Testicular Physiology

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Testicular Physiology: Objectives

- To become knowledgeable about the basic endocrine physiology of the testis, including:
  
  - Recognition of the structure and function of the major cell types in the male gonad: spermatic epithelial, Sertoli, and Leydig cells
  
  - Hormone synthesis and its control in the testis; how androgens circulate in the bloodstream; the function and sites of action of circulating androgens
  
  - The hypothalamic-pituitary control over testicular hormone synthesis; feedback inhibition on hypothalamic-pituitary peptide secretion by circulating androgens and peptides
  
  - Use of principles of hypothalamic-pituitary-testicular physiology to explain the mechanism for hormone abnormalities in a variety of clinical settings
Clinical Correlate

A 32-year-old man is sent to you for evaluation of infertility. He and his wife have been trying to conceive for 18 months. She has a child from a previous marriage, and her menstrual periods have been regular. His sperm count is 5 million sperm/mL with 30% with normal motility. His semen has an average volume of 2.5 mL (normal).

He has been in good health except for Hodgkin’s disease diagnosed at age 23. He received several courses of cyclophosphamide therapy (exact number unknown). He has been in remission for 8 years and is considered “cured” by his oncologist.
Clinical Correlate

• What would you expect this patient’s libido to be? His erectile function?
• What would you expect his circulating levels of testosterone to be?
• What would you expect the size of his testes to be?
• What would you expect circulating levels of FSH and LH to be? Which of these hormones would you administer therapeutically to try to bolster his sperm count?
• What therapy do you recommend?
Structure/Function of the Testis

- Principal functions
  - production of spermatozoa
  - synthesis of gonadal steroids and peptides

- Anatomical considerations
  - adult testis is elliptical structure, average volume of 15-20 mL; average temperature is about 2 degrees below core
  - the testicular tunica extends into the gonad to divide it into ~250 small lobules, each containing seminiferous tubules
  - the seminiferous tubules comprise 80-90% of testicular mass
Anatomical Compartments of the Testis: Germinal/Spermatic Epithelium

- Sertoli cells (nurturing cells)
  - supportive function to the developing germ cells
  - assists movement of germ cells from basal lamina to tubular lumen
  - engages in phagocytosis of damaged germ cells
- synthesis of hormones
  - androgen-binding protein (ABP): binds testosterone (T) and directs (T) from Leydig cells to germ cells
  - anti-Mullerian hormone, which induces regression of Mullerian (female) structures during fetal life
  - inhibin, which inhibits pituitary FSH secretion
Anatomical Compartments of the Testis: Interstitium

- Leydig cells
  - interstitial cells
    - responsible for 95% of male testosterone production
    - synthesize small quantities of other steroids
  - review of biosynthetic pathway
    - Key take-home points:
      - testis unique in its ability to convert androstenedione to testosterone
      - testosterone can be converted to estradiol
      - testosterone can be converted to dihydrotestosterone
Structure of Testosterone
Metabolic Pathway for Testosterone Synthesis

Cholesterol → Pregnenolone → 17alpha-OH pregnenolone → DHEA → Androstenediol

DHEA-S → DHEA → Androstenedione → Testosterone → Dihydrotestosterone

Progestosterone → 17alpha-OH progesterone → Estradiol

Estrone → Estradiol
Conversion of Androstenedione to Testosterone Occurs in the Gonad from Gonadal Steroid Precursors

Androstenedione $\xrightarrow{17\text{-keto reductase}}$ Testosterone
Metabolic Pathway for Testosterone Synthesis

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Pregnenolone → Progesterone → 17α-OH progesterone → Estrone

Progesterone → Androstenedione → Estradiol

Androstenedione → Testosterone → Dihydrotestosterone
Molecular Mechanisms of Androgen Action

- Androgen receptor part of the thyroid-steroid hormone superfamily
  - contains ligand-binding and DNA-binding domains
- T and DHT bind to the androgen receptor
- Ligand-receptor complex binds to androgen-response element on androgen-responsive genes
- Androgen response element believed to have the sequence:
  TGTACAnnnTGTTCT
- Response elements can be positive or negative!
Molecular Mechanism: Androgens Stimulate the Transcription of Androgen-Responsive Genes

TGTACAnnnTGTTCT
(Androgen Response Element)

DNA Strand
5’ → 3’
What Do Androgens Do?

Fetal Development

- Differentiation of internal and external male genital system (primary sexual characteristics)
  - Promote development of Wolffian ducts

Puberty

- Growth of the scrotum, epididymis, vas deferens, prostate, penis, support spermatogenesis
- Growth of skeletal muscle and larynx; maturation of the epiphyseal growth plate
- Pubic and axillary hair growth; facial/torso hair growth; sebaceous gland activity
- Social behavior change, libido, aggression (?)

Adult Life

- Maintenance of secondary sexual characteristics, skeletal/bone mass, hematopoiesis
Important Actions of Dihydrotestosterone

- Scrotal fusion, development of primary sexual characteristics in the male fetus
- Increases production of sebum
- Involution of the hair follicle ("male-pattern" alopecia)
- Androgen-dependent growth of prostate
Androgens in Plasma

- 98% protein bound
  - 60% bound to sex-hormone binding globulin (SHBG)
  - 38% bound to albumin/pre-albumin(s)
  - “biologically active” portion:
    - 2% that is free
    - a portion of the albumin-bound is active

- typical circulating levels of testosterone in blood are 300 to 1200 ng/dL in the male
Key Aspects of Hypothalamic-Pituitary Regulation of the Testis

- Pulsatile hypothalamic GnRH required for normal gonadotropin regulation
  - pulses occur every 1 to 1.5 hours
  - absence GnRH pulses, or continuous exposure, leads to hypogonadism
- FSH acts primarily on germinal epithelium
- LH acts primarily on Leydig cells
- Negative feedback:
  - T (via estradiol) on LH
  - T (via estradiol) and inhibin on FSH
Hypothalamic-Pituitary-Gonadal Axis

Hypothalamus

Pituitary

Testis

GnRH

LH (+)

FSH (+)

Inhibin (-)

Test. (-)
Klinefelter Syndrome (XXY)

- Occurs in approximately 1 in 500 male births
  - due to maternal X-chromosome nondisjunction
- No physical stigmata at birth; abnormal proportions (long lower body segment) later
- At puberty: hyalinization of seminiferous tubules, resulting in small, firm testes; infertility
- Leydig cells functionally abnormal, with low production of T; high LH; gynecomastia
- Can appear normally virilized
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