

ANDROGEN

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1. Core Definition and Classification

The term **Androgen** refers to a sophisticated class of natural and synthetic steroid hormones that primarily regulate the development and maintenance of male characteristics, or **virilization**, in vertebrates. While often labeled as "male sex hormones," androgens are crucial in both biological sexes, playing vital roles in metabolism, bone density, libido, and general well-being. Physiologically, they function as powerful signaling molecules, binding to specific intracellular receptors--the **Androgen Receptor (AR)**--to modulate gene transcription in target tissues, leading to complex and far-reaching cellular responses. The classification of a hormone as an androgen is based on its ability to activate this receptor pathway, regardless of its origin or precise chemical structure.

Androgens are chemically characterized as C19 steroids, derived primarily from cholesterol, making them fat-soluble molecules that can easily diffuse across cell membranes. They are structurally related to other classes of steroid hormones, including estrogens and glucocorticoids, and often serve as precursors for these other hormones, illustrating a complex web of interconnected endocrine pathways. The most potent and quantitatively important androgen is **testosterone**, synthesized predominantly in the testes of males, but critical levels of other androgens and their precursors are produced by the adrenal glands and ovaries, ensuring continuous endocrine regulation throughout the lifespan. This universality of function necessitates the study of androgens not merely as reproductive agents but as essential regulators of systemic physiology.

The concept of androgens encompasses several specific compounds, often categorized based on their relative potency and source. The primary circulating androgens include testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenedione, and androsterone. While testosterone is the most abundant, DHT, formed by the 5 α -reductase enzyme, is significantly more potent in peripheral tissues, driving key functions such as external genital development and prostate growth. Understanding these structural and functional hierarchies is essential for diagnosing and treating endocrine imbalances, as subtle changes in the ratios or metabolism of these hormones can result in severe physiological consequences.

2. Etymology and Historical Discovery

The term **androgen** is derived from the Greek words *andros* (meaning "man") and *gennan* (meaning "to produce"), literally signifying "that which produces man." The scientific recognition of

a substance capable of inducing male characteristics dates back to early experiments in the late 19th and early 20th centuries. Initial research often focused on crude extracts from animal testes, demonstrating that these substances possessed powerful biological activity. These early studies provided the empirical foundation for modern endocrinology, suggesting the existence of potent chemical messengers responsible for sexual differentiation.

The pivotal moment in androgen research occurred in the 1930s. In 1931, Adolf Butenandt isolated **Androsterone** from large quantities of male urine, providing the first purified chemical confirmation of an androgen, though it was less potent than the compound found directly in testicular tissue. Four years later, in 1935, Ernst Laqueur and his colleagues successfully isolated the primary male hormone, **Testosterone**, directly from bull testes. This isolation was quickly followed by its chemical synthesis by Adolf Butenandt and Leopold Ružička, leading to a Nobel Prize in Chemistry in 1939 for their pioneering work on sex hormones. The ability to synthesize testosterone marked the beginning of its clinical use and a profound expansion of research into steroid biochemistry.

Following the isolation and synthesis of testosterone, subsequent decades saw the discovery of other key androgens and their metabolic pathways, notably the identification of **Dihydrotestosterone (DHT)** and the function of the 5 α -reductase enzyme. These discoveries shifted the understanding of androgen action from a simple one-hormone system (Testosterone) to a complex regulatory network involving local conversion and differential receptor binding affinities. The historical development of this field underscores the crucial transition from descriptive biology to detailed molecular endocrinology, enabling targeted therapeutic interventions for conditions ranging from hypogonadism to prostate cancer.

