ADRENAL ANDROGENS REGULATION AND ADRENOPAUSE

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Adrenal androgens (AA) are mainly produced by the human adrenal cortex. ACTH is the major regulator of their secretion. However, other factors, such as gonadal sex steroids, insulin, growth hormone, prolactin, hypothalamic peptides and growth factors have been involved in AA regulation. More recently, it has become well accepted that, besides systemic factors, AA secretion is under the control of the "sympathoadrenal system" and "immunoadrenal system". Here we review the extraadrenal and intraadrenal mechanisms of AA regulation and how they may relate to endocrinoimmunosenescence.

Key words : DHEA – Adrenal androgens – Adrenopause – Aging –ACTH– Minireview

Human adrenals produce large amounts of androgens, especially dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), which are the most abundant circulating hormones in the human body (ADAMS 1985). Adrenal androgens (AA) are mainly synthesized in the inner zona reticularis (ZR) of the adrenal cortex from the precursor pregnenolone, derived from side-chain cleavage of cholesterol by cytochrome P450scc enzyme (CYPscc). Cytochrome P450-17α (CYP17), a 17α-hydroxylase with 17,20-lyase activity converts the C-21 steroid pregnenolone to the C-19 steroid DHEA, while a hydroxysteroid sulfotransferase (DHEAST) converts DHEA to DHEAS. Alternatively, the Δ^5 androgen DHEA can be converted to the Δ^4 androgen androstenedione (ADION) by the microsomal non-P450 enzyme 3β-hydroxysteroid dehydrogenase (3βHSD) or to androstenediol (ADIOL) by the 17β-hydroxysteroid oxidoreductase (17βHSOX), which can also convert ADION to testosterone (T) (PARKER 1991).

The exact biological function of AA is still a matter of discussion. However, it is well known that they may have both androgenic and estrogenic effect. ADION and T are responsible for 85-90% of the total androgenic activity of the adrenal gland, while DHEA and ADIOL account for the remaining 10%, being their androgen action mainly dependent on conversion to T and 5α-dihydrotestosterone in peripheral tissues. ADION is the most important precursor of estrone, the major circulating estrogen in postmenopausal women, while ADIOL can act as a classic estrogen both *in vitro* and *in vivo* (ADAMS 1985).

AA production follows a characteristic age-related pattern. The human fetal adrenal gland undergoes extensive growth in utero. At the end of gestation, it weighs approximately the same as the adult adrenal because of the presence of a large fetal zone. A dramatic involution of this zone occurs by unknown mechanism in the first month after birth and continues during the first years of life, being paralleled by a sharp decrease in DHEAS, which was the predominant circulating steroid at birth, while cortisol levels remain relatively constant (DE PERETTI and FOREST 1978). During the peripubertal period, the

Table 1
Physiological and pathological states characterized by a divergence of cortisol and adrenal androgen secretion.

PHYSIOLOGICAL.	PATHOLOGICAL
Fetal stage	Idiopathic hirsutism
	Obesity, fasting and anorexia nervosa
	Acute stress from illness or trauma
Adrenarche	Secondary and Tertiary
	Adrenal insufficiency
	Cushing's disease
	Primary cortisol resistance
Puberty	Congenital adrenal hyperplasia
	Ectopic ACTH Syndrome
	Partial hypopituitarism
Aging	End-stage renal disease

adrenal gland undergoes a process of maturation, with progressive broadening of the inner cortical area and creation of the zona reticularis. This is accompanied by an elevation in AA concentration called "adrenarche" which contributes to the development of pubic and axillary hair in both sexes. Again, despite this increase in AA secretion, concentration, excretion and average production of cortisol remain costant (Parker et al. 1978). Secretion of GnRH at puberty activates the pituitary-gonadal axis causing a large increase in concentrations of testosterone and estradiol in boys and girls respectively. During this time, we also observe an increase in DHEA, DHEAS and ADION, which continues through the third decade of life (Adams 1985; Parker 1991). Aging in healthy people is accompanied by only little changes in serum cortisol or aldosterone. In sharp contrast, a mark decline in both AA secretion and excretion is observed in the elderly and is commonly named "adrenopause".

