

Steroid Hormones Effected in Human Body

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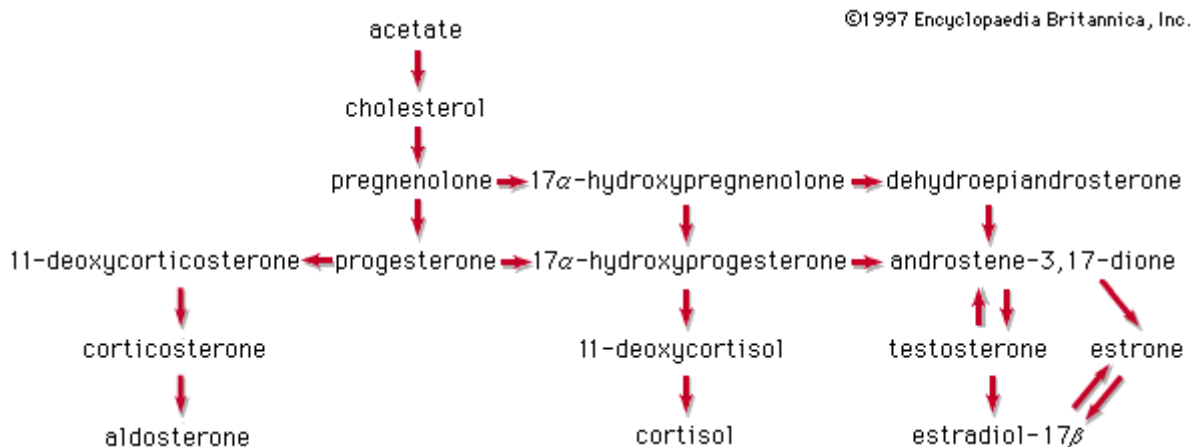
Abstract

Disturbances of the steroidogenesis or altered peripheral metabolism of steroids may result in severe clinical manifestations. Therefore, prompt diagnosis and initiation of medical treatment are desirable. The diagnostics of disorders of steroid hormone production, metabolism, and action have been previously based on immunoassay tests. However, in a modern medical laboratory, due to low accuracy of immunoassays, this technique is continuously replaced by chromatographic separation methods coupled to mass spectrometric detection systems. In this review we present current advances in the diagnostics of adrenal gland disorders, focusing on the role of mass spectrometry in prenatal and newborn screening, and in the diagnostics of sexual maturation disorders.

Keywords: Estrogens, Androgens, Steroid Hormones

Introduction

All steroid hormones are derived from cholesterol. They are transported through the bloodstream to the cells of various target organs where they carry out the regulation of a wide range of physiological functions.



The adrenal cortex produces the adrenocortical hormones, which consist of the glucocorticoids and the mineralocorticoids. Glucocorticoids such as cortisol control or influence many metabolic processes,

including the formation of glucose from amino acids and fatty acids and the deposition of glycogen in the liver. Glucocorticoids also help to maintain normal blood pressure, and their anti-inflammatory and immunosuppressive actions have rendered them useful in treating rheumatoid arthritis and preventing the rejection of transplanted organs. Mineralocorticoids such as aldosterone help maintain the balance. The steroids that are made almost exclusively in the adrenal glands are cortisol, 11-deoxycortisol, aldosterone, corticosterone, and 11-deoxycorticosterone. Most other steroid hormones, including the estrogens, are made by the adrenal glands and the gonads(1)

Types Of Steroid Hormones

Steroid hormones are produced by the adrenal glands and gonads. The adrenal glands sit atop the kidneys and consist of an outer cortex layer and an inner medulla layer. Adrenal steroid hormones are produced in the outer cortex layer. Gonads are the male testes and female are the ovaries.

Adrenal Gland Hormones

- **Aldosterone:** This mineralocorticoid acts on the kidneys promoting the absorption of sodium and water. Aldosterone aids in blood pressure regulation by raising blood volume and blood pressure.
- **Cortisol:** This glucocorticoid aids in metabolism regulation by stimulating the production of glucose from non-carbohydrate sources in the liver. Cortisol is also an important anti-inflammatory substance and helps the body deal with stress.
- **Sex Hormones:** adrenal glands produce small amounts of the male sex hormone testosterone and the female sex hormone estrogen.