3. Biosynthesis and Metabolism

The synthesis of androgens, known as **steroidogenesis**, primarily occurs in the Leydig cells of the testes in males and, to a lesser extent, in the adrenal cortex and the ovaries in females. This process begins with **cholesterol**, which is sequentially converted through a series of enzymatic steps involving cytochrome P450 enzymes. The general pathway proceeds from cholesterol to pregnenolone, then to progesterone, and finally through intermediate steps involving 17-alpha-hydroxyprogesterone and androstenedione, culminating in the production of testosterone. The adrenal cortex primarily contributes precursors like Dehydroepiandrosterone (DHEA) and androstenedione, which are weaker androgens but are crucial sources, especially in women and prepubescent children.

The regulation of androgen synthesis is tightly controlled by the **Hypothalamic-Pituitary-Gonadal (HPG) axis**. In males, the hypothalamus secretes Gonadotropin-Releasing Hormone (GnRH), which stimulates the pituitary gland to release Luteinizing Hormone (LH). LH then acts directly upon the Leydig cells of the testes, stimulating cholesterol uptake and the enzymatic cascades

necessary for testosterone production. This feedback loop is essential: high levels of circulating androgens signal back to the hypothalamus and pituitary, suppressing GnRH and LH secretion, thereby maintaining homeostasis. This intricate regulatory system ensures that androgen levels remain within a narrow, physiological range necessary for health and reproductive function.

Once synthesized and released into the bloodstream, androgens circulate mostly bound to plasma proteins, primarily **Sex Hormone-Binding Globulin (SHBG)** and albumin. Only a small fraction, the "free" androgen, is biologically active and capable of diffusing into target cells. Within these cells, testosterone can exert its effects directly, or it can be metabolized into more potent forms, chiefly **Dihydrotestosterone (DHT)**, by the enzyme 5 α -reductase, particularly in reproductive tissues, skin, and the prostate. Alternatively, testosterone can be converted into **estradiol** (an estrogen) by the enzyme aromatase, demonstrating the fundamental interconnectedness of steroid hormones and highlighting the fact that testosterone serves as a prohormone for both potent androgens and estrogens.

4. Primary Physiological Functions

Androgens are responsible for the critical biological process of **sexual differentiation**, beginning in utero. The presence of testosterone during early fetal development, specifically around the eighth week of gestation, drives the development of the Wolffian ducts into the male internal reproductive structures (epididymis, vas deferens, and seminal vesicles). Simultaneously, the conversion of testosterone to DHT is necessary for the formation of the male external genitalia (penis and scrotum). Without the appropriate presence and action of androgens during this crucial window, the default developmental pathway leads to female internal and external genitalia, underscoring the hormonal basis of sexual determination.

During puberty, androgens trigger the onset of secondary sexual characteristics in males. This transformation, often referred to as **virilization**, includes the dramatic growth spurt, the development of the musculoskeletal system, the deepening of the voice (laryngeal growth), and the increased growth of body and facial hair. Androgens also stimulate the maturation of the testes and accessory sex glands, initiating spermatogenesis and establishing reproductive capacity. Beyond reproduction, androgens exert powerful anabolic effects, promoting nitrogen retention, protein synthesis, and the corresponding increase in muscle mass and strength, which distinguishes the typical male physique.

Furthermore, the systemic roles of androgens extend far beyond reproductive and secondary sexual function. They are vital for maintaining **bone health**, promoting increased bone density and inhibiting bone resorption in both sexes throughout life. Androgens also influence the central nervous system, impacting libido, mood, spatial cognition, and aggression. In the hematopoietic system, testosterone stimulates the production of red blood cells, contributing to higher average

hematocrit levels in men compared to women. Their ubiquitous influence throughout various organ systems establishes androgens as essential modulators of overall physiological homeostasis and quality of life.

5. Key Androgens and Their Roles

While the term androgen is broad, three specific hormones dominate clinical and physiological significance: Testosterone, Dihydrotestosterone (DHT), and Androstenedione. **Testosterone** is the most widely recognized and quantitatively important androgen. It functions primarily as a circulating hormone, mediating anabolic effects on muscle and bone, regulating libido, and serving as the direct precursor for both DHT and estradiol. Its role in the onset and maintenance of spermatogenesis within the seminiferous tubules is indispensable, relying on high local concentrations achieved via its binding to **Androgen-Binding Protein (ABP)** within the testes.

