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## Pharmacokinetics of oral dehydroepiandrosterone (DHEA) in the ovariectomised cynomolgus monkey

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### Abstract

Humans and primates are unique in having adrenals that secrete large amounts of DHEA and DHEA-S in the circulation. These steroids act as precursors of active androgens and estrogens in a long series of peripheral target intracrine tissues. The marked decline of serum DHEA and DHEA-S concentrations with age in men and women has been incriminated in the development of various pathologies. This study provides detailed information on the effect of a single 50 mg oral dose of DHEA on circulating estrogen's as well as androgens and their metabolites over 10 h in adult ovariectomised (OVX) Cynomolgus monkeys. Serum DHEA, DHEA-S, testosterone (Testo) and androstenedione (4-dione) concentrations increased rapidly with a maximal value at approximately 1 h after DHEA administration followed by a 60–80% decrease during the next 2–6 h. An important sulfatation of DHEA occurs through first hepatic pass, thus, leading to a marked increase in serum DHEA-S. Serum androst-5-ene-3 $\beta$ ,17 $\beta$ -diol and androsterone glucuronide (ADT-G) levels remained elevated on a plateau for 6 h. Androstan-3 $\alpha$ ,17 $\beta$ -diol-glucuronide, estradiol and estrone levels remained unchanged. The present data indicate the predominant transformation of the adrenal precursor DHEA into active androgens in peripheral tissues and support the importance of measurement of circulating glucuronide derivatives as index of peripheral or intracrine androgen formation and action.

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### 1. Introduction

DHEA and its sulfated derivative DHEA-S are the most abundant steroids in the circulation in the human and other primates. In fact, the serum DHEA-S concentration is 200–25,000 times higher than that of the active sex steroids testosterone (Testo), dihydrotestosterone and 17 $\beta$ -estradiol in adult men and women [1]. The physiological importance and mechanisms of action of these precursor steroids are only partially understood. In fact, DHEA and DHEA-S do not possess intrinsic androgenic or estrogenic activity. Some authors have suggested a receptor mediated pathway for explaining the activity of DHEA in the immune and central nervous systems but a specific DHEA receptor has not yet been described [2].

In 1988, Labrie et al. [3] proposed a new field of endocrinology called intracrinology to describe the synthesis of active steroids from inactive adrenal precursors in

peripheral target tissues. The action of these locally made active steroids is exerted in the same cells where synthesis takes place without release in the extra-cellular space or the general circulation. The involvement of DHEA and DHEA-S as precursors of the active steroids is supported by the recent isolation and characterization of most of the genes encoding the steroidogenic enzymes responsible for the transformation of DHEA into androgens and estrogens in peripheral target intracrine tissues [4]. In fact, it is estimated that 30–50% of total androgens in men and 75–100% of estrogens in women before and after menopause, respectively, are synthesized in peripheral intracrine tissues from inactive adrenal C19 steroid precursors [1].

The marked decline of the secretion of DHEA and DHEA-S by the adrenals with age is associated with profound changes in the body's hormonal status and has been incriminated in the development of various pathologies associated with aging [5–8]. A series of studies suggest that supplementation with DHEA in animal models and humans could have beneficial and dose-dependent effects

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on multiple physiologic functions [2]. Thus, DHEA could protect against neoplasia, especially breast cancer by its preferential local transformation into androgens, which are known to inhibit the mammary gland and breast cancer [9–11]. DHEA has also been found to decrease insulin resistance, protect against osteoporosis by stimulating bone formation and increase immune competence [2,12,13]. Furthermore, DHEA exerts beneficial effects on the skin and on vaginal cytology in post-menopausal women without deleterious effects on the endometrium or on the serum lipid profile [12–14]. DHEA-S is also a neurosteroid produced locally in the brain [15,16] while DHEA supplementation has been associated with increased well-being and improved libido in post-menopausal and adrenal-deficient women [12,13,17]. In addition, DHEA could protect against neurodegenerative processes associated with the development of Alzheimer's disease [18,19] and improve depression [20]. Based upon the above-mentioned characteristics, DHEA has been proposed as a possible alternative to the management of menopause in women [1].