Gonadal Hormones

- **Testosterone:** This male sex hormone is produced by the testes and in small amounts in the female ovaries. Testosterone is responsible for the development of male reproductive organs and male secondary sex characteristics.
- **Estrogens:** These female sex hormones are produced in the ovaries. They promote development of female sex characteristics and skeletal growth.
- **Progesterone:** This female sex hormone is produced in the ovaries and important for the production and maintenance of the uterine lining during pregnancy. Estrogen and progesterone levels also regulate the menstrual cycle.”(2)”

How Steroid Hormones Work

Steroid hormones cause changes within a cell by first passing through the cell membrane of the target cell. Steroid hormones, unlike non-steroid hormones, can do this because they are fat soluble. Cell membranes are composed of a phospholipid bilayer which prevents fat-insoluble molecules from diffusing into the cell.

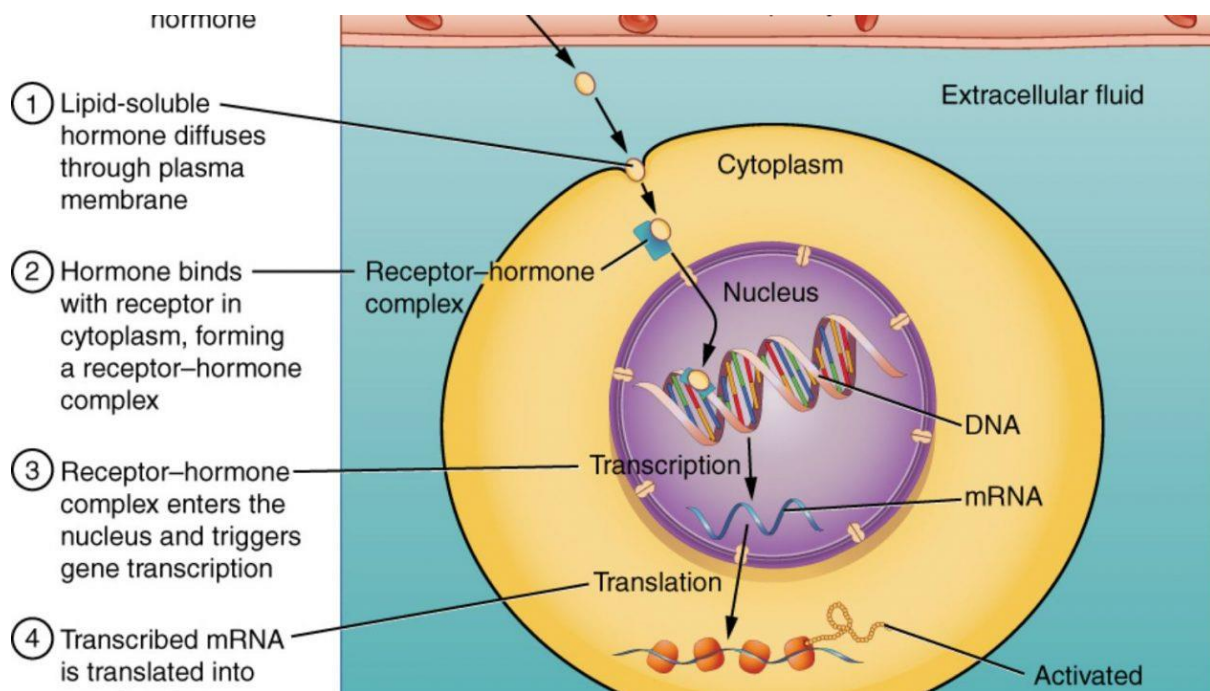


Figure 1: working of steroid hormones:

Steroid hormone Mechanism of Action

The steroid hormone mechanism of action can be summarized as follows:

- Steroid hormones pass through the cell membrane of the target cell.
- The steroid hormone binds with a specific receptor in the cytoplasm.
- The receptor bound steroid hormone travels into the nucleus and binds to another specific receptor on the chromatin.
- The steroid hormone-receptor complex calls for the production of messenger RNA (mRNA) molecules, which
- code for the production of proteins.”(3)”

Functions of Steroids

- Steroids are found in all eukaryotic organisms and display a great variety of different biological functions.
- They are subdivided into progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens, depending on their function. Cholesterol is a major component of atherosclerotic plaque deposits in atherosclerosis, one of the most frequent causes of death in industrialized countries where diet is too rich in the steroid. The progesterone function is the preparation of the uterine endometrium for the implantation of the fertilized egg and the maintenance of pregnancy.
- The mineralocorticoid aldosterone which in case of low Na^+ concentration or excessively low blood pressure, it is released from the adrenal cortex in the kidney. It directly influences the Na^+ concentration and indirectly regulates the amount of water in cells. The glucocorticoid hydrocortisone is abundant in stress or inflammation. It induces the conversion of proteins to carbohydrates; thus its function is opposite to that of insulin. Hydrocortisone also has a complex suppressant effect on the

immune system. Important male sex hormones are the androgens: testosterone and androstenedione which are responsible for the development of male characteristics. The estrogens, estradiol and estrone control the growth of female sex characteristics.”(4)”