Dihydrotestosterone (DHT) is significantly more potent than testosterone, often described as the most active androgen. Unlike testosterone, which binds moderately to the androgen receptor, DHT exhibits high affinity and stability in the receptor complex, leading to a stronger biological signal. DHT is crucial for peripheral functions, including the growth of the prostate gland, male pattern baldness (androgenic alopecia), and the differentiation of the external genitalia in the fetus. Because of its localized action, pharmaceutical inhibitors of the 5 α -reductase enzyme (which converts T to DHT) are often used to treat conditions like benign prostatic hyperplasia (BPH) and hair loss.

Androstenedione and **Dehydroepiandrosterone (DHEA)** are typically classified as weaker androgens or prohormones. They are produced in the adrenal glands and, in women, the ovaries, and often serve as the primary source of androgen activity in females and prepubertal males. These hormones can be converted into testosterone or estrogen in peripheral tissues, such as fat and muscle, providing a vital hormonal substrate for maintaining anabolic activity and providing precursors for estrogen synthesis in postmenopausal women. Their measurement in clinical settings is particularly useful for assessing adrenal function and diagnosing conditions like congenital adrenal hyperplasia.

6. Clinical Significance and Medical Applications

The clinical application of androgens is extensive, primarily revolving around replacement therapy for conditions characterized by androgen deficiency, collectively known as **hypogonadism**. Androgen Replacement Therapy (ART) or Testosterone Replacement Therapy (TRT) is used to treat symptoms in men with confirmed low testosterone, which can include decreased libido, erectile dysfunction, fatigue, depression, reduced muscle mass, and osteoporosis. Available formulations include injectable esters, topical gels or patches, and subcutaneous pellets, each

designed to mimic the natural physiological pattern of secretion and maintain stable serum concentrations.

Beyond male hypogonadism, androgens have historically been used in the treatment of various other conditions. In women, low-dose androgen therapy, usually involving testosterone or DHEA, is sometimes explored to address **Female Sexual Dysfunction (FSD)**, particularly concerning low libido, although this remains an area of active debate and regulatory scrutiny. Furthermore, due to their potent anabolic effects, androgens have been used therapeutically to combat severe muscle wasting (cachexia) associated with chronic diseases like HIV/AIDS and certain cancers, helping to preserve lean body mass and improve overall function and quality of life.

Specific anti-androgen medications are equally important clinically. These drugs function by blocking the synthesis of androgens or by inhibiting their binding to the androgen receptor. They are indispensable in treating androgen-dependent diseases, most notably **prostate cancer**, where hormonal therapy aims to suppress the growth-promoting effects of androgens on malignant cells. Anti-androgens are also used to manage conditions in women characterized by excessive androgen action (hyperandrogenism), such as **Polycystic Ovary Syndrome (PCOS)**, helping to mitigate symptoms like hirsutism (excessive hair growth) and acne.

7. Androgen Disorders and Abnormalities

Disorders related to androgen levels can result from either deficiency (hypoandrogenism) or excess (hyperandrogenism), and the resultant pathology depends heavily on the timing of the abnormality. **Androgen Insensitivity Syndrome (AIS)** is a critical example of hypoandrogenism where, despite normal or high levels of circulating testosterone, genetic mutations render the androgen receptor non-functional. The body cannot respond to the hormone signal, leading to external female characteristics in an individual who is genetically male (XY), illustrating the absolute requirement for receptor function.

In adult males, acquired hypoandrogenism (late-onset hypogonadism) is frequently associated with age, obesity, or chronic illness, manifesting as reduced energy, sexual dysfunction, and loss of secondary sexual characteristics. Treatment involves identifying the underlying cause and often initiating **Testosterone Replacement Therapy (TRT)**. Conversely, hyperandrogenism in females is most commonly associated with **Polycystic Ovary Syndrome (PCOS)**, the leading endocrine disorder in reproductive-aged women. Symptoms include menstrual irregularities, infertility, hirsutism, and metabolic disturbances, driven by elevated ovarian or adrenal androgen production.

