Dehydroepiandrosterone: Biomarker of Senescence. Biosynthesis and Regulating Mechanisms

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Abstract

This review presents and summarizes the results of recent studies on dehydroepiandrosterone (DHEA) which plays an important role in longevity regulation. During ontogenesis DHEA and DHEA-sulfate content steadily declines. At the same time, the mechanisms regulating secretion of these hormones and factors determining their age dynamics remain largely unsolved. The paper presents different mechanisms of regulation of adrenal secretion of DHEA and DHEA-sulfate involving adrenocorticotropic hormone (ACTH), prolactin, luteinizing hormone and insulin.

Keywords: androgens, DHEA, ACTH, senescence, hormonal regulation.

Interest to DHEA sharply increased in recent years, more than 30,000 works were published. This is due to a broad scope of collected information on DHEA ability to reduce the risk of several pathologies related to senescence. It was found that there is a negative feedback between the level of DHEA and obesity, cholesterol level in the blood lipoproteins, risk of cardiovascular pathology, breast cancer and osteoporosis.

Free dehydroepiandrosterone form (DHEA) and DHEA-sulfate form (DHEA-S) are synthesized and secreted by the reticular zone of adrenal cortex. The biological riddle is that DHEA is synthesized only by adrenals of primates, humans and all species of monkeys. Release of DHEA during the day repeats cortisol and ACTH dynamics. With age, the amplitude of DHEA releases decreases from 74% at a young age to 45% at the elderly age [36].

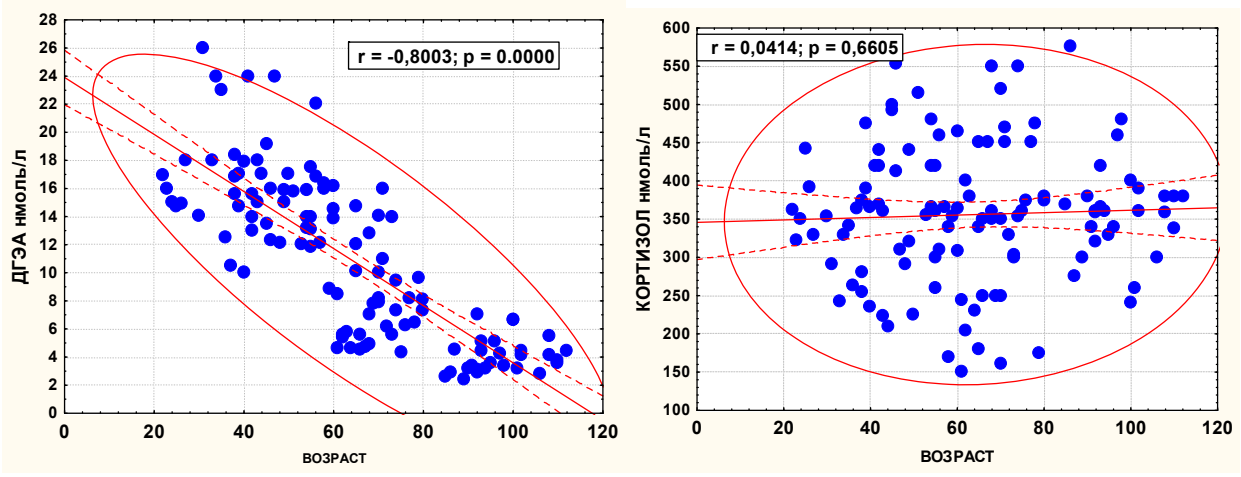
DHEA-sulfate presents the highest concentration in peripheral blood among the whole spectrum of steroids, including cortisol. DHEA-S concentration is 200-1000 times higher than testosterone content in the blood of healthy males, and 5000-25000 times greater than 17β-estradiol in women. DHEA-S level in the blood of men aged 25 - 30 years reaches 6 - 8 mmol/l, later steroids production decreases and by age 80 plasma DHEA-S content does not exceed 1.0-1.5 mmol/l [35,11,34,31]. The highest DHEA and DHEA-S concentration fall rate is presented between the ages from 50 to 60. Metabolic clearance of sulfate steroid is up to 15 l/day. While daily production in reproductive age is 25-30 mg. The half-life of the hormone is 8-10 hours, and of a free form is not more than 30 minutes. DHEA-S content during the day does not significantly change remaining stable throughout the day and night period. This can be explained by delayed metabolic clearance. At the same time its free form has distinct diurnal variations decreasing to 16-17 hours at a young age. Diurnal variations of DHEA considerably repeat cortisol diurnal rhythm [1]. DHEA-S is characterized by gender differences, in women its concentration is 15-20% lower than in men of the same age. However, the age-related decrease of DHEA-S production in women has the same pattern as that of men. According to some reports [32] DHEA levels in young women are higher than in men of similar age. After the age of 50 gender differences in plasma concentrations disappear. At the same time, DHEA-sulfate has no gender differences at a young age, but its level is significantly lower in women than in men after the age of 50. DHEA-S is characterized by pronounced individual variations regardless of gender. Some authors attribute this to genetic factors [6]. We suppose that this may also be due

