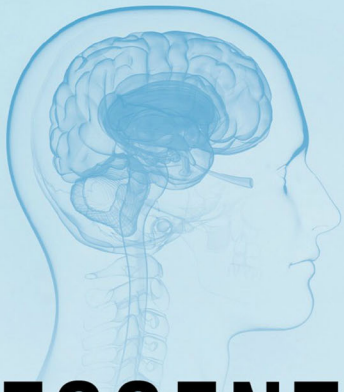
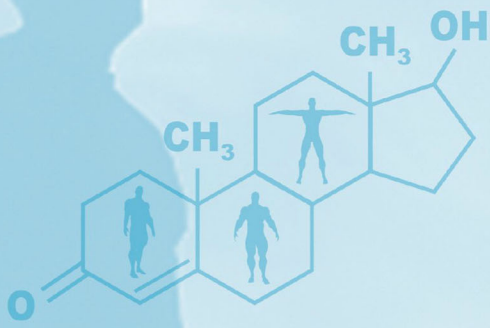
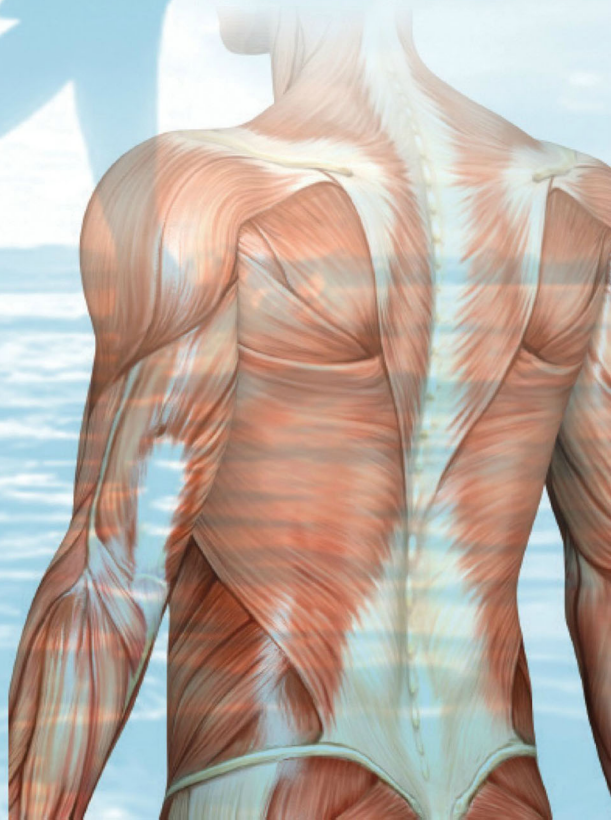




ESSENTIALS OF Men's Health

EDITOR-IN-CHIEF
SHALENDER BHASIN

Michael P. O'Leary
Shehzad S. Basaria



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EDITOR-IN-CHIEF:

Shalender Bhasin, MB, BS
Professor of Medicine, Harvard Medical School
Director, Research Program in Men's Health: Aging and Metabolism
Director, Boston Claude D. Pepper Older Americans Independence Center
Brigham and Women's Hospital
Boston, Massachusetts

ASSOCIATE EDITORS:

Michael P. O'Leary, MD, MPH
Professor of Surgery, Harvard Medical School
Senior Urologic Surgeon, Director of Men's Health
Brigham and Women's Hospital
Boston, Massachusetts

Shehzad S. Basaria, MD
Associate Professor of Medicine
Associate Director, Research Program in Men's Health: Aging and Metabolism
Brigham and Women's Hospital, Harvard Medical School
Boston, Massachusetts

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Contents

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Contributors

Bradley D. Anawalt, MD
Professor of Medicine
Vice Chairman of Department of Medicine
University of Washington
Chief of Medicine
University of Washington Medical Center
Seattle, Washington

Kevin L. Ard, MD, MPH
Director, Sexual Health Clinic
Division of Infectious Diseases
Massachusetts General Hospital
Instructor in Medicine
Harvard Medical School
Boston, Massachusetts

Stefan Arver, MD, PhD
Associate Professor
Department of Medicine
Huddinge Karolinska Institutet
Director ANOVA Andrology, Sexual Medicine Transmedicine
Karolinska University Hospital
Stockholm, Sweden

Shehzad Basaria, MD
Associate Professor of Medicine
Associate Director, Research Program in Men's Health: Aging and Metabolism
Brigham and Women's Hospital, Harvard Medical School
Boston, Massachusetts

Shalender Bhasin, MB, BS
Professor of Medicine
Harvard Medical School
Director, Research Program in Men's Health: Aging and Metabolism
Director, Boston Claude D. Pepper Older Americans Independence Center
Brigham and Women's Hospital
Boston, Massachusetts

Robert E. Brannigan, MD
Professor of Urology, Northwestern University, Feinberg School of Medicine
Vice Chair of Clinical Urology
Head, Division of Male Reproductive Surgery and Men's Health
Director, Andrology Fellowship
Assistant Director of Student Affairs
Northwestern Memorial Hospital
Chicago, Illinois

Arthur L. Burnett, MD MBA FACS
Patrick C. Walsh Distinguished Professor of Urology, Oncology
Department of Urology, The Johns Hopkins University School of Medicine
The James Buchanan Brady Urological Institute
The Johns Hopkins Hospital
Baltimore, Maryland

J. Quentin Clemens, MD
Edward J. McGuire Professor
Associate Chair for Research
Department of Urology
University of Michigan
Ann Arbor, Michigan

Iryna M. Crescenze, MD
Assistant Professor of Urology
The Ohio State University
Columbus, Ohio

Farah Daneshvar, DO
Clinical Instructor
Division of Endocrinology
University of Michigan, School of Medicine
Ann Arbor, Michigan