Steroid Programming and hormones

Estrogen

Developmental and programming effects of steroid during rat ovary development. Exposure to high levels of steroidal hormones disrupts normal endocrine function and decreases fertility in mammals including humans, especially when the exposure occurs during critical periods of vulnerability during development. The established view holds that reproductive function is regulated through the integration of information that comes from the hypothalamus, hypophysis, and ovaries, and that gonadotropins modulate folliculogenesis and steroidogenesis in the ovary. Numerous studies performed to understand the neural circuits and molecular mechanisms that regulate GnRH release and steroid feedback demonstrate important roles for classical steroid receptors, membrane steroid receptors and neurosteroids in the hypothalamus.

Parallel to the endocrine control of reproductive function, experimental evidence indicates that there is complementary regulation through the hypothalamus-celiac ganglion-ovary axis. The primary neurotransmitter acting in the ovary is noradrenaline (NA), which is released from neuron terminals originating in the celiac ganglia and acting on the thecal layer of ovarian follicles.

In mammals, ovarian folliculogenesis starts with the formation of primordial follicles, a process known as nest breakdown, which allows the oocytes to be surrounded by a layer of somatic cells, thus forming the primordial follicles in a process known as follicular assembly. In humans, this process occurs during the third trimester of gestation, whereas in rats it occurs between 24 and 72 hours after birth. Once follicular development begins, it continues throughout postnatal life in both species. During this time the oocyte enlarges while the granulosa and theca cells proliferate, increasing the layers of cells surrounding the oocyte. This proliferative phase ends as follicular fluid begins to accumulate and the antral cavity forms. Each of the different steps of follicular development is controlled by different endocrine and paracrine factors (gonadotropins, growth factors, and steroidal hormones); making this process vulnerable to hormonal changes induced by external factors.

The growing incidence of infertility and reproductive disorders in humans and wildlife has alerted many researchers to the influence that products with estrogenic activity that are produced and released into the environment have over reproductive function. The molecules that mimic or block hormonal activity are known as endocrine disruptors (EDs). They may be synthetic or natural in origin and can alter homeostasis and the hormonal system, either by environmental exposure or by inappropriate exposure during development. Exposure to EDs during the sensitive periods can alter the normal development of the ovary, causing alterations in morphological and follicular development and malfunctions during the adult period. These alterations in the rat ovary can be inherited by the next generation through changes in the pattern of DNA methylation, because cellular differentiation of the rat ovary begins around the time of birth. The germ cell re-methylation is initiated during the postnatal period and continues throughout the oocyte growth period until the preantral follicle stage. Regardless of the source of hormones or EDs during this period, they would alter the normal development of the offspring due to a reprogramming of the genes.

There are several pathological conditions in which the hormonal environment is altered during development, such as adrenal hyperplasia, obesity, and polycystic ovary syndrome (PCOS). PCOS is a

complex endocrine disorder characterized by hyperandrogenism, ovulatory/menstrual irregularity, and polycystic ovaries, which affects 5–10% of women of reproductive age . Women with PCOS exhibit a significant increase in androgen concentrations during pregnancy. An important proportion of the first-degree female relatives of women with PCOS have been shown to be at risk for developing PCOS . In fact, in comparison with control girls, PCOS girls exhibit higher levels of anti-Müllerian hormone (AMH), a marker of growing follicles, beginning at the peripubertal stage . It has been proposed that this inheritance is not the result of a genetic condition, but is due to fetal programming . Supporting this, experimental treatment of PCOS gestating mothers with the insulin sensitizer drug metformin improved the altered endocrine-metabolic environment of the PCOS mothers and the AMH levels in their daughters, suggesting the follicular alterations described in adult PCOS women may appear early during development . This is supported by several studies in animal models that have demonstrated a relationship between programmed polycystic ovary (PCO) morphology during adulthood and prenatal or neonatal exposure to endocrine-disrupting compounds such as estrogens or aromatizable androgens.