A limited number of studies have examined the pharmacokinetics and metabolism of exogenous DHEA. In the present study, we have used ovariectomised (OVX) cynomolgus monkeys as a model to investigate the effect of a single 50 mg oral dose of DHEA on circulating androgens, estrogens and their conjugated metabolites. Since circulating androstenedione and Testo have limited value as indicators of total androgenic and estrogenic activity, androsterone glucuronide (ADT-G) and androstan-3 $\alpha$ ,17 $\beta$ -diol glucuronide (3 $\alpha$ -diol-G) have also been measured as potential markers of the total androgen pool. These metabolites reflect directly the intracrine formation of androgens, which are thus, added to the androgens of gonadal origin [21]. Most studies, however, have neglected these metabolites while investigating DHEA metabolism. Although physiologic doses of DHEA lead to no or small changes of circulating androgens and estrogens levels in post-menopausal women [21], a supraphysiologic dose of DHEA (50 mg) has been used in this study to facilitate assessment of the changes in circulating sex steroid levels.

## 2. Experimental animals

Experiments were performed at the animal facilities of the Centre de Recherche du Centre Hospitalier de l'Université Laval (Québec, Canada). Monkeys were selected from the Laboratory of Molecular Endocrinology and Oncology colony. Animals were housed individually or in pairs in standard stainless steel cages in a room maintained at  $23 \pm 3^\circ\text{C}$  with a 12 (*h*) dark and light cycle (lights on at 07.15 h). Animals were fed four primate cookies twice daily at a 6 h ( $\pm 1$  h) interval. Fruits and/or vegetables were distributed twice weekly. Water was available ad libitum. Throughout this study, animals were maintained and handled in accordance to the written policies of The Canadian

council on animal care (CCAC) and the NIH Guide for the care and use of laboratory animals. This protocol has been approved by the ethical committee for animal protection of the center hospitalier universitaire de québec (CPAC).

## 3. Materials and methods

### 3.1. Study design

Adult OVX female Cynomolgus monkeys (7–11 years old) weighing 5–7 kg were in good health as verified by a complete veterinary examination, serum biochemistry and complete blood count. Ovariectomy was performed at least 3 months prior to the experiment. Eight females were assigned randomly to two groups of four animals. DHEA and placebo were administered at 08.00 h by nasogastric gavage after an overnight fast. Group 1 (placebo) received 12 ml of 0.4% (w/v) methylcellulose solution (vehicle alone) while group two (treated) received a suspension of 50 mg micronized DHEA (Diosynth, Chicago, IL) in 12 ml 0.4% (w/v) methylcellulose. Blood sampling by venipuncture of the femoral vein was performed at 07.55, 09.00, 10.00, 12.00, 14.00 and 18.00 h ( $t = 0$ ).

### 3.2. Serum steroid measurements

Adrenal and sex steroids and their metabolites were analyzed in the Laboratory of Molecular Endocrinology and Oncology. DHEA, 4-dione, androstenediol (5-diol), Testo, estrone ( $E_1$ ) and estradiol ( $E_2$ ) serum concentrations were determined using high performance gas chromatography and negative chemical ionization mass spectrometry. Intra- and inter-assay precision (%CV) did not exceed 5.9% for these assays. DHEA-S, ADT-G and 3 $\alpha$ -diol-G serum concentrations were determined using high performance liquid chromatography and mass spectrometry using a PE Sciex API 300 tandem mass spectrometer equipped with a Turbo ionspray source. Intra- and inter-assay precision (%CV) did not exceed 6.4% for these assays. The lower limit of quantification (LOQ) for DHEA and 5-diol was 0.2 ng/ml. The LOQ for 4-dione, Testo, DHEA-S were 0.04, 0.16 and 2 ng/ml, respectively, while the LOQ for ADT-G and 3 $\alpha$ -diol-G was 50 ng/ml. LOQ for the  $E_2$  and  $E_1$  assays were 2 and 8 pg/ml, respectively.