Zachary Dao, BS
Baylor College of Medicine
Houston, Texas

Chirag N. Dave, MD
Fellow
Department of Urology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Angel Elenkov, MD, PhD
Molecular Reproductive Medicine, Department of Translational Medicine
Lund University and Reproductive Medicine Centre
Skane University Hospital
Malmö, Sweden

Thiago Gagliano-Jucá, MD, PhD
Research Fellow, Research Program in Men's Health: Aging and Metabolism
Brigham and Womens' Hospital
Harvard Medical School
Boston, Massachusetts

Ramy Abou Ghayda, MD, MPH
Assistant Professor
Harvard Medical School
Center for Infertility and Reproductive Surgery
Division of Urology, Brigham and Women's Hospital
Boston, Massachusetts

Aleksander Giwercman, MD
Professor, Molecular Reproductive Medicine, Department of Translational Medicine
Lund University and Reproductive Medicine Centre
Skane University Hospital, 214 28
Malmö, Sweden

Anna Goldman, MD
Instructor in Medicine
Harvard Medical School
Associate Program Director
Endocrinology Fellowship
Brigham and Womens' Hospital
Division of Endocrinology, Diabetes and Hypertension
Boston, Massachusetts

Trevor C. Griffen, MD, PhD
Resident Physician
Department of Psychiatry
Icahn School of Medicine at Mount Sinai
New York City, New York

Ole-Petter R. Hamnvik, MB, BCh, BAO, MMSc, MRCPI
Assistant Professor in Medicine
Harvard Medical School
Program Director
Endocrinology Fellowship
Brigham and Womens' Hospital
Division of Endocrinology, Diabetes and Hypertension
Boston, Massachusetts

Frances J. Hayes, MB, BCh, BAO, FRCPI
Associate Professor of Medicine
Harvard Medical School
Associate Clinical Chief of Endocrinology, Massachusetts General Hospital
Boston, Massachusetts

Amin S. Herati, MD
Assistant Professor
Department of Urology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Tom Hildebrandt, PsyD
Associate Professor of Psychiatry and Chief
Division of Eating and Weight Disorders Department of Psychiatry
Icahn School of Medicine at Mount Sinai
New York City, New York

Ilpo Huhtaniemi, MD, PhD, FMedSci
Professor Emeritus of Reproductive Endocrinology
Imperial College London
London, United Kingdom
Professor Emeritus of Physiology
University of Turku
Turku, Finland

Amy James, BSc
Research Nutritionist
Harbor UCLA Medical Center and The Lundquist Institute
Torrance, California

Gen Kanayama, MD, PhD
Associate Director, Substance Abuse Research
Biological Psychiatry Laboratory, McLean Hospital
Belmont, Massachusetts
Harvard Medical School
Boston, Massachusetts

Martin Kathrins, MD
Assistant Professor of Surgery, Harvard Medical School
Division of Urology
Brigham and Womens' Hospital
Boston, Massachusetts

Mohit Khera, MD, MBA, MPH
Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, Texas

Peter Y. Liu, MBBS (Hons I), FRACP, PhD
Professor of Medicine in Residence
David Geffen School of Medicine at UCLA
Division of Endocrinology and Metabolism
Harbor UCLA Medical Center and The Lundquist Institute
Torrance, California

Tom F. Lue, MD, ScD (Hon)
Professor and Vice Chair of Urology
Emil Tanagho Endowed Chair in Clinical Urology
Department of Urology
University of California
San Francisco, California

Joseph Mahon, MD
Fellow in Male Health and Reconstruction
Department of Urology, Stritch School of Medicine
Loyola University Medical Center
Maywood, Illinois

Kevin T. Me Vary, MD-FACS
Director of the Center for Male Health
Professor of Urology
Department of Urology
Stritch School of Medicine
Loyola University Medical Center
Maywood, Illionois

Michael O'Leary, MD, MPH
Professor of Surgery, Harvard Medical School
Senior Urologic Surgeon, Director of Men's Health
Brigham and Womens' Hospital
Boston, Massachusetts

Robert Oates, MD, FACS
Professor of Urology
Boston University School of Medicine
Boston, Massachusetts

Manuel Ozambela Jr., MD
Resident
Division of Urology, Brigham and Womens Hospital
Clinical Fellow
Harvard Medical School
Boston, Massachusetts

Jason A. Park, SM
Medical Student
Boston University School of Medicine
Boston Medical Center
Boston, Massachusetts

Alexander W. Pastuszak, MD, PhD
Assistant Professor
Division of Urology, Department of Surgery
University of Utah School of Medicine
Salt Lake City, Utah

Michael A. Perelman, PhD
Co-Director, Human Sexuality ProgramClinical Professor Emeritus of Psychology in Psychiatry, Reproductive Medicine and UrologyWeill Cornell Medicine
NewYork-PresbyterianFounder and ChairmanMAP Education & Research Foundation, Inc.
New York, New York

Harrison G. Pope Jr., MD
Director, Biological Psychiatry Laboratory, McLean Hospital
Belmont, Massachusetts
Professor of Psychiatry, Harvard Medical School
Boston, Massachusetts

Mark A. Preston, MD, MPH
Assistant Professor of Surgery
Harvard Medical School
Associate Surgeon
Division of Urology, Brigham and Womens Hospital
Surgical Oncology, Dana Farber Cancer Institute
Boston, Massachusetts

Katherine M. Rodriguez, MD
Brady Department of Urology
Johns Hopkins School of Medicine
Baltimore, Maryland

Joshua D. Safer, MD, FACP, FACE
Professor of Medicine, Icahn School of Medicine at Mount Sinai
Executive Director, Center for Transgender Medicine and Surgery
Mount Sinai Health System
New York, New York

Alan W. Shindel, MD, MAS
Associate Professor of Urology
Department of Urology
University of California
San Francisco, California

