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STEROIDS: GENOMIC AND NON-GENOMIC ACTIONS

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Abstract: Steroid hormones are important maintainers of human body homeostasis, in addition to having important roles in the development and maturation of fetal organs and controlling male and female reproductive cycles. Human steroids are produced from a common precursor, cholesterol, in specialized endocrine cells such as the testes, ovaries, and adrenal glands. Testosterone, estrogen, cortisol and aldosterone are some examples of the best-known steroid hormones. The common mechanism of action of steroids is genomic, which occurs through the binding of these hormones with intracellular receptors, which are ligand-dependent transcription factors, affecting the cell's gene transcription. However, some rapid physiological effects cannot be explained by the traditional model of action, as changes in the gene transcription process take a certain time to take effect. Thus, the non-genomic effects of steroids are currently being studied, which include actions on the cell membrane, where they alter the opening of ion channels and their cardiovascular effects. The article in question also addresses the two-step action model of steroid hormones, focusing on reproductive hormones and vitamin D.

Keywords: Testosterone; Estrogen; Sexual Steroids; Cardiac Steroids.

INTRODUCTION

Steroid hormones are synthesized from the precursor cholesterol, derived from nutritional sources or synthesized de novo from acetyl-coenzyme A (acetyl-coA) (PAYNE; HALES, 2004). The main steroid hormones are cortisol, testosterone, aldosterone, estradiol, progesterone and cortisol, produced in the adrenal gland, testicles or ovaries. They are responsible for regulating the most diverse functions in cells, tissues and organs (COLE; SHORT; HOOPER, 2019). Steroid hormones are very hydrophobic, being carried from their point of release to their target tissue linked to specific carrier proteins, such as sex hormone binding globulin (SHBG) and androgen binding protein (ABP). In the target tissue, they cross the plasma membrane by simple diffusion or facilitated diffusion, binding to a specific receptor protein, in the nucleus or cytoplasm. The hormone-receptor complex then binds to specific sequences in the DNA, known as Hormone Response Elements (HRE) and determines the change in gene expression, either increasing or suppressing it (FALKENSTEIN et al., 2000; ROBINSON; ESCRIVA; LAUDET, 2003).

The common theory of steroid action says that steroids modulate gene transcription through their intracellular receptor, which acts as a ligand-dependent transcription factor (FALKENSTEIN et al., 2000). The non-genomic effects of steroids are recognized due to the fact that they are insensitive when in the presence of transcription inhibitors and because these actions occur within seconds to minutes, which would not be possible to result from gene transcription. In addition to these effects, direct interaction effects of steroids with the plasma membrane, direct binding with nuclear DNA and even as cofactors have been described (LUCAS-HEROLD et al., 2017; COLE; SHORT; HOOPER, 2019).

Advances in research generating an evident growth in non-genomic actions of steroids in *in vitro* and *in vivo* models have rendered the classical model of genomic action of steroids insufficient to explain the range of actions recently discovered. (PIETRAS; SZEGO, 1999; FALKENSTEIN et al., 2000). Furthermore, the speed of some actions of this class of hormones cannot be explained by a slow process as the typical mechanism for affecting gene transcription (DENG et al., 2017).

BIBLIOGRAPHIC REVIEW

STEROID HORMONES

Steroid hormones are synthesized from the precursor cholesterol, derived from nutritional sources or synthesized de novo from acetyl-coenzyme A (acetyl-coA). The main steroid hormones are cortisol, testosterone and other androgens, aldosterone, estradiol and other estrogens, progesterone and vitamin D. Cortisol and aldosterone are synthesized in the adrenal cortex, which also produces the adrenal androgen, dehydroepiandrosterone (DHEA) and androstenedione. Testosterone is produced in the testes, while estradiol and progesterone are synthesized in the ovaries (FALKENSTEIN et al., 2000; COLE; SHORT; HOOPER, 2019). Steroids synthesized in the nervous system are referred to as neurosteroids. The main steroid hormones synthesized in the central and peripheral nervous system are pregnenolone, DHEA and its sulfates and reduced metabolites, such as 3a-hydroxy-5a-pregnane-20-one (PAYNE; HALES, 2004).

