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REVIEW

11-Keto-testosterone and Other Androgens of Adrenal Origin

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Summary

The adrenal glands produce significant amounts of steroid hormones and their metabolites, with various levels of androgenic activities. Until recently, the androgenic potency of these adrenal-derived compounds were not well known, but some recent studies have shown that the production of 11-oxo- and 11β-hydroxy-derived testosterone and dihydrotestosterone evidently have high androgenic activity. This fact has clinical importance, for instance, in various types of congenital adrenal hyperplasia with androgenization or polycystic ovarian syndrome, and laboratory determinations of these substances could help to better evaluate the total androgen pressure in patients with these disorders. Another area of concern is the treatment of prostate cancer with androgen deprivation, which loses effectiveness after a certain time. The concurrent blocking of the secretion of adrenal C_{19}-steroids, whether using corticoids or adrenostatics, could increase the effectiveness of androgen-deprivation therapy.

Key words

11β-hydroxy-testosterone • 11-keto-testosterone • Congenital adrenal hyperplasia • Prostate cancer • Adrenarche

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Introduction

The androgen precursors dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are produced in high amounts by the adrenal cortex, primarily in humans (3-25 mg/d) and in a few other primates. Another direct testosterone precursor, androstenedione (androst-4-ene-3,17-dione), is produced in females in total daily amounts of 1.5-6 mg/d, half of which occurs in the ovaries and half in the adrenals. The androgenic potential of these steroids is low. However, the human adrenal also secretes 11-oxygenated androgens (11-oxy-androgens), including 11β-hydroxy-androstenedione. Plasma levels of 11β-hydroxy-androstenedione (means ± SD) in healthy persons in the morning are 8.69±2.88 (men), 7.72±2.85 (women), 8.73±5.13 (boys) and 7.88±5.23 (girls) nmol/l, respectively. The concentrations of these hormones follow the circadian rhythm pattern of cortisol, increasing markedly after corticotropin stimulation and suppressed by dexamethasone (Putz *et al*. 1987). 11β-hydroxy-androstenedione serves as the precursor of several highly potent androgens, the 11-oxygenated derivatives of testosterone and dihydrotestosterone.

11-keto-testosterone and other androgens of adrenal origin

Recently, the 11-oxygenated C_{19}-steroids 11β-hydroxy-testosterone, 11-keto-testosterone, and 11β-hydroxy-dihydrotestosterone have arisen interest due to their high androgenic activity (Bloem *et al.* 2013, Turcu *et al.* 2018). 11-keto-testosterone has been known for decades to be the chief androgen produced in the male gonads of teleost fishes, identified in salmon plasma as early as 1960 (Idler *et al.* 1960). It is essential not only for fish spermatogenesis, but also for fish migration. Its occurrence in mammals was first described by Bun Ichi Tamaoki at the end of 60´s.

In contrast to fish, serum 11-keto-testosterone concentrations are similar in male and females of particular primate species, despite significantly higher circulating testosterone in males, suggesting that 11-keto-testosterone production in primate species is not gonad-dependent and primarily originates from adrenal-derived

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11-oxy-androgen precursors (Rege *et al.* 2013, Rege *et al.* 2019, Imamichi *et al*. 2016).

The main production of 11β-hydroxy-testosterone is localized in the adrenals, and ACTH stimulates its concentration in the adrenal vein by several-fold (Rege *et al*. 2013). A small proportion of its daily secretion may occur in the ovaries, and an even smaller amount in the testes (Imamichi *et al*. 2016). The content of relative RNA for CYP11B1 is less than 2 % in the ovaries and less than 1 % in the testes in comparison with the adrenals. 11β-hydroxy-testosterone is formed principally from 11β-hydroxy-andostene-3,17-dione, by 17β-hydroxysteroid dehydrogenase. It can be converted to 11-keto-testosterone, which can be reduced extra-adrenally by 5α-steroid-reductase to the even more active 11-keto-dihydrotestosterone (Fig. 1). The relative androgenic activities of these bioactive androgens are listed in Table 1, where the values refer to the induction of the activation of androgen receptors relative to dihydrotestosterone (Storbeck *et al*. 2013). In addition, other measurements of the androgenic potency or efficacy (Rege *et al.* 2013, Pretorius *et al.* 2016) have confirmed the high androgenic potency of 11-keto-testosterone and 11-keto-dihydrotestosterone.