Ronald S. Swerdloff, MD
Professor of Medicine
David Geffen School of Medicine at UCLA
Senior Investigator
Los Angeles Biomedical Research Institute
Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center
Torrance, California

Cigdem Tanrikut, MD, FACS
Reproductive Urologist
Shady Grove Fertility
Georgetown University School of Medicine
Washington, DC

Jeanne Wallace, MD, MPH
Clinical Professor of Medicine
David Geffen School of Medicine at UCLA
Division of Sleep Medicine, Olive View-UCLA Medical Center
Sylmar, California

Christina Wang, MD
Professor of Medicine
David Geffen School of Medicine at UCLA
Associate Director of the Clinical and Translational Science Institute at Los Angeles Biomedical Research Institute
Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center
Torrance, California

Rena Xu, MD
Resident Physician
Department of Urology
Massachusetts General Hospital
Boston, Massachusetts

Elena Yanushpolsky, MD
Assistant Professor, Harvard Medical School
Center for Infertility and Reproductive Surgery
Brigham and Womens' Hospital
Boston, Massachusetts

Sigal Yawetz, MD
Assistant Professor of Medicine
Harvard Medical School
Director, Ryan White Program for HIV in Women and Youth
Division of Infectious Diseases
Brigham and Womens' Hospital
Boston, Massachusetts

Maria A. Yialamas, MD
Assistant Professor of Medicine, Harvard Medical School
Associate Program Director, Internal Medicine Residency
Brigham and Womens' Hospital
Boston, Massachusetts

Fiona Yuen, MD
Senior Research Fellow
Harbor UCLA Medical Center and The Lundquist Institute
Torrance, California

Preface

Essentials of Men's Health is unique in being the first comprehensive textbook on men's health that is directed primarily at practicing clinicians—primary care providers, family physicians, internists, endocrinologists, andrologists, and urologists—who care for men with these problems. The textbook emphasizes an evidence-based approach to disease management, integrated models of patient-centric treatment, and a pathophysiological basis of major men's health problems; it offers useful guidance on optimizing workflow, includes many patient education tools and resources, and its management strategies are well aligned with recent trends in health care delivery. The textbook has been authored by internationally recognized experts in the content areas.

The emergence of men's health as a distinct discipline within internal medicine is founded on the wide consensus that men and women differ across their lifespan in their susceptibility to disease, in the clinical manifestations of the disease, and in their response to treatment. Furthermore, men and women weigh the health consequences of illness differently and have different motivations for seeking care. Men and women experience different types of disparities in access to health care services and in the manner in which health care is delivered to them because of a complex array of socioeconomic and cultural factors. Attitudinal and institutional barriers to accessing care; fear and embarrassment due to the perception that it is not manly to seek medical help; and reticence on the part of male patients and physicians to discuss issues related to sexuality, urogenital tract problems, drug use, body image, and aging have heightened the need for a textbook tailored to address the issues that are specific to men's health.

A confluence of historical factors has rendered such a textbook timely. Gender-specific integrated clinics have long existed for women, but men's health centers have emerged only recently as a novel practice model. In a reflection of the growing attention on issues related to men's health, men's health clinics have mushroomed all over the country. Although the major threats to men's health have not changed—heart disease, cancer, and unintentional injury continue to dominate the list of major medical causes of morbidity and mortality in men—the men who attend men's health clinics do so largely for sexual, reproductive, and urological health concerns involving common conditions, such as androgen deficiency syndromes, age-related decline in testosterone levels, sexual dysfunction, muscle dysmorphia and anabolic-androgenic steroid use, lower urinary tract symptoms, and medical complications of cancer treatment, which are the focus of this textbook.

For much of human history, societal views of reproductive health and human sexuality were dictated by religious dogma, and issues of sexual health or urogenital problems were rarely discussed in public. The discovery of Viagra and the appearance of Senator Bob Dole in Viagra advertisements helped remove the stigma from genitourinary and sexual problems and have made it easier for men to discuss and seek treatment for their sexual, reproductive, and urogenital problems. The growing interest in men's health is also reflected in the extraordinary increase in prescription sales of testosterone and products for erectile dysfunction, such as Viagra. As our population ages and greater focus is placed on a holistic approach to men's health, there is a clear need for all practicing clinicians, but particularly primary care physicians, who are on the frontlines, to have a clear understanding of the issues affecting men's health, including their sexual, reproductive, and genitourinary health. As a reflection of the growing societal interest in men's

health, there are over 100 lay books on this topic on Amazon's website, but these books are written as self-help books for the lay public.

The book is contemporary and comprehensive in its coverage of topics related to men's health, including androgen disorders, various types of sexual dysfunction, reproductive problems associated with aging in men, sexually transmitted diseases and high-risk behaviors in men, body image disorders and the use of appearance- and performance-enhancing substances, infertility, contraception, reproductive problems among cancer survivors, and urological problems in primary care practice. The section on transgender health offers guidance on integrated care of transgender people and optimization of gender-affirming therapies.

The coverage of these topics that are specific to men's health in textbooks of internal medicine and in medical school curricula has remained limited in spite of the high prevalence of these conditions and their known impact on overall health, well-being, and quality of life. Primary care providers and internists receive little training in managing these problems and find themselves inadequately prepared to care for these patients. Recognizing this unmet need, several professional organizations, such as the American Urological Association, the American Society of Men's Health, and the American Society of Andrology, have deemed the development of curriculum in men's health a national priority. *Essentials of Men's Health* was developed to fulfill this mandate and address an unmet need in medical education.