to the stress situations caused by acute and chronic diseases, which can activate and inhibit production of steroid. Unlike a free form, DHEA-S has a high affinity to albumin, and this connection is strong. In contrast to glucocorticoids, testosterone, and estradiol, DHEA does not have a specific transport protein, and binds to albumin in 90% and only a small part of circulating DHEA binds to globulin.

Unlike the sulfate form, concentration of free DHEA in the blood is significantly low - in the range of 14-50 nmol/l. Age dynamics of free DHEA is the same as that of steroid sulfate. By age 80 its level generally does not exceed 5 nmol/l. Metabolic clearance of the free form is 1700 l/day. At the young age its production ranges from 2 to 7 mg/day (5,25,26), and its half-life is not longer than 8-30 minutes.

We carried out a research on the dynamics of the content of adrenal androgens of androstenedione and dehydroepiandrosterone in men of different age groups living in the Caucasus, including a group of centenarians (WHO classification) of 90-112 years old [18]. The study included only apparently healthy men.

Significant androstenedione level reduction (an average by 55%) is observed at the age of 20 - 75. Later the hormone content stabilizes at the level of 8-10 nmol/l and 10.6 nmol/l in centenarians in comparison with 19 nmol/l in young men. Along with androgens reduction the level of precursors also decreases with age: pregnenolone (beta coefficient = -0.58 P = 0.000), progesterone (beta coefficient = -0.27 P = 0.003), 17α-hydroxypregnenolone (beta coefficient = -0.78 P = 0.000), 17α-hydroxypregnenolone (beta coefficient. = -0.74, P = 0.000). Median content of DHEA progressively decreased from 17 nmol/l in men of 20-35 years old to 4 nmol/l in centenarians. According to our results, DHEA quantitative dependence on the age of apparently healthy men (beta coefficient = -0.80, P = 0.000) obeys the equation of linear regression of DHEA = 23.23 - 0.1947 x age. However, the content of the vital adaptive hormone cortisol keeps at a constant level in all age groups, including centenarians. DHEA and cortisol dynamics is presented in the figure. Age-related decrease of androgen and precursors levels reflects the tendency for the total extinction of adrenal glands capacity.



DHEA nmol /l Cortisol nmol /l

Fig. Comparative dynamics of DHEA and cortisol content in the blood of men of different age groups, including centenarians.

