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Biotransformation of Oral Dehydroepiandrosterone in Elderly Men: Significant Increase in Circulating Estrogens

WIEBKE ARLT, JOACHIM HAAS, FRANK CALLIES, MARTIN REINCKE, DORIS HÜBLER, MICHAEL OETTEL, MICHAEL ERNST, HEINRICH MARIA SCHULTE, AND BRUNO ALLOLIO

Department of Endocrinology, Medical University Hospital Wuerzburg (W.A., J. H., F.C., M.R., B.A.), 97080 Wuerzburg; Jenapharm GmbH & Co. KG (D.H., M.O., M.E.), Jena; and Institute for Hormone and Fertility Research (H.M.S.), Hamburg, Germany

ABSTRACT

The most abundant human steroids, dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS, may have a multitude of beneficial effects, but decline with age. DHEA possibly prevents immunosenescence, and as a neuroactive steroid it may influence processes of cognition and memory. Epidemiological studies revealed an inverse correlation between DHEAS levels and the incidence of cardiovascular disease in men, but not in women. To define a suitable dose for DHEA substitution in elderly men we studied pharmacokinetics and biotransformation of orally administered DHEA in 14 healthy male volunteers (mean age, 58.8 ± 5.1 yr; mean body mass index, 25.5 ± 1.5 kg/m^2) with serum DHEAS concentrations below 4.1 μmol/L (1500 ng/mL). Diurnal blood sampling was performed on 3 occasions in a single dose, randomized, cross-over design (oral administration of placebo, 50 mg DHEA, or 100 mg DHEA). The intake of 50 mg DHEA led to an increase in serum DHEAS to mean levels of young adult men, whereas 100 mg DHEA induced supraphysiological concentrations [placebo *vs.* 50 mg DHEA *vs.* 100 mg DHEA; area under the curve (AUC) 0–12 h (mean ± SD) for DHEA, 108 ± 22 *vs.* 252 ± 45 *vs.* 349 ± 72 nmol/L·h; AUC 0–12 h for DHEAS, 33 ± 9 *vs.* 114 ±. 19 *vs.* 164 ± 36 μmol/L·h]. Serum testosterone and dihydrotestosterone remained unchanged after DHEA administration. In contrast, 17β-estradiol and estrone significantly increased in a dose-dependent manner to concentrations still within the upper normal range for men [placebo *vs.* 50 mg DHEA *vs.* 100 mg DHEA; AUC 0–12 h for 17β-estradiol, 510 ± 198 *vs.* 635 ± 156 *vs.* 700 ± 209 pmol/L·h ($P < 0.0001$); AUC 0–12 h for estrone, 1443 ± 269 *vs.* 2537 ± 434 *vs.* 3254 ± 671 pmol/L·h ($P < 0.0001$)]. In conclusion, 50 mg DHEA seems to be a suitable substitution dose in elderly men, as it leads to serum DHEAS concentrations usually measured in young healthy adults. The DHEA-induced increase in circulating estrogens may contribute to beneficial effects of DHEA in men. (*J Clin Endocrinol Metab* **84:** 2170–2176, 1999)

DEHYDROEPIANDROSTERONE (DHEA) and its sulfated ester (DHEAS) are the most abundant steroids in the human circulation, but their physiological role remains to be defined precisely. It is still a matter of discussion whether DHEA exerts its effects mainly by direct action or, more probable, by peripheral bioconversion to androgens and estrogens. The amount of circulating DHEAS is highly age dependent, with peak values between the second and the third decades of life followed by a progressive decline to about 10% of maximum levels during advanced age (1–3). Thus, compared to healthy young men, a large proportion of elderly men live in a state of relative DHEA(S) deficiency.