Shalender Bhasin, MB, BS
Editor-in-Chief
Professor of Medicine, Harvard Medical School
Director, Research Program in Men's Health: Aging and Metabolism
Director, Boston Claude D. Pepper Older Americans Independence Center
Brigham and Women's Hospital
Boston, Massachusetts
sbhasin@bwh.harvard.edu

1 Pathophysiologic Basis of the Male Reproductive Disorders

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1 The Pathophysiological Basis of Androgen Disorders in Men

Ilpo Huhtaniemi

INTRODUCTION

Testicular production of male sex hormones (androgens) starts in the fetal period and continues until the end of life. Androgens are quintessential for the structural and functional differentiation and maturation of all aspects of the male phenotype. Testosterone (T) is the most important androgen; some of its actions require its conversion to 5a-dihydrotestosterone (DHT) mainly in peripheral androgen target organs. In addition, some actions of T, such as on the bone, brain, and sexual desire, require its conversion to the active estrogen, estradiol (E2). Normal testicular androgen production is critically dependent on regulatory input from the hypothalamic-pituitary level through the action of luteinizing hormone (LH) and fine-tuning by a plethora of other hormones and intratesticular paracrine signals. Androgen actions in the testis and other organs are mediated by the androgen receptor (AR), a ligand-activated nuclear transcription factor. The pivotal regulatory unit in androgen production is the hypothalamic-pituitary-testicular (HPT) axis, where feed-forward and feedback actions between the hypothalamus, pituitary, and testes maintain the physiological androgen homeostasis. Disturbances of this balance, leading to hypogonadism, may occur at any level of the HPT axis and in AR function. The pathophysiological basis of androgen disorders is localized somewhere in the cascade of androgen regulation —> production —> action, either intrinsic to the HPT function or as a consequence of primarily nonendocrine conditions or external influences. Typical causes for hypogonadism are mutations of genes functional at the HPT axis (organic hypogonadism), consequences of nonendocrine systemic illness, or the influence of exogenous/lifestyle factors (functional hypogonadism). We will first review the normal processes of testicular androgen production, action, and regulation by the HPT axis. We then review the pathophysiological basis of the various diseases and disorders that can disturb androgen synthesis or action.

THE HPT AXIS

The HPT axis forms the backbone of endocrine regulation of the testis. This regulatory circuit contains hierarchical cascades of feed-forward and feedback regulatory events (Fig. 1-1). According to the classical concept, specific hypothalamic nuclei synthesize the decapeptide gonadotropin-releasing hormone (GnRH).[1] The axon terminals of GnRH neurons in median eminence release the peptide into the hypophyseal portal circulation, where it is transported to the anterior pituitary gland to stimulate in gonadotropin cells the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[1] LH and FSH reach the testes through the peripheral circulation and exert their stimulatory effects on Leydig and Sertoli cells, respectively.

The negative feedback effects of testicular hormones on gonadotropin secretion at the hypothalamic-pituitary level maintain the functional balance of the regulatory circuit (Fig. 1-1). Testicular T, primarily after conversion to E2, inhibits LH secretion

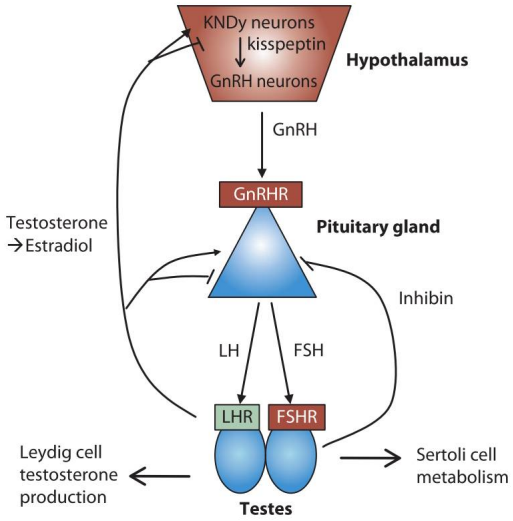

FIGURE 1-1. The hypothalamic-pituitary-testicular (HPT) axis. The main hormones functioning in the HPT axis are depicted, including the effects of kisspeptin on GnRH secretion, GnRH on LH and FSH secretion, and their effects on testicular function, followed by negative feedback effects of testicular sex steroids and inhibin. *GnRH,* gonadotropin-releasing hormone; *KiSSIR,* kisspeptin receptor; *LH,* luteinizing hormone; *FSH,* follicle-stimulating hormone; *R,* receptor.

at the level of the hypothalamus and pituitary, while inhibin B, the product of the Sertoli cell, suppresses FSH secretion at the pituitary.

The Hypothalamic Level

GnRH Neurons The hypothalamus, the most proximal level of the HPT axis, is an area in the base of the brain containing numerous discrete nuclei specialized to synthesize and secrete neuroendocrine hormones.[2] In humans, GnRH neuronal cell bodies are primarily located in the anterior hypothalamus and in the periventricular and tuberal regions.[3] GnRH is considered the master switch in the regulatory interactions between the brain and reproduction, that drives the function of the downstream HPT elements.[4]

Regulation of GnRH Neurons An array of hypothalamic hormones and neurotransmitters is involved in the maturation, regulation, and fine-tuning of GnRH neuronal function.[4] They include classical neurotransmitters (e.g., norepinephrine), excitatory and inhibitory amino acids (e.g., glutamate and ^-aminobutyric acid), and neuropeptides (e.g., neuropeptide Y, galanin-like peptide, opioid peptides, and orexins). GnRH neurons also receive signals from glial cells, including neurotrophic factors and glutamate, which participate in the timing of puberty and pulsatile GnRH secretion. They fine-tune the pulsatile GnRH secretion into the hypophysial portal circulation, which is vital for its stimulatory action on the pituitary gonadotropin.