Nowadays it is assumed that ACTH controls the biosynthesis of adrenal androgens DHEA, DHEA-S and androstenedione. The results of experimental studies with hypophysectomy prove it. In this case, we observe reticular zone atrophy along with atrophy of a zona fasciculata and adrenal weight decreased by 50% [5]. At the same time, exogenous ACTH administered in hypophysectomized chimpanzees is accompanied by cortisol production only, while secretion of DHEA and DHEA-S does not change [13]. However, ACTH exposure to the regulation of secretion of DHEA is confirmed by experiments on the other primate species which

is a male hamadryads baboons with DHEA content comparable to adult men hormone levels (20-40 nmol/l). Acute exposure of ACTH intravenous administration along with stimulation of cortisol and precursors of adrenal hormones causes increase of the blood DHEA level, although increase of its concentration is less apparent. Under repeated exposure of a prolonged-release drug, stimulatory effect of ACTH on the secretion of DHEA increases. While the first injection of ACTH causes DHEA maximum level of 48 nmol/l, the 5th injection resulted in 100 nmol/l. After monkeys were made ACTH injections, the DHEA reaction increase occurs in response to the action of endogenous trophic hormones during immobilization stress. The amplitude of cortisol maximum growth in response to the stress factor before and after ACTH administration did not differ (530 ± 237 and 570 ± 124 nmol/l), while DHEA increased twofold (24 ± 7 and 67 ± 14 nmol/l) [3].

However, there are significant quantitative differences in reaction of some adrenal cortex zones to ACTH administration. Release of cortisol increases tenfold, while secretion of adrenal androgens increases a few times only, with more apparent increase of DHEA secretion but not androstenedione and his precursor 17α-hydroxyprogesterone, i.e. activation of steroidogenesis occurs by the route pregnenolone - 17 α-hydroxypregnenolone - DHEA.

Intensity of steroidogenesis activation in the reticular zone upon ACTH administration is determined by age. It is minimal before the puberty, it grows in the initial period of puberty, and upon the end of the puberty activation of adrenal androgens synthesis is comparable to the age group of 25-30 years old, when their basal production reaches its maximum. With age, intensity of the reticular zone reaction somewhat reduces. There are differences in adrenals reaction to single and lasting (during several days) administration of ACTH. The later is accompanied by an increased secretion of DHEA along with its sulfate form [26].

A number of clinical settings illustrate the important role of ACTH in DHEA synthesis control. For example, a long-term therapy of a number of somatic diseases with glucocorticoids is known to be accompanied by inhibition of ACTH and cortisol secretion, and causes DHEA secretion inhibition as well [14].

In case of congenital adrenal hyperplasia genetic disorders lead to a decrease of activity of the various enzyme systems of steroidogenesis, resulting in reduction of cortisol secretion and increase of ACTH secretion. The latter, in its turn, activates formation and secretion of DHEA and such steroidogenesis precursors as 17α-hydroxyprogesterone, 17α-gidrooksipregnenenolon etc. Such pattern is typical for a partial defect of 3β-hydroxysteroid dehydrogenases, 21-hydroxylase but not for 11β-hydroxylase. In the latter case DHEA synthesis even reduces. Therapy of such patients with cortisol derivatives inhibits increased production of ACTH, wherein adrenal androgens synthesis, DHEA in particular, also decreases. Dynamics of corticosteroids suppression, including DHEA and DHEA-S upon e.g., dexamethasone administration, and their restoration after cancellation occurs at different rates. Cortisol returns to the initial level faster than DHEA and DHEA-S, indicating that there is the additional factor regulating steroidogenesis in the reticular zone of adrenal glands along with ACTH.

Another sample illustrating contribution of the alternative system to regulation of adrenal androgens synthesis is Cushing's disease when the level of circulating cortisol is high, DHEA-S content may increase, while the free form may decrease [1]. In this case, we observe dissociation in the activity of steroids biosynthesis in the reticular zone and zona fasciculata. Perhaps this is due to inhibitory effect of excess amount of cortisol on enzyme systems activity in the way sequence: pregnenolone - 17-hydroxypregnenolone - DHEA. Its activating effect on sulfo-transferase, i.e. at the metabolic level is also possible.

Cushing's syndrome is characterized by a high level of cortisol production and reduction of DHEA and its sulfate form concentration in peripheral blood compared with healthy people. These patients have a low ACTH blood level, i.e. its dynamics and dynamics of adrenal androgens are unidirectional which shows dependence of androgens production on ACTH. It is

interesting that upon damage of zona glomerulosa (aldosteronoma) large amounts of aldosterone are released while DHEA and DHEA-S production level does not change.