Steroid hormones, thyroid hormones and vitamin D are sufficiently lipophilic to quickly penetrate target cells through the plasma membrane, where they bind to nuclear receptors and initiate gene transcription. The messenger RNA produced is translated into proteins that then regulate biochemical and physiological processes (EDELMAN, 1975).

NUCLEAR RECEPTORS

The superfamily of nuclear receptors, the largest group of transcription factors present in eukaryotes, regulate development and metabolism by controlling gene expression (FIORETTI; SITA-LUMSDEN; BEVAN; BROOKE, 2014). This family is made up of steroid receptors, non-steroidal receptors such as thyroid hormone receptors and a legion of orphan receptors (MANGELSDORF et al., 1995; WEATHERMAN; FLETTERICK; SCANLAN, 1999).

The family of nuclear receptors is divided into three groups, based on the chemical similarity of their ligands: Steroid Receptors, including mineralocorticoid receptors (MR), estrogen receptors (ER), progesterone receptors (PR) among others; Heterodimeric RXR receptors, also known as non-steroidal receptors, which include the thyroid hormone receptor (TR), vitamin D (VDR) and Retinoic acid (RXR); the third group, known as orphan receptors, were discovered later through cloning and sequencing, but which are still, for the most part, not related to a physiological ligand (WEATHERMAN; FLETTERICK; SCANLAN, 1999). This third group includes receptors such as the Neural Growth Factor Receptor (NGFI) (ROBERTSON et al., 1997; ROBINSON; ESCRIVA; LAUDET, 2003).

Studies revealing the molecular biology of these receptors began in 1984, with the cloning of estrogen and glucocorticoid receptors (MANGELSDORF et al., 1995). However, the endogenous ligands of these receptors have been studied since the beginning of the century, such as testosterone, discovered and reproduced synthetically in the 1920s and 1930s, respectively (STILGER; YESALIS, 1999; DOTSON; BROWN, 2007). Between 1995 and 1999, the structures of several hormone-binding domains in nuclear receptors were described, with the help of crystallography (WEATHERMAN; FLETTERICK; SCANLAN, 1999).

STEROID RECEPTORS

Steroid receptors have three variable structural domains, and some functions, such as activation via hormone binding, do not correspond to a simple structural domain. These domains are the C-terminal Domain (LBD), an N-terminal Domain and the DNA Binding Domain (DBD) (TORAN-

ALLERAND et al., 1989; WEATHERMAN; FLETTERICK; SCANLAN, 1999; FIORETTI; SITA-LUMSDEN; BEVAN; BROOKE, 2014). The N-terminal domain is the least conserved throughout the family of these receptors. The DBD is the most conserved domain among the three, adjacent to the N-terminal domain and is the site of interaction with DNA. It is composed of two zinc fingers ("Zinc fingers"), which allow specific recognition of short regions of DNA in steroid receptors (LUISI et al., 1991). In some cases, the receptor does not bind directly, but rather through other DNA-binding proteins. For example, Estrogen and Glucocorticoid receptors affect transcription through receptor contact with Heterodimeric AP-1 components. The family of steroid receptors comprises androgen receptors (AR), estrogen receptors (ER), glucocorticoid receptors (GR), mineralocorticoid receptors (MR) and progesterone receptors (PR) (FIORETTI; SITA-LUMSDEN; BEVAN; BROOKE, 2014; COLE; SHORT; HOOPER, 2019).

SYNTHESIS AND MECHANISMS OF ACTION OF STEROID HORMONES

Humans produce all of their steroid hormones from cholesterol (PAYNE; HALES, 2004). Three classes of steroid hormones are produced in the cortex of the adrenal gland: mineralocorticoids, which control the reabsorption of organic ions (sodium and chlorine for example) by the kidneys, such as aldosterone; glucocorticoids, which help regulate gluconeogenesis and reduce the inflammatory response; and the androgen hormones, dehydroepiandrosterone (DHEA) and androstenedione, the main sources of androgens in women. (MILLER; ANCHUS, 2011).

Sex hormones are produced in the male and female gonads and the placenta. Among them are progesterone, one of the factors that regulates the female monthly reproductive cycle; androgens (such as testosterone); and estrogens (such as estradiol), which influence the development of secondary sexual characteristics in men and women, respectively. Steroid hormones are synthesized from the precursor cholesterol, whether derived from nutritional sources or synthesized de novo from Acetyl-coenzyme A (acetyl-coa) (YOUNG; CLYNE; COLE, 2001; KALLBER et al, 2002).