### 3.3. Statistical analyses

All data are reported as the means  $\pm$  S.E.M. The maximum and minimum serum concentrations measured during the study period for each subject are reported as  $C_{\max}$  and  $C_{\min}$ , respectively. The time at which  $C_{\max}$  occurred is reported as  $T_{\max}$ . calculations of the areas under the time-concentration curves ( $AUC_{0-10h}$ ) for placebo and DHEA-treated animals were performed by the trapezoid method and

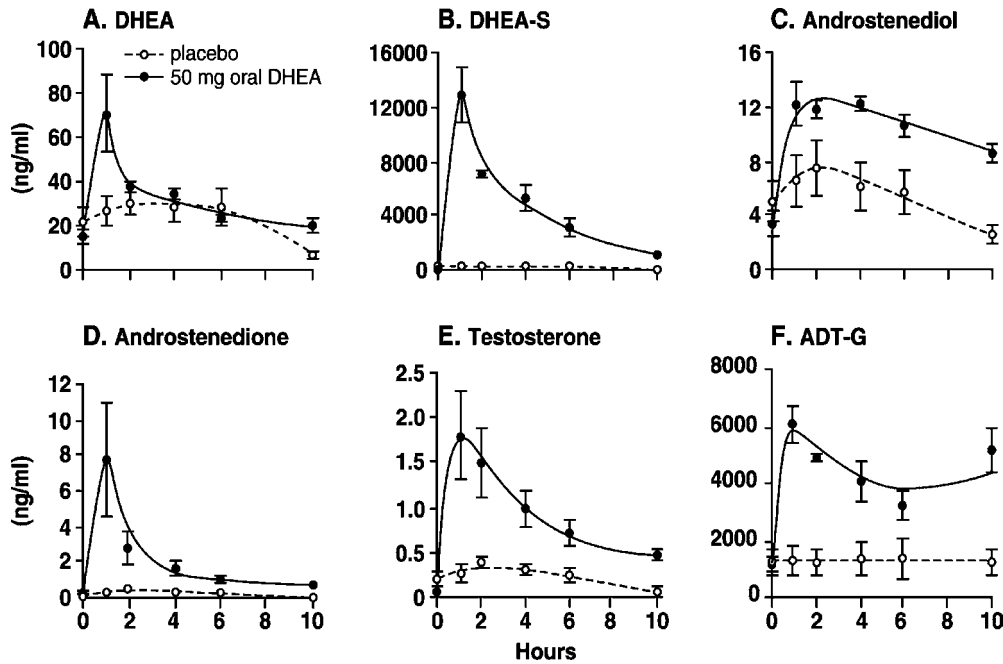


Fig. 1. Time–concentration curves of serum steroids following oral administration of 50 mg DHEA in the ovariectomized cynomolgus monkey.

compared by a Student's *t*-test for unpaired data.  $C_{\text{mean}}$  was calculated as the  $\text{AUC}_{0-10\text{h}}$  (ng/ml h) divided by the time period (*h*) of the study. For all analyses,  $P < 0.05$  was considered significant.

#### 4. Results

Following oral administration of 50mg of DHEA, maximal serum concentrations ( $C_{\text{max}}$ ) of DHEA, 4-dione and

Table 1  
Pharmacokinetic parameters of DHEA and its metabolites after a single oral dose of 50 mg DHEA in ovariectomized cynomolgus monkeys

