Steroidogenesis Mechanism, Disruption Factor, Gene Function, and Role in Male Fertility : A Mini Review

I Gede Widhiantara[1,2], Anak Agung Ayu Putri Permatasari[1], I Wayan Rosiana[1] , Putu Angga Wiradana[1], BagusKomang Satriyasa[3]

[1]Study program of Biology, Faculty of Health, Science, and Technology, Universitas Dhyana Pura, Jalan Raya Padangluwih, Dalung, North Kuta, Badung, Bali (80361) Indonesia, [2]Doctoral student of the Medical Science Study Program, Faculty of Medicine, Udayana University, Jalan PB. Sudirman, Denpasar, Bali (80234) Indonesia, [3]Department of Pharmacology, Faculty of Medicine, Udayana University, Bali (80234), Indonesia

Abstract

Male fertility can be defined as the ability of the male reproductive system to impregnate a woman, while infertility is the condition of a married couple who have been married for one year or more and have had sexual intercourse regularly or without using contraception but do not have a pregnancy or offspring. About 10% of married couples experience infertility. The main organ of male reproduction is the testes because in the testes the process of forming spermatozoa and the hormone testosterone occurs. The hormone testosterone plays a direct role in the continuity of spermatogenesis. Testosterone is produced through a series of steroidogenesis mechanisms in testicular Leydig cells. Several factors influence the course of steroidogenesis such as Leydig cells, steroidogenesis proteins, related genes to the influence of free radicals. These factors are closely related to diet and lifestyle. This study is important to understand in efforts to prevent infertility in men.

Keywords*: Male fertility, Steroidogenesis, protein StAR, steroidogenesis disorder, reproduction, animal trials.*

Introduction

The health of the reproductive and sexual systems is closely related to mental, physical attitudes, and the social relations of each individual. The incidence of sexual dysfunction (SD) is estimated to be able to affect the sexual activity of men aged over 40 years by 52% and has the same potential for fertility in men aged under 30 years. Feldman et al.[1)]A decrease in reproductive function in men can be indicated by a decrease in the quality and number of spermatozoa which can be used as biomarkers for male reproductive health [(2)]. Disease and lifestyle such as cardiovascular disease, obesity, depression, anxiety, and smoking are some examples of "classic" risk factors that correlate with reproductive and sexual system problems[(3).]

Spermatogenesisis a biochemical process in the body thatisregulated and acted on by endocrine hormones and several other related regulatory factors such as Luteinizing Hormone (LH), Folliclestimulating hormone (FSH), and testosterone and growth hormone in men.Spermatogenesisisfacilitated by the presence of other hormones, but only the hormone testosteroneplays a very important role in maintaining and maintaining the stability of the spermatogenesis process. Testosterone can beproduced by changingcholesterolthrough a steroidogenesis process initiated by the StARprotein (Steroidogenic Acute Regulatory Protein). StAR protein works under the stimulation of Luteinizing Hormone (LH) in mobilizing and transporting cholesterol to the inner membrane of the mitochondria of Leydig cells[(4)]. Research shows thatthere are severalrolesplayed by the

Corresponding Author :
I Gede Widhiantara
E-mail: widhiantara@undhirabali.ac.id

StARprotein as a biomarker of steroidogenesisactivity, one of whichisthat the inhibition of thisproteinis capable of causing disruption of the hypothalamus-pituitary-testis axis whichsubsequently impacts LH secretion[5,6]. Apart fromstimulating the performance of Leydig Cells for Steroidogenesis, LH togetherwithandrogensalsoplay an important role in the proliferation and differentiation of Leydig cells[7].

Currently, disease monitoring usingbiomarker and molecularapproaches has been widelypracticed in the field of healthresearch and clinical practice. One of the uses of biomarkersthat can bedone in monitoring sexual and reproductive healthisthroughunderstanding the pattern of steroidogenesis. The steroidogenesis process isregulated at variouslevels, especially at the level of transcription of genesencodingsteroidogenic enzymes as well as severalco-factors to post-translationa lproteinsassociatedwithSteroidogenesis. Understanding of steroidogenesisfactors can alsobefacilitated by identifyinggeneticlesions/defectsthat can disruptthis process. An understanding of steroidogenesisisvery important to be able to determine the occurrence of sexualdifferentiation, reproduction, fertility, hypertension, obesity, and physiologicalhomeostasis[8].