The synthesis of steroid hormones requires the removal of some or all of the carbons in the C-17 side chain of the cholesterol ring. Removal of the side chain occurs in the mitochondria of steroidogenic tissues and involves the hydroxylation of two adjacent carbons in the side chain (C-20 and C-22), followed by cleavage of the bond between them. The formation of the various steroid hormones also involves the introduction of hydrogen atoms. All hydroxylation and oxygenation reactions in steroid biosynthesis are catalyzed by mixed-function oxidases that use NADPH, O2 and mitochondrial cytochrome P-450 (KALLBER et al., 2002; COLE; SHORT; HOOPER, 2019).

Steroid hormones are very hydrophobic, being carried from their point of release to their target tissue bound to specific carrier proteins, such as sex hormone binding globulin (SHBG) and androgen binding protein (ABP) (). In the target tissue, they cross the plasma membrane by simple diffusion or facilitated diffusion, binding to a specific receptor protein, in the nucleus or cytoplasm. The hormone-receptor complex then binds to specific sequences in the DNA, known as Hormone Response Elements (HRE) and determines the change in gene expression, either increasing or suppressing it (EDELMAN, 1975; FALKENSTEIN et al., 2000).

The DNA sequences to which the complexes

bind are similar in length and arrangement, but differ in their nucleotide sequence for the various steroid hormones. Each receptor recognizes an HRE consensus sequence, to which the hormone-receptor complex binds tightly and which consists of two sequences of six nucleotides, typically in a palindromic arrangement. Hormone receptors have a highly conserved DNA-binding domain with two zinc fingers. The hormone-receptor complex binds to DNA as a dimer with the zinc finger domains of each monomer recognizing one of its nucleotide sequences (ROBINSON; ESCRIVA; LAUDET, 2003).

GENOMIC EFFECTS OF STEROID HORMONES

The common theory of steroid action says that steroids modulate gene transcription through their intracellular receptor, which acts as a ligand-dependent transcription factor (MANGELSDORF et al., 1995; FALKENSTEIN et al., 2000). The detailed explanation of the mechanism of action of steroids was possible due to research dating back to the beginning of the 20th century, but it took a crucial step forward with the discoveries of Clever and Karlson (1960), who saw chromosomal reactions, as they called it, when injecting the hormone steroid Ecdysone in insect larvae. They noticed that the injection of Ecdysone altered the structure of the chromosomes after two hours, and the effect ceased after 24 hours, cited in the review by Henrich and Brown (1995).

These receptors act as transcription factors to regulate gene expression, recognizing palindromes known as Hormone Response Elements (HRE) in DNA after the hormone-receptor complex undergoes homo- or heterodimerization. Thus, transcription is initiated together with the basal transcription complex, coactivators, corepressors and transcription regulators (BEATO; KLUG,

2000). Some steroid hormone receptor coactivators act as acetyltransferases on histones, reducing the affinity of histones to DNA, revealing the access of steroid receptors to the HRE on DNA (FALKESNTEIN et al, 2000). The ligand-dependent modulation of transcription became known as the Genomic Effect of these steroid hormones, since these actions are inhibited in the presence of transcription and translation inhibitors (ROBINSON; ESCRIVA; LAUDET, 2003).

Nuclear receptors are structurally organized into different domains: a variable N-terminal region, a highly conserved central region, the DNA binding site (DBD), and the C-terminal binding site region (LBD) (FIORETTI; SITA-LUMSDEN; BEVAN; BROOKE, 2014). In the absence of the binding hormone, the receptor is normally in an inactive form, linked to other proteins such as the hsp90 shock protein. Binding of the hormone to the ligand-binding domain triggers the release of hsp90, enabling the DNA-binding domains and receptor to fold into their functionally active conformations so that the activated receptor initiates transcription of target genes (COLE; SHORT; HOOPER, 2019).

The mechanism used by hormones to activate or suppress gene expression has two therapeutically important consequences: first, all hormones produce their effects with a minimum lag period of thirty minutes to several hours, the time necessary for the synthesis of new proteins; second, the effects of these agents may persist for hours or days after their use. As a result, the beneficial or toxic effects of a gene-active hormone generally diminish slowly when administration is stopped (LIGGINS, 1994; AMOUTZAN, 2007).