The administration of a single dose of estradiol valerate (EV) to neonatal rats (at 12 hours postnatal) induces early vaginal opening, disrupted cyclicity, appearance of a PCO phenotype, absence of corpus luteum, and infertility . In addition, this exposure decreases the total number of ovarian follicles mainly due to a reduced number of primordial follicles suggesting that estradiol acts in the first stages of folliculogenesis when primordial follicles are organizing and reprogramming the genes that control ovarian function . At the molecular level, AMH expression is increased in the ovary of these rats when adults. In contrast to AMH expression, AR expression in granulosa cells decreased at the same stage of development suggesting that the regulatory region of AR and AMH genes could be involved. These results have been confirmed by protein expression data found by immunohistochemistry. In summary, these data suggest that estradiol exposure during the neonatal critical period reprograms AR and AMH expression in the ovary possibly through epigenetic mechanisms that become evident in the adult period, when the full PCO phenotype is acquired .”(5)”

Testosterone

Mammals are exposed to gonadal, placental and maternal hormones during early development. Hormones must be maintained within an appropriate range over time to program proper development of the reproductive axis and adult behavioral responses . Males develop in an environment of elevated T secreted by the fetal testes that acts to masculinize and defeminize brain structures, physiological processes and behaviors. Differences in T concentrations and sensitivity occur naturally between individuals and can result from environmental challenges during pregnancy. The question of whether the occurrence of same sex partner preferences originates from variations in the prenatal hormonal environment has been studied in using a unique ram model In conclusion, the sheep model has advantages and disadvantages for studying the programming effect of T during fetal life on reproductive and metabolic parameters in offspring. Despite its limitations it could help elucidate the sequelae associated with inappropriate androgen exposure during fetal development and uncover the cause of the neuroendocrine disturbances observed in the affected offspring. It is now apparent that both females and males are susceptible to the reprogramming effects of a hyperandrogenic intrauterine environment.

Protective Effects of steroid hormones

Under physiological conditions, progesterone is traditionally associated with female reproductive functions and pregnancy. Additionally, this steroid exerts neuroprotective and pro-myelinating effects in the central and peripheral nervous system in acute and chronic diseases such as traumatic brain injury, stroke, ischemia, peripheral neuropathy of traumatic or diabetic origin, Alzheimer's dementia and amyotrophic lateral sclerosis (ALS). At the cellular and molecular level, progesterone modulates neuronal survival and plasticity, increases adult neurogenesis, favors the myelination process, inhibits lipid peroxidation, exerts anti-inflammatory properties and regulates astroglial plasticity. The central nervous system (CNS) expresses several specific progesterone receptors such as: the classical intracellular progesterone receptor (PR), several isoforms of the membrane PR (mPR α , β and γ), the progesterone receptor membrane component type 1 (abbreviated PGRMC1 and formerly known as 25DX), and sigma 1 receptors. Once progesterone reaches the nervous system, either from systemic circulation or produced locally in the brain, it can be metabolized into 5 alpha dihydroprogesterone (DHP), which is further converted into 3 alpha, 5 alpha tetrahydroprogesterone or allopregnanolone. Thus, the metabolism of progesterone inside the nervous system has a profound impact on its mechanism of action: while progesterone and DHP interact with the classical intracellular PR, allopregnanolone is a potent allosteric modulator of GABA α receptors.

The Wobbler mouse is an animal model of ALS, the most common motoneuron disease. Wobblers develop a chronic, progressive motoneuron degeneration with selective involvement of brain stem and cervical motoneurons. In contrast to ALS patients who show a sex difference in disease incidence, with higher frequency in men than in women, the onset or the progression of the Wobbler disease did not correlate with sex. Histologically, ventral horn motoneurons of the cervical spinal cord experience a dramatic cytoplasmic vacuolar degeneration, associated with astrogliosis and microglial activation. Oxidative stress events participate in this mechanism, a finding supported by abnormalities of mitochondrial function in Wobbler mice. In this regard, mitochondria contribute to the production of certain free radicals; namely, superoxide anion and nitric oxide (NO); the latter caused by the elevated activity of a mitochondrial nitric oxide synthase (mtNOS). Excess levels of NO in association with increased generation of superoxide anions produce the formation of peroxynitrite (ONOO $^-$) leading to oxidative damage. This situation leads to mitochondrial swelling and inhibition of the electron transport chain. At the ultrastructural level, vacuolated motoneurons from Wobbler mice present cristolysis and disruption of outer and inner mitochondrial membranes.

Progesterone administration to Wobblers exerts neuroprotective and anti-inflammatory effects such as: lower number of damaged/vacuolated motoneurons, increased expression of brain derived neurotrophic factor in motoneurons and oligodendrocytes, restoration of cholinergic neurotransmission and of axonal transport and inhibitory effects on astrogliosis. Recent work suggests that the motoneuron protective effects of progesterone may also depend on the regulation of mitochondrial function.”(6)”

Anabolic steroid hormones

Anabolic steroid hormones are synthetic substances that are related to the male sex hormones. They have the same mechanism of action within the body. Anabolic steroid hormones stimulate the production of protein, which is used to build muscle. They also lead to an increase in the production of testosterone. In addition to its role in the development of reproductive system organs and sex characteristics, testosterone

is also critical in the development of lean muscle mass. Additionally, anabolic steroid hormones promote the release of growth hormone, which stimulates skeletal growth.