In thisreview, wewillprovide information and some important findingsregarding the mechanism, disordersfactors, genefunction, and the role of steroidogenesis in male fertility. Severalexamples of research on Steroidogenesisdisorderswillalsobepresented in thisreview.

Methods

This studyisbased on the results of scientificresearchrelated to Steroidogenesis published from various local and international scientific sources, thesis, and dissertation. The internet isalsoused for data collection that has been published in various scientific journals[9].

Testis and Leydig Cells

The testes are the reproductive organs in male and male animals. Men have two testes that are wrappedwith a scrotum. In mammals, the testes are locatedoutside the body, are connected by the spermatic tubule, and are locatedinside the scrotum. This is consistent with the factthat the spermatogenesis process in mammalsis more efficient at temperatureslowerthan body temperature (<37°C). The testes are covered by a fibrous layer called the Tunica Albuginea. In the spermatic tubule, thereis a cremaster muscle whichwhencontractedwill lift the testiclecloser to the body. When the temperature of the testicleswillbelowered, the cremaster muscles will relax and the testes will move awayfrom the body. This phenomenonisknown as the cremaster reflex[10,11].

The testes have two main functions, namely, where spermatogenesis and steroidogenesis occur. Spermatogenesis occurs in a structure called the seminiferous tubule. These tubules are grooved in lobules where all the ducts then leave the testis and enter the epididymis. Androgen production by Leydig cells contained in the interstitial space. The hormones testosterone and spermatozoa are the two main products of the testes. The seminiferous tubule is the site of the Spermatogenesis process and Leydig cells which have a role in producing the hormone testosterone are located in the cavity between the seminiferous tubules. Leydig cells can be a single number or in groups. Apart from Leydig cells, there are also cells in the interstitial space such as macrophages, master cells, fibroblasts, nerves, and endothelium cells. Leydig cells are surrounded by fibroblasts, macrophages, and binding tissue [12].

Biomarker Related to Steroidogenesis

The regulationcarried out by steroid hormones includesvariousprocessesboth in development and physiology from the fetal phase to the adult phase. All components of steroid hormones are synthesized from cholesterol and have a structure known as Cyclopentanophenanthrene. This structure wasdiscovered in the 1930s and became a precursor to the understanding of steroidogenesis[13].

Substantially, studies have focused more on the performance of steroid hormones than on how theyoccur. This couldbebecausesteroids are a widelyuseddrug and

somethinkthatsteroid hormone disruption onlyoccurs in people with rare geneticlesions. Advances in science and technology, especially in the healthsector, have succeeded in providing the latest information regardingsteroidogenic enzymes and the role of theirgenesused in the diagnosis of certain diseasessuch as hypertension and polycysticovary syndrome throughthisapproach[13]. A list of genes in humansthat can beused as biomarkers in studyingsteroidogenicfunctionispresented in Table 1 below.

Table 1. List of humangenescoding for enzymes and steroidogenic and theirrolesthatpotentialcan beused as a reference for biomarkers

Enzyme	Gene	Gene size (kb)	Function and References
StAR	STAR	8	Steroidogenesis, cholesterol transports to cytochrome P450scc in the inner mitochondrial membrane(14)
P450scc	CYP11A1	30	Catalysis of the synthesis of cholesterol, sex hormones, and othersteroid hormones such as estrogen, testosterone, aldosterone, and cortisone(15) Loss of enzyme activitywill cause hermaphroditism, decreased estradiol, decreasedtestosteronewhich leads to male fertility.
P450c11β	CYP11B1	9.5	Neurosteroidbiosynthesisexpressed in the brain(16)
P450c11AS	CYP11B2	9.5	Gene expression occursonly in the adrenal zona glomerulosa and has an important role in adrenalsteroidogenesis(17).
P450c17	CYP17A1	6.6	Androgensynthesisregulator and the only enzyme that has the capacity to convert the C21 precursor to the androgenprecursor, 17-ketosteroid(18).
P450c21	CYP21A2	3.4	Synthesis of cortisol, as well as a decrease in this enzyme, causes congenitaladrenal hyperplasia(19).
P450aro	CYP19A1	130	Regulates the calcium-binding protein, calbindinwhich has the potential to determinesexuallydimorphicbrain structures(20)
3 β HSD1	HSD3B1	8	Synthesis of potentintratumoralandrogensfromextragonadalprecursors(21)
3 β HSD2	HSD3B2	8	Adrenal and gonadalsteroidbiosynthesis and deficiency/mutation of thesegenes and enzymes will cause a rare disease of congenitaladrenal hyperplasia(22).
11 β HSD2	HSD11B2	6.2	Blood pressure regulationactivates 11-hydroxy steroids in the kidneyso as to protect non-selectivemineralo-corticoid (MR) receptorsfrom occupation by glucocorticoids(23)