Steroid	Group	$C_{\text{max}}$ (ng/ml)	$T_{\text{max}}$ (h)	$C_{\text{mean}}$ (ng/ml)	$\text{AUC}_{0-10\text{h}}$ ng/(ml h)
DHEA	Placebo	32.1 ± 6.4	3.5 ± 1.0	23.6 ± 5.8	236 ± 57
	50 mg DHEA	71.8 ± 16.7	1.8 ± 0.8	31.0 ± 1.5	310 ± 15
DHEA-S	Placebo	239.3 ± 57.4	3.0 ± 1.0	181.2 ± 45.3	1812 ± 453
	50 mg DHEA	12790 ± 2023**	1.0 ± 0.0	4528 ± 351**	45275 ± 43511**
5-Diol	Placebo	7.6 ± 2.0	3.0 ± 1.0	5.5 ± 1.4	55.2 ± 14.4
	50 mg DHEA	13.2 ± 1.0	2.5 ± 0.9	10.5 ± 0.5*	105 ± 5.3*
4-Dione	Placebo	0.6 ± 0.06	3.5 ± 0.9	0.4 ± 0.06	3.7 ± 0.6
	50 mg DHEA	7.8 ± 3.3	1.0 ± 0.0	2.0 ± 0.6*	19.8 ± 5.9*
Testo	Placebo	0.4 ± 0.05	1.5 ± 0.3	0.2 ± 0.07	2.4 ± 0.7
	50 mg DHEA	1.8 ± 0.5*	1.3 ± 0.3	0.9 ± 0.2*	9.1 ± 1.9*
3 $\alpha$ -Diol-G	Placebo	1617 ± 918	2.5 ± 0.5	1531 ± 878	15314 ± 8779
	50 mg DHEA	1915 ± 583	2.5 ± 2.5	1250 ± 329	12495 ± 3290
ADT-G	Placebo	1526 ± 627	5.3 ± 1.9	1277 ± 562	12768 ± 5617
	50 mg DHEA	6607 ± 452*	3.3 ± 2.3	4195 ± 413**	41952 ± 4131**
Estrone	Placebo	BLQ	N/A	N/A	N/A
	50 mg DHEA	BLQ	N/A	N/A	N/A
Estradiol	Placebo	BLQ	N/A	N/A	N/A
	50 mg DHEA	BLQ	N/A	N/A	N/A

Data are presented as mean ± S.E.M., below limit of quantification (BLQ), not applicable (N/A).  $\text{AUC}_{0-10\text{h}}$  = area under the time–concentration curve by trapezoidal method,  $C_{\text{mean}} = \text{AUC}_{0-10\text{h}} / \text{time interval (10h)}$ .

\* Significant statistical difference between placebo and DHEA group ( $P < 0.05$ ).

\*\* Significant statistical difference between placebo and DHEA group ( $P < 0.01$ ).

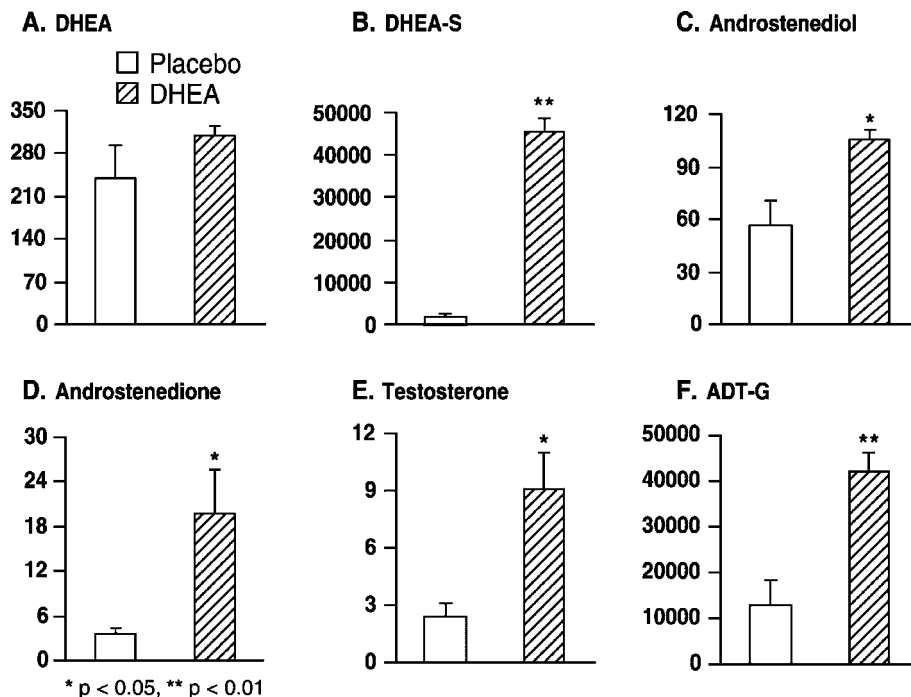


Fig. 2. Effect of 50 mg DHEA administered orally on the areas under the time–concentration curves (AUC<sub>0–10h</sub> in ng/ml h ± S.E.M.) in the ovariectomized cynomolgus monkey.

