriptional activity of these two ERs differs with ERα exhibiting a lower transcriptional activity due to the presence of different ERβ isoforms. Furthermore, the co-expression of both ERα and ERβ in the same cell results in a complex cross-talk that eventually results in the antagonistic effect of ER on ER-dependent transcription [14].

10. Gonadal proteins

The gonadal proteins are inhibins, activins, and anti-Mullerian hormone/Mullerian-inhibiting substance. In the following session, I will be discussing these protein substances in relation to testicular function.

11. Inhibin

Inhibin is a dimeric glycoprotein secreted by Sertoli cells that suppresses follicle-stimulating hormone (FSH) secretion from the pituitary. Two bioactive forms of inhibin exist, inhibin A and B. Observational and experimental evidence from several studies suggest that inhibins are gonadal messengers that exert a physiological negative feedback control on FSH release at the pituitary gland. During increased rate of spermatogenesis, there is a simultaneous increase in inhibin secretion to acts on anterior pituitary and inhibits the secretion of FSH, leading to decrease in the pace of spermatogenesis [15]. Inhibin B is the circulating form of inhibin produced primarily in the testis by Sertoli cells. With the changing role of the Sertoli cell in immature and adult testes, there are temporal changes in inhibin expression and secretion. Inhibin B levels in adults are positively correlated with Sertoli cell function, sperm number, and spermatogenic status and negatively correlated with FSH. It is also important to note that a complex interaction between FSH, Sertoli cells, Leydig cells, and germ cells regulates inhibin B production. Inhibin may also play a role at an autocrine or paracrine level in modulating the actions of activin. Concerning the mechanism of action of inhibin, it is important to note that the receptors, co-receptors and intracellular signaling molecules thus far implicated in the inhibin mechanism of action are all expressed in the testis. Type II activin receptor and Mothers against decapentaplegic homolog (SMAD) proteins have been localized in Sertoli, Leydig, and germ cells, whereas the inhibin co-receptors betagly-can and inhibin-binding protein seem to be restricted to Leydig cells. However, the physiological role of paracrine/autocrine inhibin effects within the testis has not been clarified [16].

12. Activin

Like inhibin, activin is a member of the transforming growth factor beta (TGFβ) superfamily of ligands initially identified based on their abilities [16] to augment the gonadotropin-releasing hormone (GnRH)-mediated release of FSH. The hormone is named "activin" due to its opposing effects on the functionalities of inhibin. This protein also augments erythropoietin (EPO)-dependent hemoglobin production in K562 erythroleukemia cells and enhances the proliferation of

erythrocyte precursors from human bone marrow cells. Like inhibin, there are two classes of activin called activin-A and active-B [17].

Activin B from the anterior pituitary has paracrine effects on gonadotropes, enhancing GnRH-induced FSH expression and release while activin-A augments GnRH-induced LH production and is antagonized by testosterone. Activin-A has its highest concentrations in the immediate post-natal period during which it is involved in the developmental regulation of both germ cells and Sertoli cells under the modulation of follistatin [18]. Although activin-A levels are much lower in adult testes, interleukin-1 stimulates its formation in the Sertoli cell while FSH inhibits it. Due to a lack of an appropriate assay, little is known about activin-B synthesis [17].

13. Anti-Mullerian hormone (AMH)

Anti-Mullerian hormone (AMH) is a 140-kDa dimeric glycoprotein of the transforming growth factor-beta superfamily produced by the Sertoli cells of the testis. It induces regression of the Mullerian ducts during the male sex differentiation [19]. The hormone is initially synthesized as pre-prohormone, forming homodimers. The mature hormone is glycosylated and dimerized before being secreted, resulting in a 144-kDa dimer made up of identical disulphide-linked 72-kDa monomer subunits. Each monomer contains an N-terminal domain (pro region) and a C-terminal domain (mature region). The N-terminal domain enhances the activity of the C-terminal domain, which houses the molecule's bioactivity. Between 5 and 20% of AMH is cleaved during cytoplasmic transit at a particular location between the N-terminal and C-terminal domains of the 72-kDa monomer, resulting in two polypeptides of 58-kDa (pro region) and 12-kDa (mature region). These two components of the molecule are still attached non-covalently. The AMH gene is found on the short arm of chromosome 19 and has been sequenced and isolated in humans [19].