In addition to the regulation of gene expression through transcription levels, gene expression can be modulated via interactions of nuclear receptors with sequence-specific

transcriptional factors (FALKESNTEIN et al, 2000). This type of action is considered a non-transcriptional effect of classic steroid receptors, already described among glucocorticoids, which affects the levels of a modulator of inflammatory cytokines known as NFkB. Glucocorticoids genomically increase an inhibitor of this modulator, increasing its entrapment in the cytoplasm and raising its levels, in addition to acting in a protein-protein relationship with a subunit of NFkB, known as p65 (RAY; PREFONTAINE, 1994).

In addition to this example, there is a described action of progestin, stimulating a mitogen-activated kinase through the interaction of the estrogen receptor (ER) with c-Src kinase. (MIGLIACCIO et al., 1998). Direct interactions of steroids with nuclear DNA have also been demonstrated (HENDRY, 1988).

NON-GENOMIC EFFECTS OF STEROID HORMONES

The non-genomic effects of steroids are recognized due to the fact that they are insensitive when in the presence of transcription inhibitors and because these actions occur within seconds to minutes, which would not be possible to result from gene transcription. These effects are believed to be mediated by receptors with pharmacological properties distinct from those of intracellular steroid receptors. The 80s and 90s added a lot of information, increasing interest in the field of non-genomic actions of steroids (FALKENSTEIN et al., 2000).

Many of these non-genomic effects appear to be mediated by non-classical steroid receptors, found in cell membranes, with pharmacological properties distinct from those of classical intracellular steroid receptors. Although pharmacological differences alone are not sufficient to prove the existence of receptors other than the classical

ones, some arguments, such as the rapid and non-genomic action of some steroids in cells lacking classical receptors, greatly reinforce the hypothesis (FALKESNTEIN et al., 2000; DENG et al, 2017)

Studies show that classical steroid receptors may be involved not only in the genomic actions of these hormones, but also in their rapid and non-genomic actions (FALKENSTEIN et al., 2000). Histochemical studies found a very similar form of the estrogen receptor in the plasma membrane of pituitary cells in rats; these receptors are involved in rapid and non-genomic actions, such as the rapid release of prolactin when treated with micromolar concentrations of estradiol (PAPPAS et al., 1995). A study carried out by Clarke and collaborators (2000), using cultured hippocampal neurons, revealed the presence of estrogen receptors on the membrane, showing antibodies bound to the receptor on the membrane in non-permeable neurons. When using permeable cells, most of these receptors were found in the perinuclear region.

In neurons isolated from the CA1 region of the hippocampus, estradiol can amplify the action of a protein kinase A (PKA), an effect that is not blocked by the steroid receptor antagonist known as ICI-182,780 (GU et al., 1999). Using a labeled form of estradiol, functional analyzes showed a rapid increase in intracellular calcium concentration, repeated when using an estradiol conjugate known as BSA-17B-estradiol, which is unable to penetrate the cytoplasmic membrane (LUCONI et al., 1999).

Research such as that by Baran and his team (2000) increases the evidence that some non-genomic actions of vitamin D are induced through membrane receptors different from the classical receptor for these hormones. In their experiments, they discovered that an antibody to a membrane protein called annexin II blocks the actions of vitamin

D on the increase in intracellular calcium concentration.

OTHER EFFECTS OF STEROID HORMONES

In recent decades, many studies have focused on metabolism and the actions of steroids on the central nervous system and brain. These studies revealed functions of steroids as agonists and antagonists, very different from the genomic and non-genomic actions previously described. The first steroids to demonstrate effects on modulating the excitability of neurons through interaction with GABA A receptors were synthetic forms of progesterone and corticosterone (MAJEWSKA et al., 1986). The mechanisms by which active neurosteroids alter the excitability of GABAergic neurons depend on the structure of these receptors, mainly with their ligand-responsive ion channel-forming subunits. The synthetic forms of progesterone and corticosterol mentioned above act as potent barbiturates for GABA receptors, which are chlorine ion channels. They also act by increasing chlorine uptake and the inhibitory actions of GABA in cultures of rat hypothalamic neurons (WETZEL et al., 1999).