Cont... **Table 1. List of humangenescoding for enzymes and steroidogenic and theirrolesthatpotentialcan beused as a reference for biomarkers**

11 β HSD1	HSD11B1	7	Regulation of conversion from inactive cortisone to active cortisol. Thus, this enzyme isconsidered an effective marker for the treatment of diabetes(24).
17 β HSD1	HSD17B1	3.3	Synthesis of estradiol and currentlyknown inactivation of dihydrotestosterone (DHT), whichexhibits dual function in breast cancer cellproliferation(25).
17 β HSD2	HSD17B2	63	Estradiol estrogenmetabolism(26)
17 β HSD3	HSD17B3	67	Markers are used in endocrine evaluation in prepubertal patients by measuringlevels of androstenedione and testosterone(27)
17 β HSD6 (RoDH)	HSD17B6	24.5	Regulation of retinoidhomeostasis in the eye(28)
AKR1C1	AKR1C1	14.3	Accelerate the progesteronemetabolism to 20α-hydroxyprogesterone in cervical fibroblasts. The increase in thisgene can impact the possibility of prematurebirth(29)
AKR1C2	AKR1C2	13.8	Progesteronereceptors(30)
AKR1C3	AKR1C3	13.0	Producingintratumoraltestosterone and 17β-estradiol by reducingandrogen and estrogenprecursors(31)
AKR1C4	AKR1C4	22.1	Specificfunctionsrelated to the liver can alsobeassociatedwithhypomanics in men(32–34)
5α-Reductase 1	SRD5A1	36	Trans-activation of androgenreceptors and inhibitors in the treatment of benign prostate disease(35)
5α-Reductase 2	SRD5A2	56	Testosterone production and deficiency of this enzyme have an impact on male fertility(36)
SULT2A1	SULT2A1	17	Contributes to the metabolic activation of procarcinogens and iswidelyexpressed in the liver, small intestine, and adrenal cortex(37)
PAPSS2	PAPSS2	85	Contributesphysiologically to androgen activation(38)
P450-oxidoreductase	POR	69	Steroid hormone metabolism and deficiency of this enzyme can lead to impairedsexualdevelopment(39)
Ferredoxin	FDX1	35	The main regulator of mitochondrial steroidogenesisattempted in the zebrafishinterrenal glands(40)

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Ferredoxinreductase	FDXR	11	Steroidbiogenesis(41)
Cytochrome b5	CYB5A	32	Steroidogenesisregulates and has a number of functions in clinical conditions(42)
H6PDH	H6PD	36.5	Glucocorticoidsynthesis and possiblyotherroles in electrontransfer for the steroidogenic enzyme P450(43)

Note: Enzyme, Gene, and Gene Size sourcedfrom Miller and Auchus et al.[13]

SEVERAL FACTORS INHIBITOR OF STEROIDOGENESIS PROCESS

Severalfactors can cause Steroidogenesisdisorders in men, including:

a. Decrease in the Number and Function of Leydig Cells

The incidence of infertility in men is a fundamentalproblemfrom the initial failure of the spermatogenesis process[44,45]. Geneticfactors are only a small part of severalfactorscausing the decrease in the number of Leydig cells[46–48]. One indicatorthat can beused as a basic referenceregarding the potential for male infertilityislowserumtestosteronelevels[49]. In addition, the decline in the function of Leydig cellswithincreasingageisalsothereasonfortheincidenceof infertility in men [50]but untilnowthisisstillbeingdebated. This isevidenced by the results of researchfrom Petersen et al[51]whoconductedexperimentsusing male subjects of variousages and paid attention to the total number of Sertoli and Leydig cells in their testes. Theseresultsindicatethatthereis a significantdecrease in the number of Sertolicells as men age. It isinterestingthattherewas no decrease in Leydig cellswith a unilateralmeannumber of 99×10^6 (range: 47×10^6 to 245×10^6, coefficient of variation (CV) = 0.48).