Testo were 125, 1260 and 360% above placebo levels, respectively, while the  $C_{max}$  value for DHEA-S was 5250% above control at the same time interval (Fig. 1 and Table 1). 5-diol, on the other hand, showed a more moderate (75%) increase over control at its maximal concentration. The serum concentration of all these steroids increased rapidly with a maximal value observed at 1.0–2.5 h in individual animals (Table 1). DHEA and 4-dione concentrations had already decreased by about 75% 2 h after DHEA administration. Serum Testo decreased about 75% at 6 h, in parallel with DHEA-S (Fig. 1). The relatively rapid drop in serum DHEA-S occurred even though the reported metabolic clearance rate of this steroid is about 100 times lower than that of DHEA in women [21]. Serum 5-diol concentration, on the other hand, remained on a plateau until 6 h. Serum  $E_2$  and  $E_1$  levels did not reach the minimal sensitivity of the assay namely 2 and 8 pg/ml, respectively, after DHEA administration (data not shown).

ADT-G and 3 $\alpha$ -diol-G are the two major metabolites of androgens in the circulation in the monkey and human. These glucuronidated steroids reflect the inactivation of locally synthesized androgens in peripheral tissues in addition to the inactivated androgens of gonadal origin. Serum ADT-G already showed a 330% increase as compared to placebo 1 h after DHEA administration with no tendency to decrease up to 10 h of the study (Fig. 1). The 3 $\alpha$ -diol-G serum concentration did not change significantly over the 10 h period (Table 1).

The areas under the curve (AUC) best reflect exposure of the organism to various steroids and their metabolites. The

oral administration of 50 mg of DHEA caused a 31% but not statistically significant increase of the DHEA AUC<sub>0–10h</sub> value as compared to placebo while the DHEA-S AUC<sub>0–10h</sub> value, on the other hand, increased by 2400% ( $P < 0.01$ ) after DHEA administration, thus, suggesting an important sulfatation during first hepatic pass. The Testo and 4-dione AUC<sub>0–10h</sub> values showed 280 and 435% increases over placebo ( $P < 0.05$ ) (Table 1 and Fig. 2). The 5-diol AUC<sub>0–10h</sub> value, a direct product of DHEA possessing weak estrogenic intrinsic activity, increased by 90% above control ( $P < 0.05$ ) (Fig. 2) while the ADT-G AUC<sub>0–10h</sub> value (Fig. 2), on the other hand, showed a 230% increase ( $P < 0.01$ ) after DHEA administration and no significant difference was observed for 3 $\alpha$ -diol-G (Table 1).

## 5. Discussion

The main objective of this study was to determine the amplitude and time course of circulating levels of all active sex steroids and the two principal androgen metabolites, namely ADT-G and 3 $\alpha$ -diol-G after oral administration of DHEA in adult OVX cynomolgus monkeys.

Using a limited number of sampling intervals, previous studies on the pharmacokinetics of DHEA in humans were limited to the time course of serum concentrations of DHEA, DHEA-S and active sex steroids in order to determine the dose required to restore youthful or normal hormone concentrations and avoid potential deleterious exposure to high steroid levels [22–27]. The present study, using a relatively

high 50 mg dose of DHEA, provides clear evidence that serum concentrations of androgenic and estrogenic steroids alone do not reflect adequately the metabolism of DHEA into active androgens and estrogens in peripheral target tissues. In fact, no increase in circulating estrogens could be detected.