There is circumstantial epidemiological evidence that low DHEAS levels are associated with an increased risk of cardiovascular disease in men, but not in women (4–7). Cross-sectional studies revealed a significant positive correlation between serum DHEAS and functional status in the oldest subjects (8, 9). As a neuroactive steroid, DHEA may influence cognitive processes and sleep architecture (10, 11). Oral administration of DHEA (50 mg/day) to elderly men and women led to an increase in self-reported well-being (12). The administration of 100 mg DHEA has been recently shown to induce an increase in muscle mass and strength in 50- to 65-yr-old men (13). Furthermore, DHEA may have a regulative function in interleukin-6 and interleukin-2 secretion and affect immunosenescence (14–16). Thus, DHEA replacement in elderly men with low endogenous DHEAS levels may be beneficial.

The aim of our study was, therefore, to define a DHEA dose suitable for restoration of low DHEAS levels in elderly men to concentrations usually found in young healthy adult men. To this end, we studied the pharmacokinetics and biotransformation of orally administered DHEA in healthy men between 50–70 yr of age with endogenous serum DHEAS concentrations below 4.1 μmol/L (1500 ng/mL), which is equivalent to the lower limit of the normal range for serum DHEAS in 15- to 39-yr-old men (1).

Subjects and Methods

Subjects

All subjects participating were recruited by advertising the study via local broadcasting asking for elderly men in good health with possibly low serum DHEAS concentrations. Main inclusion criteria for participation in the study were a serum DHEAS concentration below 4.1 μmol/L (<1500 ng/mL), an age between 50–70 yr, a body mass index (BMI) between 20–30 kg/m^2, and a state of general good health. Further

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Address all correspondence and requests for reprints to: Dr. Wiebke Arlt, Department of Endocrinology, Medical University Hospital, Josef Schneider Strasse 2, 97080 Wuerzburg, Germany.

inclusion criteria were normal blood cell counts and normal hepatic and renal function parameters. Exclusion criteria were any chronic diseases (including diabetes mellitus and severe arterial hypertension), any medication known to affect hepatic biotransformation, treatment with steroids within the last 3 months, as well as significant hypogonadism [serum testosterone (T), <8.7 nmol/L (<2.5 ng/mL)].

A total of 106 men (mean age, 59.6 ± 5.8 yr; age range, 49–70 yr) volunteered for measurement of their individual serum DHEAS levels. Serum DHEAS concentrations below 4.1 μmol/L (<1500 ng/mL) were found in 35 of 106 men (mean age of this subgroup, 61.3 ± 5.3 yr; age range, 51–70 yr). Twenty-one of the 35 patients with low DHEAS were excluded because of elevated liver enzymes (n = 7), history of prostate neoplasia (n = 3), serum T level below 2.5 ng/mL (n = 2), BMI above 30 kg/m^2 (n = 5), or probable compliance problems (n = 4).

Fourteen healthy male volunteers, aged 51–66 yr (mean age, 58.8 ± 5.1 yr; 13 nonsmokers and 1 smoker) were included in the study. The mean BMI was 25.5 ± 1.5 kg/m^2 (range, 23.5–29.2 kg/m^2). Before the initiation of the study, the protocol had been approved by the ethics committee of the University of Wuerzburg, and written informed consent was obtained from all volunteers.

Study protocol

The study was performed in a single dose, randomized, cross-over design. All subjects were studied on three occasions. On study days 1–3 either placebo or 50 or 100 mg DHEA were administered orally at 0900 h in a randomized order. The wash-out period between the 3 study days lasted at least 14 days and less than 6 weeks. On all 3 study days, 24-h frequent blood sampling was performed starting after an overnight fast at 0830 h and ending at 0900 h the following day [−30 (0830 h), 0, 30, 60, 90, 120, 150, 180, and 210 min and 4, 5, 6, 7, 8, 10, 12, and 24 h]. Standardized meals were served at 1000, 1300, and 1800 h.

DHEA preparation

The capsules containing 50 mg DHEA as well as the placebo capsules were both provided by Jenapharm (Jena, Germany). As determined by high performance liquid chromatography, the mean DHEA content of the capsules was 49.3 ± 0.20 mg. To assess the liberation rate, DHEA capsules (n = 20) were given in 1000 mL water with 0.4% SDS. DHEA was measured by high performance liquid chromatography at 10, 20, 30, and 45 min, respectively, giving an *in vitro* liberation rate of 82.8% within 45 min.