GnRH neurons are regulated by the neuromodulatory peptide kisspeptin, encoded by the *KISSI* gene (Fig. I-l).[5] Some kisspeptin neurons co-express neurokinin B and dynorphin; thus, they are termed kisspeptin-neurokinin B-dynorphin (KNDy) neurons. The KNDy neurons are localized in the hypothalamus in the infundibular nucleus and in the rostral preoptic area, whereas neurons in the preoptic area only express kisspeptin.[6] Kisspeptin and GnRH neurons have close anatomic proximity and cell contacts, enabling kisspeptin to evoke GnRH secretory pulses. Kisspeptin activates a G protein-coupled receptor (GPCR) KISSIR (formerly called GPR54) in GnRH neurons, thereby stimulating *GnRH* expression and secretion.[5] Because estrogen receptor a is expressed in the kisspeptin neurons but not in the GnRH neurons, the negative feedback action of sex steroids on GnRH secretion is indirect through the inhibition of kisspeptin production.[5,7]

GnRH and GnRH Pulse Generator The larger propeptide encoded by the *GnRH* gene is cleaved into the 24-amino acid signal peptide, the GnRH decapeptide, and the 56-amino acid GnRH-associated peptide with unknown function.[8] These peptides are secreted in median eminence from the GnRH neuron terminals to the hypophysial portal circulation in 1 to 2-min pulses of varying amplitude, at a frequency of one pulse every 1 to 2 h. The exact nature and location of the GnRH pulse generator remain important unanswered questions in GnRH neurobiology, but recent research indicates that kisspeptin neurons in the hypothalamic arcuate nucleus may be the anatomic site of the pulse generator.[9]

The Anterior Pituitary Gland

GnRH Action In the anterior pituitary, GnRH binds to its high-affinity receptor (GnRHR) on the

gonadotropin cells. The GnRHR is a GPCR, and evokes the Ca^{2+}/diacyl glycerol/protein kinase C/mitogen-activated protein kinase second messenger signaling cascade.[10] GnRH secretion must be pulsatile for a stimulatory effect on gonadotropins; tonic GnRHR activation (e.g., upon GnRH agonist treatment) causes GnRHR desensitization by blocking the signal transduction and suppressing gonadotropin synthesis and release. After a GnRH pulse, the secretory peaks of LH are more distinct than those of FSH because of the shorter circulatory half-life of the former. The pulsatility of serum gonadotropins reflects the mode of GnRH action, but it is not essential at the gonadal level, as continuous treatment with gonadotropin can maintain testicular function.

Gonadotropins LH and FSH, with molecular masses of 30 kDa and 35 kDa, respectively, along with thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG), belong to the family of glycoprotein hormones. Most gonadotropin produce both LH and FSH, and only a minority of cells are monohormonal. The partial dissociation of the secretory profiles of LH and FSH is due to differential LH and FSH responses to the different patterns of pulsatile release of GnRH, with high-frequency GnRH secretory pulses favoring LH release.[11]

LH and FSH are composed of a common a-subunit that is noncovalently coupled to the hormone-specific P-subunit to form a heterodimer. The common ot-subunit has two, LHp has one, and FSHp has two N-linked carbohydrate side chains.[12] The carbohydrate termini of LH are heavily sulfated (50%), while in FSH they are mainly sialylated. The differences in glycosylation explain the longer half-life of FSH in circulation as compared to LH (3 to 4 h vs. 20 min). In addition, a specific hepatic receptor for sulfated glycoproteins accelerates the elimination of LH from circulation.[13] There is considerable microheterogeneity (isoforms) in the carbohydrate residues of the circulating gonadotropin molecules.[12] The isoforms vary in bioactivity, and their relative proportions are apparently hormonally regulated, but the physiological significance of this variability remains uncertain.

The circhoral (every 1 to 2 h) release of GnRH pulses from the hypothalamus is superimposed with the episodic ultradian (24-h interval) activity of GnRH release. The result is the circadian rhythmicity of LH pulses from the pituitary, with peak activity in the morning and a trough in the evening. There is also good synchrony between serum LH and T pulses.

The Testis

Trophic Stimulation of Testicular Function LH and FSH bind in the testis to their cognate receptors, LH to LH/chorionic gonadotropin receptor (LHCGR) in Leydig cells and FSH to FSH receptor (FSHR) in Sertoli cells. Both gonadotropin receptors reside on the plasma membrane and belong to the class A GPCRs.[14,15] Their functional domains are (1) the extracellular domain with distinctive leucine-rich repeats forming the primary ligand binding site, (2), the short hinge-region with a role in determining specificity of the hormone binding, (3) the transmembrane domain whose conformational change after ligand binding transfers the gonadotropin signal across the plasma membrane, and (4) the intracellular tail that participates in the termination of signaling through receptor desensitization (by phosphorylation) and downregulation (by internalization).

The main second messenger system involved in the signaling of both gonadotropin receptors is the adenylyl cyclase/cAMP/protein kinase A cascade,[14,15] but other signaling mechanisms also are involved, especially at higher hormone and receptor concentrations.

Functional Compartments of the Mature Testis The two functions of the adult testis are to produce sex hormones and sperm. Leydig cells in the interstitial tissue are the site of androgen synthesis under LH stimulation. Spermatogenic cells are harbored in seminiferous tubules within and between the large, metabolically active Sertoli cells. The latter are regulated by the endocrine action of FSH and by the paracrine action of T from the Leydig cells. T and FSH stimulation is vital for the maintenance of Sertoli cell metabolism, which provides paracrine stimuli and nutrients for “nursing” the spermatogenic cells. The peptide hormone inhibin B is a Sertoli cell product; it has paracrine functions within the testis, and its hormonal function is to mediate the testicular negative feedback on FSH secretion. The seminiferous tubules are circumscribed by a layer of peritubular myoid cells, which promote sperm movement with their smooth muscle-like activity. Besides Leydig cells, the intertubular (interstitial) space harbors various immune cells

(e.g., macrophages), fibroblasts, and blood and lymphatic vessels.