A different example, where steroids act with the participation of cofactors, was observed by Mehta and Ticku (1999), showing that in the hippocampus, neurosteroids act together with nitric oxide (NO). When in the absence of NO, the action capacity of pregnenolone in the hippocampus of rats is reduced.

In addition to the receptor-mediated functions already described, direct interactions of steroids with membranes occur without the presence of receptors. These actions alter membrane properties such as fluidity and the microenvironment of membrane receptors. Wilson proposed, in 1961, that steroids can adhere to the lipid bilayer, altering its fluidity. Subsequent studies with progesterone indicated that this hormone, in concentrations lower than estradiol and testosterone, has the ability to aggregate vesicles, induce the fusion of these vesicles to the membrane, increasing the permeability of hydrophilic molecules, in artificial membranes and in the sperm membrane (SWAIN et al., 1993).

Recent research such as COLE et al. (2019) highlight the importance of steroid hormones for maintaining body homeostasis, for controlling the female and male reproductive system, the participation of glucocorticoids in controlling blood pressure and also the use of these glucocorticoids by the body of the developing fetus, mainly affecting the maturation of the respiratory and renal systems. Disorders of some steroids such as glucocorticoids are also related to an increase in the amount of blood glucose, generating a state similar to diabetes (LU; CIDLOWSKI, 2006)

REPRODUCTIVE STEROIDS

Sex hormones are produced in the male and female gonads and the placenta. Among them are progesterone, one of the factors that regulates the female monthly reproductive cycle; androgens (such as testosterone); and estrogens (such as estradiol), which influence the development of secondary sexual characteristics in men and women, respectively (OMATE et al., 1994; RUSSEL, 1994; COLE, SHORT; HOOPER, 2019)

The main estrogens produced by women are Estradiol, estrone and estriol. Estradiol is the main secretory product of the ovary. When released into the circulation, estradiol binds strongly to an alpha-globulin, known as sex hormone binding globulin (SHBG), and, with lesser affinity, to albumin. Estrogens dissociate from SHBG to penetrate the cell and bind to its receptor (SIMPSON, 1994; RUSSEL, 1994; COLE, SHORT; HOOPER, 2019).

Estrogen receptors are predominantly

found in the nucleus, linked to shock proteins that stabilize them in the absence of the hormone. The binding of the hormone to its receptor modifies its conformation, allowing the release of stabilizing proteins (FALKENSTEIN et al., 2000). The hormone-receptor complex forms homodimers, which bind to a specific sequence of nucleotides, called estrogen response elements (ERE), in the promoters of several genes, regulating their transcription. The interaction of a receptor dimer with the ERE also involves several nuclear proteins, the coregulators (ROBINSON; ESCRIVA; LAUDET, 2003; AMOUTZAN, 2007).

The genomic effects of estrogens are produced mainly by proteins synthesized through the translation of an RNA transcribed from a responsive gene. They involve known effects such as the synthesis of progesterone receptors, a decrease in the rate of bone absorption by promoting the apoptosis of osteoclasts, and the production of leptin by adipose tissue. Animal behaviors in heat and libido in humans are also among the range of genomic effects of these hormones (COLE; SHORT; HOOPER, 2019).

The rapid effects induced by estrogens, such as calcium uptake by granulosa cells and increased uterine blood flow, do not require gene activation. They appear to be mediated by non-genomic effects of the classical estrogen-receptor complex, influencing several intracellular signaling pathways. These effects may be due to the enzymatic addition of palmitate and increased localization of these receptors in the vicinity of the plasma membrane, as described in glucocorticoids (DENG et al., 2017; IORGA et al., 2017).

Progesterone is the most important progestin in humans. In addition to exerting important hormonal effects, progesterone acts as a precursor of estrogens, androgens and adrenocortical steroids (IORGA et al., 2017).

It is synthesized in the testicles, ovaries and adrenal cortex, from circulating cholesterol. The mechanism of action of progesterone is similar to that of other steroid hormones (DENG et al., 2017).