14. Mechanism of action/signal pathway of AMH

As a member of the TGFβ family of growth factors, it employs the same signal transduction mechanism as the other members of the family. These factors communicate via a serine–threonine kinase receptor complex made up of ligand-specific type II receptors and more generic type I receptors known as activin receptor-like protein kinases (ALKs) [20]. The cytoplasmic SMAD proteins are phosphorylated and activated by an active receptor complex, translocate to the nucleus and influence gene expression directly or indirectly. Anti-Mullerian hormone type II receptor (AMHRII) has been identified as being particularly necessary for AMH signaling. Furthermore, the AMH receptor gene is located on the long arm of chromosome 12. However, this gene is only expressed in the testis and neighboring mesenchymal cells to the Müllerian ducts [19].

15. Physiologic roles of AMH in males throughout life

Together with inhibin B and FSH, anti-müllerian hormone is said to be the earliest hormone secreted by the Sertoli cells in males. Therefore, the hormone is an important indicator of Sertoli cell function and it plays a vital role in the development and functions of the male reproductive system [19]. For example, this hormone is necessary for fetal sex differentiation throughout the prenatal period. Before the seventh week of pregnancy, male and female fetuses have

separate gonads, bipotential external genitalia, and two pairs of unipotential internal ducts (the Müllerian ducts and the Wolffian ducts). In the XY fetus, the expression of the SRY gene, the sex reversal gene on the Y chromosome, causes testicular differentiation [19].

From the eighth week of pregnancy onwards, the developing testes' somatic cells, Leydig cells, and Sertoli cells release testosterone, Insulin-like factor-3 and AMH necessary for the individual's normal male differentiation. Although testosterone has been discussed earlier, it is important to state here that it promotes the differentiation of the Wolffian ducts into seminal vesicles, vasa deferentia, and the epididymis during fetal development. Insulin-like factor-3, also produced by Leydig cells, acts as an important signal during the first phase of testicular descent. The regression of the müllerian ducts leading to differentiation of the genitalia into differentiated into the oviducts, uterus, and upper portion of the vaginal canal in the female fetus is due to the action of AMH [21].

The infantile GnRH surge causes a significant increase in gonadotropins (LH and FSH) in the first few weeks of life, followed by an increase in levels of testosterone, AMH and inhibin B. AMH levels remain high throughout the prepubertal period of life and are reduced during puberty as testosterone levels rise. During prepubertal periods, Leydig cells produce low amounts of testosterone and Sertoli cells are still immature, making the process of formation of spermatozoa arrested in a premeiotic stage while AMH remains secreted at a high level till the onset of puberty. Leydig cells in men undergo additional differentiation at the start of puberty following the secretion of GnRH and the consequent "LH surge" [19].

There is also an increase in testosterone biosynthesis, which leads to the maturation of Sertoli cells. Sertoli cell maturation causes germ cells to undergo meiosis, which starts the process of sperm formation. The inhibitory action of testosterone triumphs over FSH stimulation, resulting in a decrease in AMH expression and the consequent decrease in its circulating levels. In adult males, AMH secretion reaches a plateau and remains nearly constant for the rest of a man's life [19].

16. Control of endocrine functions of the testis

The endocrine functions of the testis are controlled by the hypothalamus and the pituitary gland. The hypothalamus secrets gonadotropin releasing and inhibitory substances that regulate the release of the gonadotropins from the anterior pituitary. Gonadotropins, in turn, regulate the hormone-producing activities of the testis vise vasa [2].

17. Conclusion

The testes (male gonads) secrete the steroid and protein hormones. While the testicular steroid hormones are testosterone, dihydrotestosterone and estrogen, the protein hormones are inhibins, activins and anti-Mullerian hormone (Mullerian-inhibiting substance). Collectively, these hormones maintain the health of the testes, ensure proper production of sperm cells, and control the entry of the sperm cells into the female reproductive tract during ejaculation.

Objectives of the chapter

By the end of this chapter, the reader should be able to:

i. Identify the hormone produced by the testes

ii. Describe the mechanisms of action of testosterone, estrogen, inhibin, activin and a*nti-Mullerian hormone*

iii. State the roles of the various testicular hormones on male reproduction

iv. Define androgen insensitivity disorder

v. Enumerate the physiological roles of a*nti-Mullerian hormone* in males.

Author details

Emojevwe Victor[1*], Igiehon Osarugue[1], Oyovwi Mega Obukohwo[2], Nwangwa Eze Kingsley[3] and Naiho Alexander Obidike[3]

1 Department of Physiology, University of Medical Sciences, Ondo City, Ondo State, Nigeria

2 Department of Human Physiology, Achievers University, Owo, Ondo State, Nigeria

3 Department of Physiology, Delta State University, Abraka, Delta State, Nigeria

*Address all correspondence to: vemojevwe@unimed.edu.ng

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