Extra- and intra-adrenal regulation of adrenal androgens

The mechanisms underlying AA control are still object of animate debate. Without any doubt, adrenocorticotropin (ACTH) plays an important role in stimulating AA production. However, several instances of dissociation between cortisol and AA secretion (Tab 1) suggest that besides ACTH, other factors are involved in AA regulation (Cutler et al. 1979).

Gonadal androgens, for example, have been shown to inhibit 11β and 21α hydroxylases

(Fujieda et al. 1982), while estrogens have been reported to stimulate DHEA and DHEAS *in vitro* (Gell et al. 1998) and *in vivo* (Sobrinho et al. 1971). In addition, DHEAS levels are higher in males *vs* females and sex hormone therapy may reverse this difference (Polderman et al. 1994)

Insulin at physiological concentrations increases mRNA levels of 17α-hydroxylase and type II 3βHSD in the absence of cAMP or ACTH in primary cultures of human adrenocortical cells (Kristiansen et al. 1997), while insulin growth factor I (IGF-I) stimulates androgen biosynthesis through the interaction with IGF-I receptor and IGF-I binding proteins in human adrenal primary cultures (Fottner et al. 1998).

Growth hormone (GH) increases DHEAS levels in human fetal adrenals (Brown et al. 1978), but on the other hand, AA are suppressed in patients with GH deficiency (Cohen et al. 1981).

Prolactin (PRL) stimulates steroidogenesis in guinea-pig (O' Connell et al. 1994) and human (Glasow et al. 1996) adrenals *in vitro*. However, no correlations between PRL and AA levels through different stages of life have been found (Parker et al. 1978; Hammond et al. 1979).

Among the pituitary peptides, β-endorphin, β-lipotropin and other peptides derived from pro-opiomelanocortin (POMC) have been linked to AA regulation. B-endorphin and β-lipotropin levels rise with adrenarche (Genazzani et al. 1983) and are high in polycystic ovary syndrome (Aleem and McIntosh 1984). Another POMC-derived peptide, the so-called "joining peptide" has been shown to stimulate AA secretion *in vitro* (Parker et al. 1989; Clarke et al. 1996; Orso et al. 1996). However, such findings have been contested (Mellon et al. 1991; Penhoat et al. 1991; Robinson et al., 1991).

More recently the corticotropin-releasing hormone (CRH) has been shown to stimulate DHEA secretion from human fetal adrenals (Smith et al. 1998) and in young men (Ibanez et al. 1999). Recent evidence also suggests that the CRH-induced increase of adrenal steroidogenesis can be blocked by CRH type-I receptor antagonists, which may suggest a role for this receptor in AA regulation (Willenberg et al. 2000).

Some growth factors have been related to AA regulation. Epidermal growth factor (EGF) and fibro-

blast growth factor (FGF) stimulate growth of bovine adrenocortical cells *in vitro* (Hornsby 1985), while transforming growth factor β (TGF-β) reduces DHEAS by increasing mRNA accumulation of 3βHSD and decreasing those of CYP17 (Lebrethon et al. 1994; Stankovic et al. 1994).

The existence of a specific "adrenal androgens stimulating hormone" (AASH) has been postulated twenty years ago. However, despite claims for the isolation of such a tropic hormone (Parker et al. 1983), the evidence for this is not so striking and the need for the existence of a separate AASH other than ACTH has been often disputed. Neville and O'Hare (1982), for example, emphasize the lack of relevant pathophysiological syndromes AASH-related, such as AASH-secreting pituitary tumors. Anderson (1980) states that the AASH does not exist and adrenarche is related to morphological and functional change in the ZR. According to this author, the slow flush-out of reticularis blood vessels after each pulse of ACTH would expose the inner-zone cells to the highest cortisol levels (the cortisol they produce themselves plus that secreted from all the cells upstream) for the longest time. Progressively, ZR cells would start responding to these high cortisol levels by undergoing modifications in enzymatic activities, with a decrease in 3βHSD and an increase in 17,20-lyase, which would explain the increased production of AA during adrenarche. (Anderson 1980). Differently, Rich et al. (1981) are opposed to the need for an AASH, but suggest that a pituitary "adrenarche factor" may be required to control the ACTH-response of ZR.