Food has been reported to reduce the number of Leydig cells in severalstudies. As reported by Dantas et al[52]thatfoodcontaminated by synthetic herbicides such as Ametryn can cause reproductive performance disorders (decreased Leydig cells, lipidperoxidation, Superoxide dismutase, catalase) and animal life (male Wistar rats). Consumption of foods high in fat can also cause a decrease in the number and diameter of Leydig cells in male Wistar rats[53].

b. Adrenal steroidogenesis defects

The incidence of defectiveadrenalsteroidogenesis can cause impairedsexualdevelopment. This incident not only affects the disruption of sexualdevelopment but isalso capable of causingmild to severedisturbances in the synthesis of glucocorticoids and mineralocorticoids. Therefore, an examination of glucocorticoids and mineralocorticoids can bedone to find out information about steroidogenesisdefects in patients.

c. StAR protein

Steroidogenic acute regulatoryprotein (StAR) is a mitochondrial proteinthat has a molecularweight of 30 kDa in the adrenal and gonads and plays an important role in facilitating the rapidmovement of cholesterolfrom the outside to the innermitochondrial membrane[54]. On the other hand, StARprotein has a characteristicrole in regulatingsteroidbiosynthesis in steroidogenic tissues[55].

The role of StAR in regulatingsteroidogenesis has been demonstrated in patients suffering from congenital lipoidadrenal hyperplasia (lipoid CAH), an autosomal recessive disorder that causes impairedadrenal and gonadalbiosynthesis due to mutations of the StARgene[56–58]. Recentresearch has shownthat hormone-sensitive lipase (HSL), a neutral cholesteryl ester hydrolase (NCEH), plays an important role in regulating the expression of the StARgene in adrenal and gonadalcells[59].

The results of other studies confirm that StARprotein plays an important role in the steroidogenesis process. According to the results of research by Walsh et al.[60]usingenvironmentalpollutants, organochlorine insecticide lindane and organophosphate insecticide Dimethoate on MA-10 cells directlyinhibits the expression of StARprotein which correlates withsteroidogenesis in Leydig cellsduringconsumption. vegetable and fruit products contaminated with insecticides.

d. Free radicals by cytochrome P450

Free radical production and lipidperoxidation are potential initial mediators in the physiologicalprocesses of the testes and their disruption. Increasedlevels of ReactiveOxygenSpecies (ROS) are seenin 80% of infertility men. Certain levels of free radicals are necessary for normal spermfunction, but in excess, they can have a detrimentaleffect on the steroidogenesis process. Oxidative stress can occurwhen an imbalance arises between the process of free radical formation and antioxidantlevels in the male reproductive system, especially in the spermatogenesis process.

DEVELOPMENT OF STEROIDOGENESIS RESEARCH IN ANIMAL STUDIES

Currently, molecularmechanisms have led to the use of biomarkers in understanding the function of steroidogenesis in the testes. Severalgrowthfactorssuch as fibroblasts 9 (FGF9) are alsoreported to be able to beused as an indicator of earlygonadaldevelopment and testicularsteroidogenesisfunctionduring the process of sexualmaturity[61]. The role of the steroidogenesisgene can beidentifiedfrom histone H3K9 trimethylation (H3K9me3) whichwasstudied in vivo in rat testes exposed to arsenic for a long time. The function of steroidogenicgenessuch as Lhr, Star, P450scc, Hsd3b, Cyp17b, and Aromdecreasedafter arsenic exposure, but increased histone H3K9me3 methyltransferase. Theseresultsindicatethat arsenic exposureis able to suppresssteroidogenicgene expression by activating the H3K9me3 status in the process of inhibitingsteroidogenesis in rat testes [62]. The following are some of the results of research reports on the effects of severaltoxic substances on steroidogenesis in the testes (Table 2).

Table 2.Effects of severaltoxic, drug, and chemical exposures on testicularsteroidogenesis in several Animal trial research

No	Animal subject	Material induction (dose & duration)	Results and References
1	Male guineapig	Exposure to aluminum (300 mg AlCl3 / L) and fluoride (150 mg NaF / L) orally for 13 weeks	Fluoride exposure can induce a decrease in testosterone and sperm count as well as downregulation of Steroidogenesisgenessuch as StAR and P450scc. Al isonly able to attenuate the toxicityeffects of F to a certain time(63)
2	Male mice	Copper sulfate pentahydrate (CuSO4.5H2O, 200 mg / kg, p.o) wasgiven for 90 days. And three groups weregiventreatmentwithTribu lusterrestrisextract (TTE) (10 mg / kg, p.o); Enalapril (30 mg / kg, p.o), and Losartan (10 mg / kg, p.o).	TTE and Enalapril can protectagainst damage to testicularsteroidogenesiscaused by excessexposure to Cu, sothey can bedeveloped as prophylacticdrugs of choice in the face of hypertension and testiculardysfunction(64)