Progestins penetrate the cell and bind to progesterone receptors (PR) that are distributed between the nucleus and the cytoplasm. The ligand-receptor complex binds to a progesterone response element (PRE), activating gene transcription. The progesterone-receptor complex forms a dimer prior to its binding to DNA. This hormone stimulates the activity of lipoprotein lipase and appears to favor the deposition of fat. It also acts by increasing basal insulin levels and its response to glucose. In the liver, it promotes glycogen storage (DENG et al., 2017).

The testis, like the ovary, performs both gametogenic and endocrine functions. Sertoli cells in the seminiferous tubules may be the source of estradiol produced in the testes through aromatization of locally synthesized testosterone. With the stimulation of Luteinizing Hormone (LH), testosterone is synthesized by the interstitial or Leydig cells that are found in the spaces between the seminiferous tubules. In many target tissues, testosterone is converted to dihydrotestosterone by 5a-reductase, while in others, such as the liver and adipose tissue for example, it is converted to estradiol by aromastase (RUSSEL, 1994).

In men, testosterone is the most important androgen produced in the testicle, 95% of which is produced by Leydig cells and around 5% by the adrenal glands. The testis also secretes small amounts of another potent androgen, dihydrotestosterone, as well as two weak androgens, androstenedione and dehydroepiandrosterone (DHEA). Around 65% of circulating testosterone is bound to sex hormone-binding globulin, with the remaining majority bound to albumin and

around 2% is free, available to penetrate the cell, where it binds to intracellular receptors.

Like other steroids, testosterone has an intracellular action on target cells (LUSSETI, 2015). In the skin, prostate, seminal glands and epididymis, it is converted into dihydrotestosterone, which constitutes the dominant androgen in these tissues. Testosterone and dihydrotestosterone bind to the intracellular androgen receptor, triggering a series of events similar to those described for estradiol and progesterone, leading to the differentiation and synthesis of a variety of enzymes and other functional proteins.

In men, testosterone and dihydrotestosterone are directly related to the development of secondary sexual characteristics, such as those seen at puberty. Thus, through their classic genomic effect, these steroids act on the growth of body tissues, such as the penis and scrotum. Increased hair, growth of the larynx and deepening of the voice, growth of the skeleton and closure of the epiphyses, in addition to sexual maintenance in men.

Anabolic Androgenic Steroids (AAS) are synthetic compounds derived from testosterone, the male hormone, having the same structure of 4 rings with 19 carbon atoms. (CLARK; HENDERSON, 2003). Testosterone and its derivatives bind to androgenic receptors, where they exert their two effects, anabolic (related to increased muscle mass) and androgenic (related to secondary male characteristics) (LUSSETI, 2015). Because they exert their effects through the same receptor, it is practically impossible to dissociate the anabolic effects from the androgenic ones, even in synthetic anabolic steroids, optimized for anabolic effects in relation to testosterone itself, there is still the presence of androgenic effects (LUSSETI, 2015).

Currently, 3 classes of anabolic steroids are produced by pharmaceutical industries: in the first class are esters of the 17-beta-hydroxyl group, which have slow systemic release and prolonged action due to esterification. Its best-known compounds are Testosterone Propionate and Cypionate (Sold commercially in Brazil as Deposteron®). The second class is made up of testosterone derivatives that have undergone the addition of a long carbon chain at carbon 17 (C17) and replacement of a hydrogen by a methyl at carbon 19 (C19), the most famous example of which is Nandrolone Decanoate (sold in Brazil as Deca-Durabolin®). In the third and final class are compounds alkylated at carbon 17 (C17), with the introduction of an ethyl or methyl group, making liver metabolism difficult, which made this class suitable for oral administration. As an example of this third class we can mention Stanozolol, sold in Brazil as Winstrol Depot® (SHAHIDI, 2001; BASARIA, 2001; CLARK, HENDERSON, 2003).

EAAs have the following main characteristics: ability to fix proteins; ability to retain water and nitrogen, increase the number of red blood cells, reduce body fat stores, among some other characteristics. Both essential for the development and increase of muscle tissue (SANTOS, 2007).

EAA were initially produced with the intention of being used in male individuals with androgen deficiency in cases where the testicles were removed, in testicular cancer, delayed puberty, always aiming at the development and maintenance of secondary male characteristics. Today it has consolidated use to treat some diseases and disorders, such as: some types of cancer, osteoporosis, hypogonadism, catabolic states (rickets, HIV and severe burns), deficiencies in testosterone levels, testicular problems, neonatal micro penis, contraception male hormone, anemia due to bone marrow or kidney failure (SILVA; DANIELSKI; CZEPIELEWSKI, 2007; CONWAY et al., 2000; KENNEDY, 2000).