Presence of the specific steroidogenic enzymes responsible for DHEA transformation to androgens and estrogens, namely  $3\beta$ -HSD,  $17\beta$ -HSD,  $5\alpha$ -reductase and aromatase, has been demonstrated in a large series of peripheral target tissues [28]. ADT-G and  $3\alpha$ -diol-G are the two major metabolites of androgens in the circulation in the monkey and human. These steroid derivatives reflect the total androgen pool, namely the local androgen synthesis in peripheral tissues in addition to the androgens of gonadal origin which enter the same tissues. DHEA administration at the oral dose of 50 mg led to a comparable relative increase of the  $AUC_{0-10h}$  values for ADT-G and Testo. In absolute values, however, the increase in serum ADT-G following DHEA administration is much larger than for serum testosterone. In fact, at the 1 h maximal value, serum ADT-G increased by 5017 ng/ml while serum testosterone increased by only 1.4 ng/ml. In addition, as compared to Testo, the  $AUC_{0-10h}$  value for ADT-G is most probably greatly underestimated since the serum concentration of this metabolite is still near maximal at 10 h while the testo serum concentration is almost back to basal levels at that time interval. Further studies, including direct sampling from various venous sites, will be required to explain the lack of change in serum  $3\alpha$ -diol-G. An increase in serum  $3\alpha$ -diol-G following the 10 h sampling period is a possibility.

Differences in the metabolism of exogenous DHEA according to sex and age have been described [22,26,29]. DHEA is reported to be preferentially metabolized to androgens in women and estrogens in men [22,23,27,30,31]. The present study shows that DHEA administration to the female OVX cynomolgus monkey leads predominantly to the formation of androgens and not estrogens. Similarly, pharmacologic doses or chronic exposure to DHEA in women caused no significant increase of serum estrogens while androgens were slightly increased. In this context, Labrie et al. [21] administered a 10% DHEA cream at a daily dose of 20 mg for 14 days in post-menopausal women. They found 125 and 140% increases over control of ADT-G and  $3\alpha$ -diol-G, respectively, while Testo and 4-dione showed more moderate 100 and 50% increases, respectively, and DHT showed no significant change. Furthermore, they did not observe any increase of circulating estrogens but rather observed 70 and 30% increases in serum  $E_1$ -S and  $E_2$ -S, respectively.

In women, it has been estimated that the intracrine formation of estrogens in peripheral tissues from the adrenal precursor DHEA is in the order of 75 before and close to 100% after-menopause [1]. It should be mentioned that the absence of change in circulating estrogens after DHEA administration does not necessarily reflect an absence of estrogenic exposure in specific tissues, which contain the

required enzymes. Circulating levels of the sulfated metabolites of estrogens could potentially better reflect the estrogenic metabolism of DHEA in peripheral tissues although a reliable biomarker of the metabolism of estrogens is yet to be determined. Replacement therapies to achieve youthful hormonal levels by DHEA supplementation should take into consideration the fact that steroid concentrations in tissues and not their circulating levels are physiologically meaningful.

The considerable increase of the  $C_{max}$  and  $AUC_{0-10h}$  values of DHEA-S reflect an important sulfatation of DHEA after its oral administration. In fact, sulfotransferase is expressed at high levels in hepatocytes as well as in other tissues in the human and monkey [28]. Sulfatation of orally administered DHEA occurs most probably to a large extent in the liver because sublingual, transdermal and transvaginal administration of DHEA that avoid the first hepatic pass induces a lower DHEA-S to DHEA ratio [21,32,33]. Serum DHEA-S concentrations decrease at a somewhat lower rate than DHEA after the 50 mg dose. This finding can be explained by the fact that the DHEA-S metabolic clearance rate is considerably lower than that of DHEA [34]. DHEA-S is also probably continuously converted back to DHEA by the ubiquitous sulfatase enzyme and, thus, acts as a reservoir for DHEA and the resulting active androgens in peripheral target tissues.

The present study describes for the first time the time course of all the major active and conjugated metabolites of DHEA after a single oral dose of this precursor steroid in the monkey, which is clearly the most appropriate model for studies on DHEA. In addition to the information provided, our results suggest that future studies on the metabolism of DHEA should include tissue concentrations of the active sex steroids to definitively assess DHEA transformation, distribution and, consequently, the hormonal exposure in peripheral target tissues and the potential role of these DHEA metabolites in various pathophysiological processes.

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