Adrenal gland disorders, such as **Congenital Adrenal Hyperplasia (CAH)**, involve defects in the enzymatic pathways of cortisol synthesis, leading to the shunting of precursor steroids toward the androgen pathway. This results in significant prenatal exposure to excessive androgens, causing virilization of female external genitalia (ambiguous genitalia) and precocious puberty in both sexes.

Detailed hormonal profiling and genetic testing are necessary to differentiate between the various causes of androgen abnormalities and to tailor appropriate endocrine or surgical management.

8. Pharmacological and Synthetic Androgens

The pharmaceutical industry has leveraged the anabolic properties of natural androgens to develop synthetic derivatives known as **Anabolic-Androgenic Steroids (AAS)**. These compounds are chemically modified versions of testosterone, designed primarily to enhance the ratio of anabolic (muscle-building) effects relative to androgenic (virilizing) effects, although a complete separation of these two activities is impossible. Examples include oxandrolone, nandrolone, and stanozolol. Medically, these agents are used in specific clinical contexts, such as treating hypogonadism, delayed puberty, and severe catabolic states, as discussed previously.

However, the non-medical use and abuse of AAS have become a major public health concern, particularly in sports and bodybuilding, constituting **doping**. Athletes misuse these substances to gain an unfair competitive advantage by dramatically increasing muscle mass, strength, and recovery time. This abuse carries significant health risks, including severe cardiovascular toxicity (e.g., cardiomyopathy, hypertension), hepatic damage (liver tumors, jaundice), and psychiatric disturbances (aggression, mood swings). Furthermore, chronic high-dose use can lead to suppression of natural testosterone production, resulting in testicular atrophy and infertility.

The development of pharmacological agents that selectively modulate the androgen receptor, known as **Selective Androgen Receptor Modulators (SARMs)**, represents the next generation of research. SARMs aim to provide the beneficial anabolic effects on muscle and bone while minimizing unwanted side effects on the prostate, skin, and reproductive axis. While promising, many SARMs are still in the experimental phase or lack long-term safety data, but they illustrate the ongoing scientific effort to harness the therapeutic potential of the androgen pathway with greater precision and safety profiles.

9. Further Reading

The study of androgen signaling continues to be one of the most dynamic areas of endocrinology, with ongoing research focused on understanding the precise molecular mechanisms of receptor activation, the role of androgens in metabolic syndrome and cardiovascular health, and the development of highly specific pharmaceutical targets. The complex interplay between androgens and estrogens, particularly through the aromatase enzyme, means that a holistic view of steroid endocrinology is required to fully grasp the homeostatic balance maintained by these hormones. Future investigations will likely focus on gene-environment interactions that influence individual responses to circulating androgen levels.

Ongoing ethical and regulatory debates surround the clinical use of testosterone replacement

therapy, particularly regarding its long-term cardiovascular risks in aging men and its use in transgender hormone therapy. While androgens are fundamental for male development, their function as precursors for estrogens and their crucial regulatory roles in female physiology necessitate moving beyond the traditional, strictly gendered view of these hormones. This broader perspective emphasizes their systemic importance in maintaining health across the human lifespan, regardless of biological sex.

The regulatory landscape regarding synthetic androgens remains fraught with challenges, balancing legitimate medical necessity with the prevention of athletic doping and recreational abuse. Educational initiatives and strict international regulations are continuously evolving to curb the illicit trade and usage of anabolic steroids. Ultimately, the robust academic study of androgen signaling is paramount, enabling clinicians to harness these powerful molecules safely and effectively to treat diseases and promote overall well-being.

[Androgen - Wikipedia](#)

[Testosterone - Wikipedia](#)

[The Endocrine Society Official Website](#)