Testicular Steroid Production and Secretion Leydig cells are the testicular site of steroid hormone production, particularly T. All steroid hormones are metabolic products of cholesterol, which can originate from a number of sources, including *de novo* synthesis, intracellular stores of cholesterol esters, circulating lipoprotein-bound cholesterol, and plasma membrane.[16] An array of steroidogenic enzymes regulates the conversion of cholesterol to T (Fig. 1-2A). The enzymes are either cytochrome P450s (CYP) or hydroxysteroid dehydrogenases (HSD).

Steroid synthesis starts with the transfer of cholesterol from the outer to the inner mitochondrial membrane in a rapid LH-regulated fashion. The transfer is augmented by a protein complex containing the steroidogenic acute regulatory protein (StAR) and the 18-kDa translocator protein (TSPO).[17] The first and rate-limiting step of steroid biosynthesis in mitochondria is the conversion of cholesterol to pregnenolone, catalyzed by the CYP cholesterol side-chain cleavage enzyme (CYP11A1, P450scc) and auxiliary electron-transferring proteins. The next steps occur in the smooth endoplasmic reticulum, including the conversion of pregnenolone via 17-hydroxypregnenolone to dehydroepiandrosterone by 17a-hydroxylase/17-20-lyase (CYP17A1, P450cl7), then to 5-androstene-3(3,17(3-diol by 17(3-hydroxysteroid dehydrogenase type 3 (17(3HSD3), and finally to T by 3(3-hydroxysteroid dehydrogenase type 2 (3|3HSD2). This sequence of conversions (called the A5 pathway) is preferred in the human testis. The A4 pathway involving the initial conversion from pregnenolone to progesterone by 3(3HSD2 dominates in rodents. The most important steroidogenic end product in the testis is T, but about 0.5% of T is converted by aromatase (CYP19A1) to E2 and by the steroid 5a-reductase type 2 (SRD5A2) to DHT in peripheral androgen target tissues (prostate, genital skin, hair follicles).

An alternative pathway, also referred to as the backdoor pathway, was recently discovered for DHT synthesis, which bypasses T as a precursor.[18] In this pathway, DHT is produced from progesterone via 5a-dihydroprogesterone, allopregnanolone, 17-hydroxy-allopregnanolone, androsterone, and androstanediol as intermediates (Fig. 1-2B). This "backdoor" pathway of DHT formation, using androsterone produced by the placenta as a substrate, may play an active role in the masculinization of male fetal genitals.[18,19]

The testes produce 6 to 7 mg of T daily. In adult men, about 95% of T originates from the testes and the rest from peripheral metabolism of adrenal androgenic precursors. In addition to T, the human testes store and secrete intermediates and metabolites of the androgen synthetic pathway (Table 1-1, Fig. 1-2B), particularly as sulfate conjugates,[20,21] which apparently represent storage and secretory forms with no bioactivity of their own.

The secretion of steroids from Leydig cells is considered a passive process due to their lipid solubility and easy transit through cell membranes. T and the sulfate conjugates of T—pregnenolone, dehydroepiandrosterone, and 5-androstene-3(3,17(3-diol—are the quantitatively most abundant steroids in the human testis (Table 1-1). T concentration in the testis tissue is over 100-fold higher than in the peripheral circulation. The intratesticular T has been considered necessary for spermatogenesis, although its importance has recently been challenged by animal experiments where full spermatogenesis was evoked in hypogonadal mice by T doses that only reached about 2% of normal intratesticular T.[22] The intratesticular T concentration may be high only because the testis is the site of T production.

There is a diurnal variation in testicular steroid secretion, which follows a similar variation in circulating LH levels. The synchrony between secretory pulses of T and those of LH is less consistent, apparently due to the sluggish response of human testicular steroidogenesis to gonadotropin stimulation (only up to 30% to 50%)[23] and to the buffering effect of steroid hormone binding to plasma transport proteins.[24]

Only about 2% of serum T is free, while 44% is bound to sex hormone-binding globulin (SHBG) and 54% to albumin and other transport proteins.[24] The plasma level of SHBG is under endocrine regulation; it is increased by estrogen and with aging, and is reduced by androgens and obesity. If function of the HPT axis is normal, changes in SHBG levels do not alter the androgen milieu, as the free testosterone concentrations are maintained in the normal range as a result of feedback regulation.