Anabolic steroids have therapeutic use and may be prescribed to treat problems such as muscle degeneration associated with disease, male hormone issues, and late onset of puberty. However, some individuals use anabolic steroids illegally to improve athletic performance and build muscle mass. Abuse of anabolic steroid hormones disrupts the normal production of hormones in the body. There are several negative health consequences associated with anabolic steroid abuse. Some of these include infertility, hair loss, breast development in males, heart attacks, and liver tumors. Anabolic steroids also effect the brain causing mood swings and depressions.”(7)”

Side Effects And Risks

As with all medicines, some people will have side effects. These are more likely if you’re on a high dose or if you’re taking steroids for a long time.

The person treating you will make sure you’re on the lowest possible dose to keep your condition under control. You might also be given a drug called a proton pump inhibitor or another medicine to protect your stomach.

Some of the side effects of steroids are shown below:

Tablets, liquids and soluble tablets

- weight gain and increased appetite
- pains, indigestion or heartburn
- sleep problems
- changes in mood
- bruising easily
- thinning of the skin
- stretch marks.

Creams and gels

- stinging or burning where the cream has been applied
- changes in skin colour
- thinning of the skin
- stretch marks
- increased hair growth where the cream has been applied.

Eye drops and ointments

- stinging or burning in eyes after putting drops in
- a funny taste in the mouth after putting drops in.”(8)”

Effects on other treatments

Steroids can be taken along with other drugs. However, some drugs can interact with steroids, so you should discuss any new medications with your doctor before starting them, and you should tell anyone else treating you what you’re taking.

Don't take over-the-counter preparations or herbal remedies without discussing them first with your doctor, rheumatology nurse or pharmacist.

Some of the following drugs may interact with steroids, so let your doctor know if you're taking any of these drugs:

- blood thinners or anticoagulants, such as warfarin
- drugs for epilepsy, such as phenytoin or carbamazepine
- drugs for diabetes
- Xofigo, a drug used to treat prostate cancer

Side effects of anabolic steroids

The effects of anabolic steroid use can differ from person to person. Some people may experience:

- fluid retention (also called water retention or oedema)
- difficulty sleeping
- damage to nerves from injecting steroids
- irritability, mood swings, aggression or depression
- increased sex drive (libido)
- skin changes – acne that results in scarring
- more colds.

Men may experience:

- testicle and penis shrinkage
- reduced sperm count
- erectile dysfunction (or impotence)
- prostate problems
- gynaecomastia (breast development)
- baldness (patterned hair loss)
- involuntary and long-lasting erection.

Women may experience:

- irregular menstrual cycle or loss of periods (amenorrhoea)
- shrunken breasts
- deepened voice
- facial and body hair growth (such as hirsutism)
- abnormal growth of the clitoris.

Young people may experience:

- stunted growth
 - premature balding
 - acne scarring
 - injury caused by excessive, intense workouts
- Physical effects

Effects of anabolic steroids in men can include:

- reduced sperm count
- infertility

- shrunken testicles
- erectile dysfunction
- hair loss

In women, anabolic steroids can cause:

- facial hair growth and body hair
- loss of breasts
- swelling of the clitoris
- a deepened voice
- an increased sex drive
- problems with periods
- hair loss
- severe acne

In addition, both men and women who take anabolic steroids can develop any of the following medical conditions:

- heart attack or stroke
- liver or kidney problems or failure
- high blood pressure (hypertension)
- blood clots

Long-term effects of anabolic steroids

Anabolic steroids can produce many unpleasant and often permanent side effects, including:

- damage to the gonads (testicles or ovaries)
- liver disease
- malfunctions of the kidneys, liver or heart.”(9)”

Conclusions

- The present review shows that fluctuations in steroid hormones, influenced by factors such as age and health status, have consequences at the level of CNS and PNS.
- Utilizing both classical and non-classical pathways, neurosteroids participate in the physiological regulation of neurogenesis, neuronal survival, synaptic function, and myelin formation, thus influencing neuronal plasticity.
- Because of these effects, neurosteroids will have different modulatory actions, exerting control over mood, cognition, and behavior.
- Additionally, they have a neuroprotective role in relation to certain neurocognitive paths.

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