ERC RAMS (Endocrinology Research Center of Russian Academy of Medical Sciences) Laboratory of Biochemical Endocrinology and Hormonal Analysis along with WMA abdominal surgery clinic (St. Petersburg), carried a research on amount corticosteroids in blood of patients with Cushing's disease at different periods after bilateral adrenalectomy. It was found that cortisol level, as expected, had sharply reduced and did not exceed 60 nmol/l, which is several times less than the lower limit of normal and that circadian rhythm was absent. Corticosterone and aldosterone had a similar quantitative pattern. However, DHEA-S plasma concentration was reduced, but in a less degree. Notably DHEA-S level remained high, primarily in young patients with a 3-year period after adrenalectomy. They had DHEA-S of 1162 ± 882 nmol/l in the morning (2800 ± 400 nmol/l in control), and 1607 ± 958 nmol/l in the evening (2300 ± 301 nmol/l in control). In the period of 10 years after adrenalectomy DHEA-S level did not exceed 440 ± 200 nmol/l in the morning. All cases are characterized by wide individual variations. It can be assumed that there are two possible sources for DHEA formation in adrenalectomized patients: increase of their synthesis in the gonads or their production stimulation in additional adrenal cortex tissue by excessive production of ACTH. There is also the third source - residual tissue of a removed adrenal. In this case we also observe dissociation in amounts of cortisol and aldosterone on the one hand and DHEA on the other hand [4].

Defining the role of ACTH in regulation of DHEA production is complicated by the fact that, unlike the system ACTH - cortisol with feedback mechanism, such a mechanism does not exist in ACTH - adrenal androgens system. Exogenous administration of large doses of DHEA is not accompanied by suppression of ACTH production by adenohypophysis. So far there is no explanation for this phenomenon.

In 1983 Parker, a well-known researcher in the field of Biochemical Endocrinology announced the excretion of glycoprotein with a molecular weight of 66 kD from human pituitary, which selectively activates secretion of adrenal androgens [28]. All attempts to repeat these data have not been successful, so now this opinion is rejected. The second candidate for the role of adrenal androgen production controller is prolactin. In this direction a large number of clinical and experimental studies were conducted. Their results are contradictory. Prolactin receptors were detected in the reticular zone [33]. Some authors established DHEA-S increase upon hyperprolactinemia caused by adenohypophysis micro adenoma [29]. However, this clinical setting when prolactin inhibits production of gonadotropins and biosynthesis of steroids in the gonads, the influence of prolactin is presumably mediated.

During our research a direct, significant correlation of prolactin and DHEA was found in a large cohort of patients with the normal prolactin level [22].

Hitherto prolactin exposure to regulation of adrenal androgens synthesis is not proven. In "in vitro" conditions prolactin stimulates DHEA production, but it is not a specific exposure of the hormone to the reticular zone as both cortisol and aldosterone production greatly increases [17]. Moreover, no regular connection between age dynamics of adrenal androgens and prolactin during adrenarche and senescence was found.

In 1942 F. Albright who was one of the pioneers in the field of biochemistry steroids put forward the hypothesis of a possible role of gonadotropins in regulation of adrenal androgens production [9]. This hypothesis was not confirmed. In children without gonads and with a high level of both gonadotropins, DHEA secretion remains unchanged [23].

Receptors for LH were defined in the reticular zone and zona fasciculata of the adrenal cortex, the expression of which increases with prolonged increase of gonadotropin level. It was discovered that hCG stimulates production of DHEA-S by human fetal adrenals, but specificity of this effect has not been proved. However up to the present imbalance of adrenal steroidogenesis and influence of LH on this process remains a big question. Relatively recently,

it was reported that the tissue of human adrenal glands expresses LH receptor gene, which is found in the reticular zone and adjacent parts of the zona fasciculata [27].

It is known that insulin has a stimulating effect on synthesis and secretion of androgens by gonads, activating testosterone production by Leydig's cells and ovarian theca - cells.