Steroid abuse, so common among

professional and amateur athletes, is characterized by a series of side effects, in the most diverse systems of the body, and all of them are based on and described according to the genomic effects of testosterone, with no description of any side effect. the use of anabolic steroids directly related to the non-genomic effect of these steroid hormones. These effects range from changes in biochemical and hematological profiles to effects on the liver, heart and brain. Steroids are known for their psychoactive and behavioral effects (MHILLAJ et al., 2015) and studies show a possible relationship between steroid abuse and an increase in neuropathologies and oxidative stress (POMARA, 2015). The most observed behavioral effects among EAA users is the increase in aggressiveness among adults and young people. Anxiety disorders are also commonly reported, and the use of AASs is related to the development of these two negative behaviors (anxiety and aggression) simultaneously (PAGONIS, 2006).

CARDIOVASCULAR STEROIDS

The main function of the steroid aldosterone, in vivo, is to regulate the homeostasis of solutes and body fluids, through its actions in the kidneys and colon (ROGERSON; FULLER, 2000).

In the renal collecting ducts, aldosterone acts by increasing the reabsorption of sodium and water, and increasing the excretion of potassium. Together, these changes increase blood volume, raising blood pressure. The synthesis and secretion of aldosterone by the adrenal gland is regulated by the renin-angiotensin system. In short, any decrease in blood volume, sodium concentration or an exacerbated increase in plasma potassium concentration stimulates the production and release of renin by renal juxtaglomerual cells. Renin, as a protease enzyme, cleaves circulating angiotensinogen into angiotensin,

which stimulates the synthesis and secretion of aldosterone by the adrenal glomerular zone (HATTANGADY et al., 2012).

Aldosterone fulfills its function by binding with mineralocorticoid receptors (MR). These receptors are also sensitive to cortisol, however, the aldosterone target tissues are equipped with an enzyme that cleaves cortisol into cortisone, its inactive form for MR receptors. However, syndromes such as Cushing's and severe cases of anxiety disorders greatly increase the amount of circulating cortisol, overcoming the action of enzymes and activating mineralocorticoid receptors more frequently, generating increased blood pressure and cardiovascular problems (FUNDER et al., 1988; ZANNAD et al., 2011). Today, some medications used to treat hypertension are mineralocorticoid receptor antagonists (PIT et al., 1999; ZANNAD et al., 2011).

GLICOCORTICOID STEROIDS

Cortisol is an essential steroid in the response related to fear and stress, in addition to fulfilling several other fundamental physiological roles, both in fetal development and in adult life (SAPOLSKY; ROMERO; MUNCK, 2000).

Cortisol has actions on the immune system and inflammation, and is therefore widely used in severe chronic or acute inflammation and also in autoimmune conditions, with its synthetic versions being most commonly used: Dexamethasone and Prednisilone (BARNES et al., 1998).

Cortisol is released according to our circadian cycle, being considered a hormone related to the waking part of the sleep-wake cycle, since its peak production and secretion occurs in the morning, related to awakening and its lowest levels are found in the circulation. at dusk, where it makes room for melatonin to act during the sleep period.

It participates in the regulation of metabolism as a catabolic hormone, stimulating the breakdown of proteins and the release of amino acids, which will be used by the liver in gluconeogenesis. Furthermore, it has the action of breaking down stored glycogen and releasing fatty acids stored in adipose tissue (LU; CIDLOWSKY, 2006).

In the fetus, cortisol plays an important role in the maturation of organs, mainly in the respiratory system, kidney system, gastrointestinal tract and brain. So much so that synthetic glucocorticoids are used in premature newborns, helping with the development of organs that would occur in the final phase of pregnancy (LIGGIN, 1994; BIRD et al., 2015).

VITAMIN D

Vitamin D, also known as cholecalciferol, is a steroid hormone that enters the blood and extracellular fluid from the diet and through the action of ultraviolet light on 7-dihydrocholesterol in skin cells. The initial form of Vitamin D is converted in the liver to 25-hydroxycholecalciferol and then undergoes hydroxylation to the active form, 1,25-dihydroxycholecalciferol, in the kidneys. Active vitamin D binds to plasma proteins and acts to increase plasma calcium concentration and promote bone mineralization (MULLER; KLEINEWIETFELD; KVAKAN, 2011).