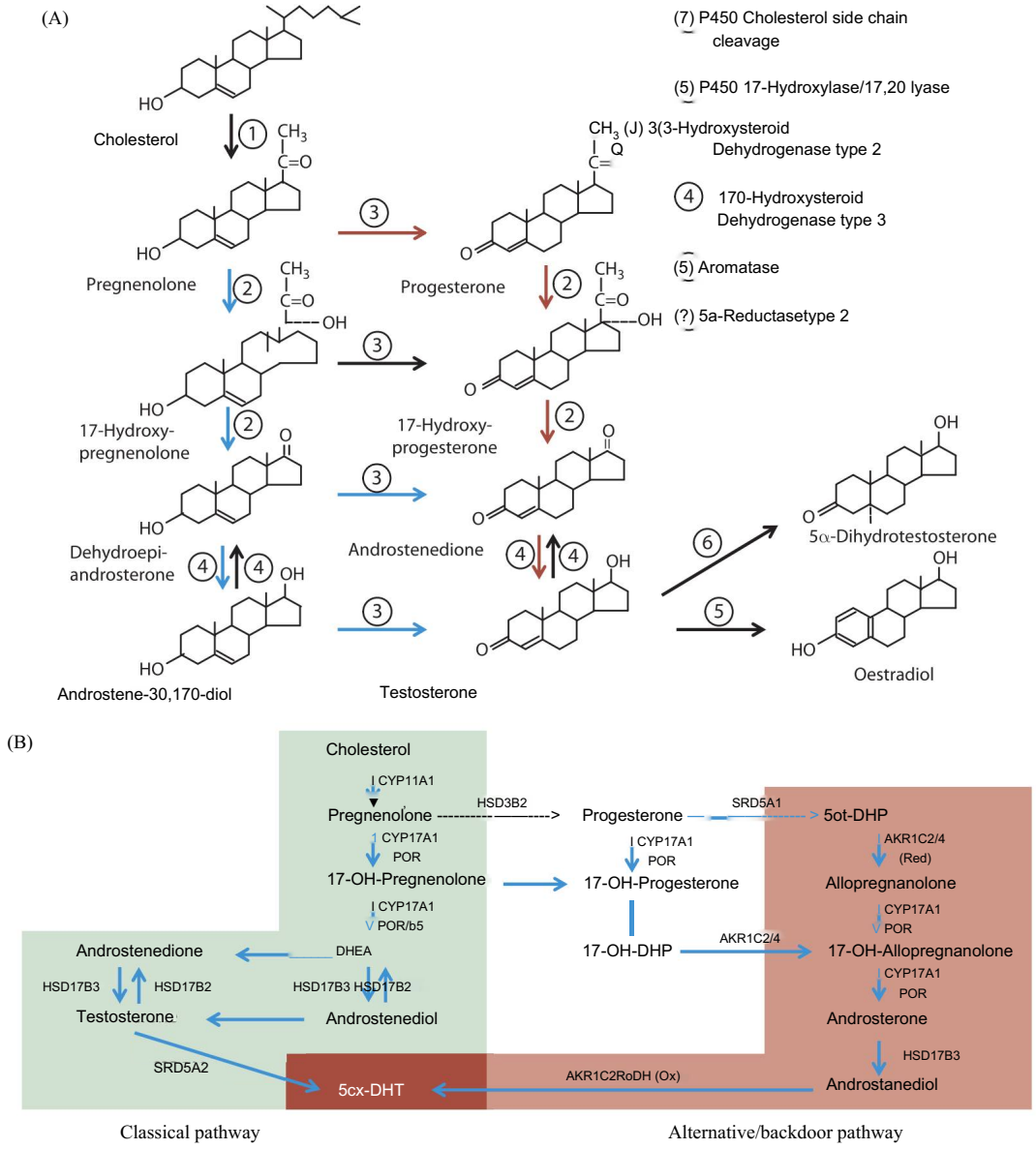

FIGURE 1 -2. A. The key steroid metabolic steps in the testis leading to formation of T, 5a-DHT, and E2. The A5 pathway (blue arrows) is used by the human testis, and the A4 pathway (red arrows) is more important in rodents. The same enzyme with a dual function, P450 17-hydroxylase/17,20-lyase (CYP17A1), catalyzes both 17-hydroxylation and D-ring side chain cleavage in pregnenolone and progesterone. Apart from the interconversion of 17-keto and 17-hydroxy steroids, all other reactions in the steroid metabolic pathway are irreversible. B.The"classical"(blue background) and alternative/backdoor (pink background) pathways of 5a-DHT synthesis.The factors functional in the classic pathway are CYP11A1 (cholesterol side-chain cleavage enzyme, P450scc), CYP17A1 (17a-hydroxylase/17,20-lyase, P450c17), HSD3B2 (3[3-hydroxysteroid dehydrogenase, type 2), HSD17B3 (170-HSD3 [17(3-hydroxysteroid dehydrogenase, type 3]), and 5a-reductase, type 2 (5a-reductase 2, encoded by SRD5A2).The alternative/backdoor pathway uses the following additional enzymes: 5cv-reductase, type 1 (5ct-reductase 1, encoded by SRD5A1), AKR1C2 3 (3a-reductase, type 3), and possibly AKR1C4 (3a-reductase, type 1) and RoDH (3-hydroxyepimerase, encoded by HSD17B6). The trivial names and abbreviations of the steroids are 17-hydroxy-dihydroprogesterone (17OH-DHP), 5a-pregnane-17a-hydroxy-3-20-dione; 17-hydroxy-allopregnanolone (17OH-allo), 5a-pregnane-3a,17a-dihydroxy-20-one; 5a-di hydro prog esterone (5a-DHP), 5a-pregnane-3,20-dione; and allopregnanolone, 3a-hydroxy-5a-pregnan-20-one. From Ref. 67, with permission.

TABLE 1-1. The Mean Testicular, Spermatic Vein, and Peripheral Vein Concentrations (in nmol/L) of the Key Testicular Steroids in Man[20,21]

STEROID	TESTIS	SPERMATIC VEIN	PERIPHERAL VEIN
Pregnenolone sulfate	2600	430	90
Progesterone	130	23	0.8
17-Hydroxyprogesterone	690	45	3.2
Dehydroepiandrosterone	680	35	8.2
Dehydroepiandrosterone sulfate	2000	1400	1000
5-Androstene-3(3,17(3-diol	820	590	500
Androstenedione	740	45	2.5
Testosterone	2600	720	20
Testosterone sulfate	1400	150	13
5o-Dihydrotestosterone	50	14	1.5
Estradiol	15	0.4	0.1

Hormonal Regulation of Spermatogenesis Spermatogenesis is regulated by the hormonal action of FSH and paracrine action of testicular T, supplemented by other endocrine, paracrine, and autocrine factors, as well as nutrients. The crucial role of LH-stimulated T production in spermatogenesis is well recognized, but the role of FSH remains somewhat unclear. It is apparent that the regulatory requirements are different at puberty for the initiation of spermatogenesis, its subsequent maintenance, and its reinitiation after transient suppression in adult life. Testosterone alone may be insufficient to drive spermatogenesis to completion in the immature testis. After prepubertal hypophysectomy in experimental animals, LH alone only partially reverses germ cell loss. In contrast, full spermatogenesis can be initiated in various gonadotropin-deficient adult animal models by T treatment alone (see Ref. 22). In men with postpubertal gonadotropin deficiency, prolonged hCG treatment alone can initiate spermatogenesis without FSH.[25]

Treatment with T suppresses LH and FSH secretion via negative feedback, which reciprocally leads to marked suppression of intratesticular T, while maintaining peripheral androgen actions. This leads to suppression of spermatogenesis to the extent that T treatment provides a successful means of male contraception.[26] If such men receive LH or hCG injections, their spermatogenesis recovers qualitatively, due to the restoration of intratesticular T levels,[27] although in the absence of FSH, the sperm counts remain about 50% suppressed. These findings suggest that T action alone is sufficient for the reinitiation of spermatogenesis, but full quantitative recovery may also require FSH. Indeed, addition of FSH to the treatment of these men fully restored spermatogenesis.