As far as we know, no study has yet assessed the relationships between 11-oxygenated C_{19}-steroids and sex hormone-binding globulin (SHBG), and therefore to what extent the active free form contributes to its total activity.

The biosynthesis of 11-keto-testosterone and 11β-hydroxy-testosterone occurs as shown in Figure 1. 5α-steroid reductases then produce 11-keto-dihydrotestosterone and 11β-hydroxy-dihydrotestosterone. The adrenal has low concentrations of the necessary 5α-steroid reductases, and therefore the production of dihydrotestosterone derivatives takes place external to the adrenals. There may also be a back-door pathway in which 11β-hydroxy-androstenedione is converted through 11β-hydroxy-5α-androstanedione to 11β-hydroxy-dihydrotestosterone (du Toit and Swart 2019). An analysis of the inactivation and reactivation of the metabolites also showed that dihydrotestosterone is more readily inactivated than 11-keto-dihydrotestosterone (du Toit and Swart 2020).

The high androgenic activity of the various metabolites (Table 1) as well as their relatively high concentrations in circulation was the reason why they have been the subject of much interest along with the classic androgens, especially testosterone. It has been observed that in control groups of healthy individuals the

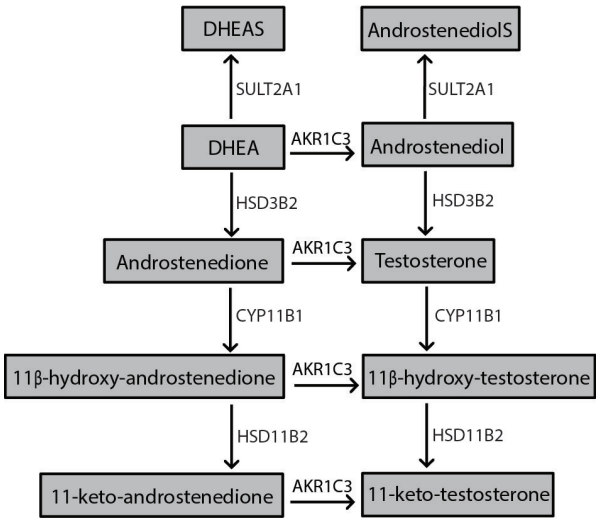

Fig. 1. Scheme of adrenal androgen formation. SULT2A1 – sulfotransferase 2A1, AKR1C3 – 17β-hydroxysteroid dehydrogenase type 5, HSD3B2 – 3β-hydroxysteroid dehydrogenase type 2, CYP11B1 – 11β-hydroxylase, HSD11B2 – 11β-hydroxysteroid dehydrogenase type 2.