Infusion of insulin to diabetics maintaining euglycemic condition causes a decrease of insulin-like growth factor I and globulin binding sex hormones (SHBG) and DHEA-S. The content of free and total testosterone does not change [7].

Insulin infusion is followed by a decrease of concentration of DHEA and its sulfate form only in men, apparently due to decrease activity of 17.20 desmolases and 50% increase of metabolic clearance and possibly also due to change of DHEA-S in lipid DHEA-S form [15].

Our research showed that in patients with type 1 diabetes, reducing of adrenal androgens DHEA and DHEA-S outruns the age dynamics of hormones. The average level of DHEA-S in patients with diabetes aged under 30 years is 3604 ± 484 nmol/l, and 5185 ± 350 nmol/l (P = 0.047) in the same age control group. The level of DHEA-S in patients of 30-45 years old is 2477 ± 550 nmol/l and 3588 ± 350 nmol/l in the control group. In men older than 45 years, the differences between patients with IDDM and control group are almost absent: 2713 ± 235 nmol/l and 2535 ± 215 nmol/l, respectively [2]. Uncontrolled hyperglycemia induces decrease production of DHEA and its sulfate form in diabetics [19]. Medicamental reduction of insulin resistance is followed by increase DHEA-S production [16]. And conversely DHEA-S secretion in men decreases upon the age-related increase of insulin resistance.

It turns out the role of immuno-endocrine mechanisms in regulation of adrenal androgen production. They play an important role in maturation and zone differentiation of the adrenal cortex. Direct intercellular contacts between lymphocytes and steroid secreting cells of the reticular zone were discovered. Activated macrophages of the reticular zone secrete IL-1 and IL-6 interleukins and α - tumor necrosis factor (TNF - α). IL-6 is a local factor regulating steroidogenesis in the reticular zone, where a high density of IL-6 receptors was found [30,24,10,20].

Regulation of synthesis and metabolism of DHEA and DHEA-S during pregnancy has its own characteristics [21,37,11,25,8]. This is due to formation of fetoplacental system as a functional complex. Low density lipoprotein cholesterol produces pregnenolone and progesterone in placenta. Pregnenolone entering the fetus is used for the synthesis of DHEA-S, which transforms into 16-hydroxy DHEA-S in liver and adrenals of the fetus. Then it undergoes hydrolysis by steroid sulfatase in the placenta and is disposed along with DHEA for the formation of estrone, estradiol and estriol in the placenta, i.e. estrogens are formed from the fetus C19 steroids as activity of 17α-hydroxylase / C17-20 desmolases is very low in the placenta. Estriol conjugates in the mother's liver and then is excreted in urine. It is the main marker of the fetoplacental system function. It must be noted that there are quantitative differences in DHEA-S production by adrenals of the fetus and an adult: fetal production of DHEA-S (200 mg/day) is much higher than in adults (up to 30 mg/day). This is considerably due to a very low activity of 3 β-hydroxysteroid dehydrogenase in the germinal zone of the fetus adrenal cortex. The germinal zone reduces during 3 months after a childbirth, along with decrease of DHEA blood level which remains low up to 6 years old. Later some unidentified factors "turn on" the production of DHEA, which gradually increases and reaches a maximum up to 30 years old, and then begins to decline steadily at 60 ng/ml/year.

Summarizing the results of various researches mentioned above, it should be admitted that the question of what factors are directly involved in the regulation of adrenal androgens production remains open. Influence of ACTH is very important, but not the only one. Possibly dissociation of ACTH, cortisol and adrenal androgens dynamics during adrenarche and senescence can be explained not so much by additional factors, but primarily by changes in the enzyme systems activity providing synthesis of steroids by Δ 4 - and 5 Δ - route.

Currently DHEA is widely used as an "anti-aging" hormone in the United States and Western Europe. It slows the aging process, promotes metabolism in obesity, stimulates the immune system and has anti-cancer effect. Thereby we observe improving of health-related quality of life of older people, which is particularly important for post-menopausal women, providing them with the missing estradiol, which outside the gonads can in an "intracrine" way transform into estradiol in target tissues.

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