Cont... **Table 2.Effects of severaltoxic, drug, and chemicalexposures on testicularsteroidogenesis in severalAnimal**

3	3-month-old rams (pre-puberty)	Eight rams wereused as control and eightothersweregivenlinseedoil (LO) (4% dry matter of total feed) for 81 days.	LO administration was able to increase the development of the testes (seminiferous tubules and the number of Sertolicells) during the peri-pubertyperiodwith the expression of expressions related to Steroidogenesis in the testes of rams(65)
4	Male golden hamster	Male hamsters wereexposed to differentphotoperiod conditions, namelycritical (CP; 12.5L: 11.5D); short days- (SD; 8L: 16D) and Long days- (LD; 16L: 8D) for 10 weeks	Photoperiod by regulating circulation and local melatoninlevels and expression of the MT1R gene in the testes can enhance the steroidogenesis process to improve the reproductive status of male golden hamsters(66)
5	Male mice	Bisphenol A (BPA) exposurewasgivenorally at a dose of 0.005; 0.5; 50; and 500 µg / kg body weight / day) for 45 days.	BPA is able to interferewithinsulinsignaling and glucose transport processes in the testes of rats, resulting in impairedtesticularfunction(67)
6	Male Wistar rat	Administration of tert-butylhydroquinone (tBHQ) (50 mg / kg bw / day) for 14 daysagainst a single injection of Cisplatin (Cis) (7 mg / kg BW, intraperitoneal on day 8)	Cis triggers upregulation of NF-kB, TNF-α, IL-10, and IL-1β genes, decreasedtesticulargermcellproliferation, testicularsteroidogenesis (expression of StAR, CYP11A1, 3β-HSD and 17β-HSD and protein), decreasedstimulating hormone follicles, luteinizing, and testosterone. Cis also triggers decreasedsperm count, motility, viability, morphology, and Johnsen score(68) However, induction withtBHQis able to reduceoxidative stress by upregulating the Nrf2 gene, suppressing inflammation, apoptosis, and increasingtesticulargermcellproliferation, steroidogenesis, and spermquality.
7	Male mice	Vitamin D3 treatment in d-gal induced rats	Vitamin D3 can regulatetesticularsteroidogenic markers by increasing CYP19A1 and decreasing AR expression in the testis of old and normal micewith d-gal induction(69)
8	Puberty Sprague Dawley Rat	Dexmedetomidine (DEX) (0.015-1.5 µM) induction for 3 hours.	DEX is can inhibit the activity of steroidogenic enzymes and down-regulate the Cyp17a1 and Srd5a1 genes. An increase in ROS alsooccurswhich causes a decrease in androgen production in immature Leydig cells in the process(70)
9	Male mouse	Male rats wereinduced by streptozotocin and nicotinamide (60 mg / kg + 120 mg / kg). Stevia rebaudianaBertoniextract (400 mg / kg)	Decreased body weight, serum LH and testosteronelevels, expression of genesassociatedwithStARSteroidogenesis, changes in testicularstereology, and increasedlevels of FBS in the diabetes group. Stevia rebaudianaBertonisignificantlyincreases body weight, testicular volume, sperm count, and motility and is a potentialdrug for the reproductive system(71)

Conclusion

Nearly 40% of the incidence of married couples' infertility is caused by malefactors. Steroidogenesis is an important aspect of male fertility. The important point of steroidogenesis is the transport of cholesterol as a base material for testosterone from the outer membrane to the inner mitochondria by the StAR protein. Testosterone as a result of steroidogenesis is a male sex hormone produced through steroidogenesis which functions to maintain the spermatogenesis process. Several factors can inhibit steroidogenesis, including Leydig cells, adrenal steroidogenesis defects, StAR enzyme activity, cytochrome P450, and exposure to free radicals.

Acknowledgment: The author would like to thank the Study Program Biology, Faculty of Health Sciences, Science and Technology, Universitas Dhyana Pura and Faculty of Medicine, Udayana University, Bali, Indonesia for supporting the writing of this scientific article.The author also thanks reviewers who have provided useful criticism, suggestions, and input for our writing.

Competing of Interest: The authors declare they have no competing interest.

Ethical Approval: Ethical approval was not obtained to review this article because it did not involve participants, humans, or experimental animals.

Source of Funding: Self.

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