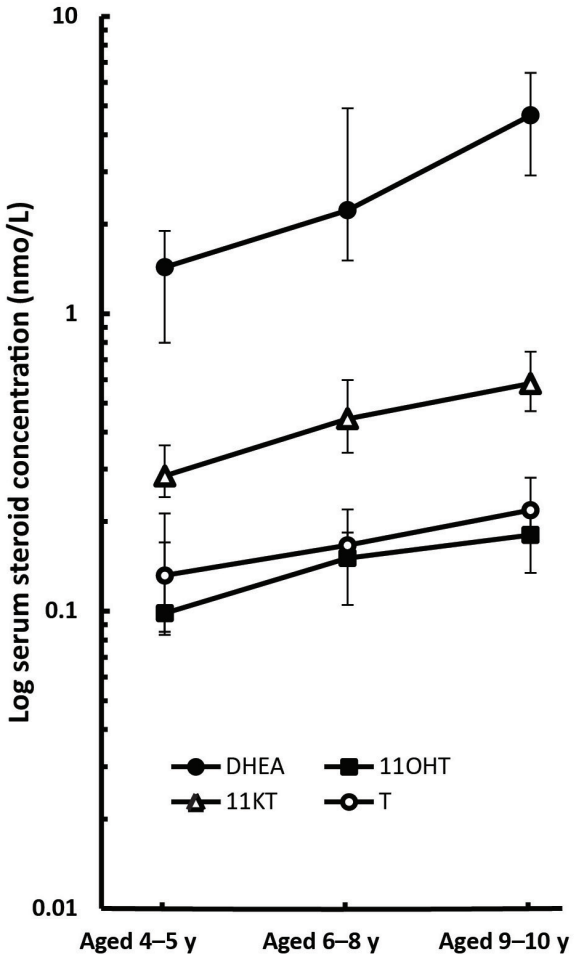

Fig. 2. Levels of C_{19}-steroids in the course of adrenarche of girls aged 4-10 years (Rege *et al.* 2018). Data are expressed as median with corresponding interquartile range. DHEA – dehydroepiandrosterone, 11KT – 11-keto-testosterone, 11OHT – 11β-hydroxy-testosterone, T – testosterone.

Table 1. Relative androgen potency of C_{19}-steroids measured by androgen receptor activation (Storbeck *et al.* 2013).

Steroid	% (dihydrotestosterone = 100)
Androstenedione (androst-4-ene-3,17-dione)	NM (0.6; 2.0)
Testosterone	60.9
Dihydrotestosterone	100
11β-hydroxy-androstenedione	2.3
11-keto-androstenedione	3.4
11β-hydroxy-testosterone	30.0
11-keto-testosterone	62.1
11β-hydroxy-dihydrotestosterone	47
11-keto-dihydrotestosterone	96.2

% – per cent induction of AR activation at 1 nmol concentration. NM – not measured in original study.

Table 2. Serum steroid concentrations (nmol/l) in patients with congenital adrenal hyperplasia due to the block of 21-hydroxylase (21OHD) and controls (Turcu *et al.* 2016).

Steroid	21OHD (n=38)	Controls (n=38)	Fold	*p-value*
11KAD	3.20 [1.93-4.76]	1.03 [0.67-1.40]	3.1	< 0.0001
11OHT	1.94 [0.69-3.41]	0.49 [0.30-0.67]	4.0	< 0.0001
11KT	5.66 [3.48-12.12]	1.66 [0.96-2.58]	3.4	< 0.0001
DHEA	1.01 [0.56-2.95]	6.07 [4.09-11.04]	0.2	< 0.0001
DHEAS	507.96 [212.65-1742.75]	3788.15 [1582.88-5059.49]	0.1	< 0.0001

Data are expressed as median [interquartile range]. Folds represent the 21OHD/controls ratio and were calculated using the medians for each steroid. 11KAD – 11-keto-androstenedione, 11OHT – 11β-hydroxy-testosterone, 11KT – 11-keto-testosterone.

levels of 11-keto-testosterone can be double the levels of testosterone. Concentrations of almost all 11-oxygenated C_{19}-steroids have been found to be up to three times higher in patients with adrenal hyperplasia due to 21-hydroxylase deficiency compared to controls (Table 2) (Turcu *et al.* 2016, Storbeck *et al*. 2019). In addition, girls were shown to have more than doubled levels of 11-keto-testosterone compared to testosterone throughout the period of adrenarche (Fig. 2).