In recent years, it has become well accepted that besides systemic factors, the AA secretion is regulated by a sophisticated intraadrenal neuroimmune network. Contacts between nerve endings and steroid-producing cells of the adrenal cortex have been reported (Parker et al. 1993; Vinson et al. 1994). This could be the anatomical basis of a paracrine "cross-talk" between the "sympathoadrenal system" and the adrenal cortex (Bornstein et al. 1990; Ehrhart-Bornstein et al. 1998). Stimulation of the splanchnic nerves and epinephrine, for instance, may induce release of androstenedione (Ehrhart-Bornstein et al 1994), while VIP, a neuropeptide occurring in nerve fibers and chromaffin cells in rat (Holgert et al. 1998) and human adrenal glands (Heym et al. 1994), stimulates both the release of androstenedione and DHEA (Bornstein et al. 1996; Haidan et al. 1998).

Similarly, direct cellular contacts between lymphocytes and ZR cells through filopodia and gap junctions have been recently described (Wolkersdorfer et al. 1999). Moreover, activated macrophages, producing IL-1, IL-6 and TNF α have been demonstrated in ZR, (Bornstein and Chrousos 1999). This intraadrenal immune-system may play a role in the regulation of AA secretion. IL-6 stimulates the release of DHEA in human adrenal primary cell culture (Paeth et al. 1997) while TNF α has been shown to blunt the effects of ACTH on DHEA sulfotransferase mRNA and, with less extent, on CYP17 mRNA in human fetal adrenal cells (Langlois et al. 1998 ; Parker et al. 1998).

Adrenal androgens and adrenopause: a hypothesis

As mentioned earlier in this paper, AA secretion in humans increases dramatically just before puberty, during the so-called "adrenarche", reaching peak levels in the third decade of life (Adams 1985; Parker 1991). Then, AA levels start falling, with values of 20% (men) to 30% (women) of the peak by the age of 70 to 80 and the greatest decline occurring by the ages of 50-60, the so-called "adrenopause" (Kroboth et al. 1999). This decline is associated with morphological changes within the human adrenal gland, especially in the ZR. For instance, a study conducted by Parker et al. has shown a decrease of the ZR width, with a 2-fold increase in the ratio of the width of zona fasciculata (ZF) + zona glomerulosa (ZG) to that of ZR and irregularity of the border between ZR and ZF becomes (Parker et al. 1997).

This "rearrangement" of the adrenal cortex could explain the modifications in the adrenal steroidogenic pathway observed in the elderly. In fact, since the human ZR other than CYP17 contains low levels of 3βHSD and high levels of DHEAST – which makes it producing high quantities of DHEA/S but only a small amount of cortisol – a reduced size of ZR with no change in ZF may result in reduced DHEA secretion without affecting cortisol secretion (Parker et al., 1997).

The sequence of events which causes these morphological changes in the adrenal cortex is still un-

clear. According to our model (Alesci and Bornstein 2001), local T helper cells could induce apoptosis of the "immunocompetent" androgen-producing cells through an interaction mediated by FAS and MHC class II (Marx et al. 1998). The presence of free radicals from both exogenous sources and metabolites of catecholamines produced by medullary chromaffin cells, together with a decrease in antioxidants, such as ascorbate (vit C) and alpha-tocopherol (vit E), which are normally highly concentrated in the adrenal (Bahr et al. 1996) would be responsible for endothelial cell damage, weakening the ZR cells and promoting their apoptosis. This will cause a decrease in cortical cell number and a parallel decrease in CYP17 activity and DHEA production, creating an imbalance AA and cortisol.

The balance between AA and glucocorticoids regulates the differentiation of T helper cells (Th) into Th1, which promote cellular immunity, and Th2, which initiate humoral immunity and counteracts the Th1 response (Elenkov et al. 1996; Marx et al. 1998).

Therefore, changes in the hormone balance occurring with adrenopause would ultimately cause changes in the immune balance, with a switch of the immune response towards a Th2-type and an increase in Th2 cytokines (IL-3, 4, 5, 10, 13). The cytokine dysregulation may explain the propensity to disease observed in aged people. In fact, high levels of IL-10 have been related with HIV, tuberculosis, melanomas, lymphomas. Interestingly, DHEAS treatment on aged mice, which have increased levels of IL-10, decreases the level of such cytokine (Spencer et al. 1996).

We conclude that a better understanding of AA regulation, adrenopause and age-related changes in adrenal morphology and physiology may help to prevent and eventually treat some of the common disorders associated to endocrinoimmunosenescence.

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