When plasma calcium levels decrease, parathyroid hormone (PTH) cleaves and stimulates 1-a-hydroxylase to increase the formation of active vitamin D. PTH will increase calcium-phosphate reabsorption from bones and increase renal calcium reabsorption. Active vitamin D binds to its intracellular steroid receptor to exert its genomic effects, a receptor known as Vitamin D Receptor (VDR), found in the most diverse tissues, ranging from the heart to immune cells (MULLER; KLEINEWIETFELD; KVAKAN, 2011). It acts in the small intestine by increasing calcium absorption, through an increase in calbidins (calcium-binding proteins) and basolateral calcium ATPases. This increases the absorption of calcium and phosphate in the intestine. In bones, it stimulates bone remodeling and mineralization through its effects on both osteoclasts and osteoblasts (BARAN et al., 2000).

The synthesis and actions of vitamin D take time, due to the need for gene transcription and production of new proteins, but they act to increase calcium supplementation from the diet (BARAN et al., 2000). Thus, while the short-term regulation of plasma calcium levels is carried out by PTH, in the long term the activation of vitamin D by PTH is important in calcium homeostasis.

Levels of active vitamin D in the blood are strictly regulated and controlled by feedback. The concentration of 25-hydroxycholecalciferol remains constant even with an increase in dietary vitamin D intake. Furthermore, the liver can store this form for several months and release it when necessary, creating an additional level of regulation for plasma levels of vitamin D. This general control of vitamin D is important, as overproduction of this hormone in the active form can cause bone resorption rather than deposition. (CASHMAN et al., 2016).

Due to its actions, vitamin D is essential for the absorption and maintenance of normal calcium concentrations, with its deficiency being the cause of rickets in developing children and osteomalacia in adults (MISRA et al., 2008). With studies in recent decades, vitamin D deficiency has been recognized as a public health problem, being considered a pandemic in the United States (HOLICK, 2005) while in Europe, the term that has been discussed for the situation of vitamin D deficiency Vitamin D is a pandemic (CASHMAN et al., 2016).

TWO-STEP MODEL OF STEROID ACTIONS

Advances in research generating an evident growth in non-genomic actions of steroids in *in vitro* and *in vivo* models have rendered the classical model of genomic action of steroids insufficient to explain the range of actions recently discovered. (PIETRAS; SZEGO, 1999; FALKENSTEIN et al., 2000). Steroids rapidly increase intracellular levels of cyclic AMP (cAMP), and these have been shown to be able to influence the genomic effects of the steroids themselves on transcription (LIM-TIO et al., 1997).

This interaction brought to light a new model of steroid action, better known as the Two-Step Model, which encompasses the slow and genomic actions and also the fast and non-genomic actions of aldosterone, proposing that the action on transcription and protein synthesis of this hormone would occur in response to intracellular changes, such as signaling cascades and active ion transport, caused by the non-genomic actions of steroids (CHRIST; WEHLING, 1998). Although developed for aldosterone, the two-step model can be extended to other steroids, such as estrogen and vitamin D (FALKENSTEIN et al., 2000).

The rapid nongenomic actions of steroids precede the traditional genomic mechanism of these hormones. Increased second messengers, such as cAMP or changes in pH (NORDEEN et al., 1994; FALKENSTEIN et al., 2000) or through steroidal actions that lead to an increase in the activity of kinases, such as MAP kinase (ENDOH et al., 1997) exert influence on the genomic effect of steroids (BUNONE et al., 1996). Evidence such as that observed by Moyer and his team (1993) reinforces this two-step model of steroid actions, as they observed a modulating effect of a second messenger on transcription exerted by glucocorticoids.

CONCLUSIONS

The study of the genomic and non-genomic functions of steroid hormones reinforces the importance of these hormones in human development, in the maintenance of female and male reproductive characteristics and in body homeostasis. Knowledge of the diverse physiological functions of this class of hormones allows us to understand and seek new and better treatments for common disorders today, such as high blood pressure and chronic inflammation.

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