Feedback Regulation of Gonadotropins The functional balance of the HPT axis is maintained through the feedback action of T and E2, as well as inhibin B, at the hypothalamic-pituitary level[1]; inhibin B specifically inhibits FSH synthesis and secretion at the pituitary level. Unlike the menstrual cycle in females, the function of the male HPT axis is tonic and regulated only by negative feedback from the gonad at the hypothalamic-pituitary level. In the hypothalamus, T on its own, but more importantly after conversion to E2, suppresses GnRH secretion indirectly by suppressing the activity of kisspeptin neurons, which then results in the suppression of GnRH and gonadotropin secretion.

Although testicular steroids also regulate FSH, it is mainly regulated at the pituitary level by the Sertoli cell peptide hormone inhibin B,[28] the only type of inhibin present in the male serum. FSH stimulates Sertoli cell inhibin B production, thus forming the other side of a classical feedback regulatory loop. Inhibin also has complex intratesticular para/autocrine functions. Serum inhibin B levels correlate negatively with FSH levels and positively with sperm production and testis volume. It is low in patients with impaired spermatogenesis, idiopathic azoospermia, Klinefelter syndrome, and cryptorchidism.[29] Pituitary gonadotropin are the site of inhibin action through the inhibin co-receptor beta glycan.[30] The inhibitory action of inhibin B on FSH secretion is explained by its inhibition of the stimulatory effects of activin, a pituitary paracrine factor that stimulates FSH synthesis.

ANDROGEN ACTION

All T actions within and outside the testis are mediated by the same AR (NR3C4) (Fig. 1-3), a ligand-activated nuclear transcription factor belonging to the group of steroid nuclear receptors.[31] The human *AR* gene is located on chromosome X; hence, the male has only one copy of the gene. This, together with the fact that loss of androgen action is not essential for human survival, may explain the large number of known *AR* mutations.[32]

AR actions induce the male-type sexual differentiation and maturation in fetal life and during puberty. In adult men, androgens maintain spermatogenesis

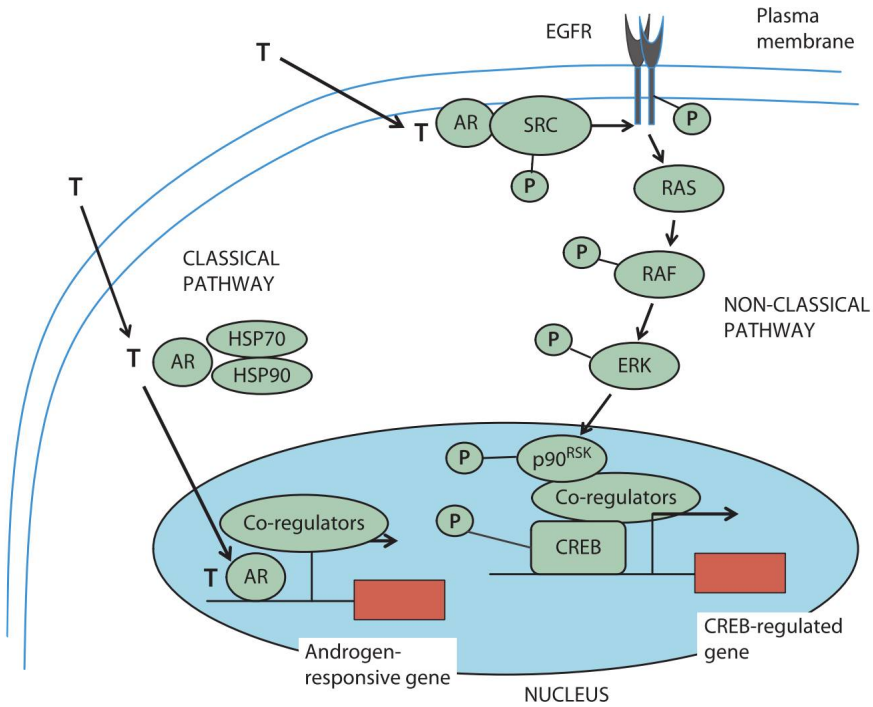

FIGURE 1-3. The classical and non-classical T signaling mechanisms of androgen action. In the classical pathway (left) T crosses the plasma membrane and binds to androgen receptor (AR). A conformational change in AR releases it from heat shock proteins (HSP). AR therafter translocates to the nucleus, where it binds to target gene androgen response elements, recruits co-regulator proteins, and regulates gene expression. In the non-classical pathway (right), T stimulation transiently localizes AR to the plasma membrane, followed by AR interaction with and activating SRC tyrosine kinase. The latter can alter numerous physiological processes, including the phosphorylation and activation of the epidermal growth factor (EGF) receptor that in turn activates the mitogen-activated protein (MAP) kinase cascade (RAF, MEK, and ERK). Further signaling through p90RSK kinase results in phosphorylation of the CAMP-response element binding protein (CREB) transcription factor and increased transcription of CREB-regulated genes.