Clinical importance

When testosterone levels are followed for diagnostic or monitoring reasons, it seems reasonable to also measure levels of androgens of adrenal origin, especially 11-keto-testosterone and 11-keto-dihydrotestosterone (Dušková *et al*. 2018). This is particularly true in cases of enzyme disorders with androgenization (Turcu *et al*. 2016, Turcu *et al*. 2017, Storbeck *et al*. 2019). In congenital adrenal hyperplasia due to 21-hydroxylase deficiency, levels of 11-keto-testosterone are on average three-times higher than in controls, while in contrast low levels are expected in 11β-hydroxylase deficiencies, i.e. in CAH with hypertension. Following 11-keto-testosterone level can be useful in interpretation the significant androgenization of the skin and normal or only non-significantly increased testosterone level that occurs oft in the most common female endocrine disorder – polycystic ovarian syndrome (PCOS) (O'Reily *et al*. 2017, Yoshida *et al*. 2018). No evidence of the 11β-hydroxylation of androstenedione has been found in granulosa cells from the ovaries of women with PCOS (Owen *et al.* 1982), though another study indicated that 11-keto-testosterone is produced in the gonads (Imamichi *et al*. 2016). Higher adrenal activity in women with PCOS has been repeatedly observed (Turcu and Auchus 2017), but the concentrations of 11-oxygenated C_{19}-steroids cannot be regarded as a marker for this syndrome. In some milder cases of female androgenization, for instance idiopathic

hirsutism, the determination of 11-keto-testosterone and 11-keto-dihydrotestosterone could also help explain the conflict between the intensity of clinical features and the levels of testosterone or dihydrotestosterone.

In the recent publication (Skiba *et al.* 2019) has been demonstrated that 11-ketoandrostenedione and 11-ketotestosterone are stable across the menstrual cycle and make major quantitative contributions to the circulating androgen pool. All C_{19} androgens declined with age before menopause; hence, age-specific reference ranges are required for the interpretation of androgen levels in premenopausal women.

From a therapeutic standpoint, the adrenals are an important source of androgens that can fundamentally influence the current outlook regarding androgen-deprivation therapies for prostate cancer (Storbeck *et al*. 2013, Swart *et al.* 2013, Pretorius *et al*. 2016, Barnard *et al.* 2018). Benign prostatic hyperplasia (BPH) tissue analysis has identified high levels of 11β-hydroxyandrosterone (4-14 ng/g) and 11keto-androsterone (9-160 ng/g), together with androstenedione (7.5 ng/g) (du Toit and Swart 2020). The high activity of 5α-steroid reductases in lymph node metastasis of prostate carcinoma (LNCaP) allows the production of the potent adrenal androgen 11-keto-dihydrotestosterone in the cells of prostate tumors (Barnard *et al*. 2018). Androgen deprivation therapy for prostate cancer relies on the principle of blocking the activity of gonadal androgens, either at the androgen receptor level or their production at the level of the hypothalamic-pituitary-testicular axis. After a certain time, usually around two years, initially successful therapies begin to become ineffective. It is likely that active adrenal androgens play a biologically-important active role during blockage of the biosynthesis of gonadal androgens. It is possible that together with blocking the gonadal production of androgens, a concurrent blocking of adrenal function, either through corticoids, adrenostatics, or even adrenalectomy, could allow androgen deprivation therapy to continue to be effective.

Conclusions

The finding that some 11-oxygenated C_{19}-steroids have androgenic activity as high as the classical androgens testosterone and dihydrotestosterone, with levels in circulation similar to these steroids, has led to a change in perspective in current laboratory diagnostics for markers of androgenization. In the future, it would be advantageous to measure not just testosterone, free testosterone and dihydrotestosterone, but also levels of 11-keto-testosterone and 11-keto-dihydrotestosterone in particular. These data should make the hormonal picture of hyperandrogenic disorders such as some types of congenital adrenal hyperplasia or polycystic ovarian syndrome more complete. Blocking the adrenal production of 11-oxygenated C_{19}-steroids together with blocking testicular hormone production could also lead to improvements in therapies for conditions where the presence of androgens are a negative factor, such as prostate cancers.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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