Hormone assays

All serum hormones were determined by established specific direct RIAs: cortisol, Diagnostic Systems Laboratories (Sinsheim, Germany); DHEA, Diagnostic Systems Laboratories; DHEAS, Diagnostic Products Biermann (Bad Nauheim, Germany); 4-androstene-3,17-dione (A'dione), Diagnostic Systems Laboratories; 5α-androstane-3α,17β-diol-17-glucuronide (ADG), Diagnostic Systems Laboratories; total T, Diagnostic Products Biermann; free T, Diagnostic Products Biermann; 5α-dihydrotestosterone (DHT), Diagnostic Systems Laboratories; 17β-estradiol (E_2), Biochem Immunosystems (Freiburg, Germany); and estrone (E_1), Diagnostic Systems Laboratories. The cross-reactivities provided by the respective manufacturers are given in Table 1. For all assays, the intra- and interassay coefficients of variation were less than 8% and less than 12%, respectively.

Statistics

All data are reported as the mean ± SD. The maximum serum concentration measured during a study period for a subject was reported as c_{max}. The time at which c_{max} occurred was reported as t_{max}. The terminal elimination rate constant (λ) was calculated by means of log-linear regression. The area under the concentration-time curve (AUC) was calculated by means of trapezoidal integration. For data comparison we used AUC 0–12 h instead of AUC 0–24 h, as blood samples at 24 h were not obtained from all volunteers (period 1, 9 of 14; period 2, 6 of 14; period 3, 6 of 14). The mean concentrations of the various hormone concentrations, AUC 0–12 h as well as t_{max} and c_{max} were calculated and compared by ANOVA with repeated measurements, *t* tests, and Wilcoxon signed rank test for paired samples. Nonparametrical analysis (Wilcoxon signed rank test) was performed if parameters were not normally distributed. Significance was defined as $P < 0.05$.

Results

Cortisol

During all 3 study days, serum cortisol concentrations exhibited the typical diurnal variation (Fig. 1A), which was not altered by DHEA administration.

DHEA and DHEAS

After oral administration of DHEA, serum DHEA concentrations significantly increased in a dose-dependent manner, with maximum concentrations (c_{max}) measured between 60–480 min (t_{max}, 2.6 ± 2.0 h and 2.5 ± 1.2 h for 50 and 100 mg DHEA, respectively; Fig. 1B). Also, serum DHEAS increased rapidly, peaking between 120–480 min (t_{max}, 4.2 ± 2.1 and 3.8 ± 1.5 h for 50 and 100 mg DHEA, respectively; Fig. 1C). After reaching c_{max}, both DHEA and DHEAS decreased only slowly to levels still above baseline at 12 h, with serum DHEA more rapidly declining ($t_{1/2}$ of DHEA < $t_{1/2}$ of DHEAS; see Table 3). Comparing the AUC 0–12 h, the administration of 50 mg DHEA led to an increase of 234% of baseline serum DHEA and 343% of baseline serum DHEAS, whereas 100 mg induced increases of 323% and 494%, respectively (Table 2). While 50 mg DHEA induced increases in serum DHEA and DHEAS to levels found in young adult men, 100 mg DHEA clearly induced supraphysiological con-

TABLE 1. Cross-reactivities of RIAs

Hormone	Cortisol	DHEA	DHEAS	A'dione	T	DHT	E_1	E_2	Others[a]
Cortisol	100	0.02	NA	NA	0.14	NA	NA	0.02	
DHEA	ND	100	0.02	0.46	0.03	NA	ND	NA	
DHEAS	0.01	0.08	100	0.12	0.10	0.004	0.01	0.02	E3 0.03
A'dione	0.03	0.04	ND	100	NA	0.05	0.08	0.01	E3 0.03
Total T	0.05	0.002	0.006	NA	100	3.40	0.01	0.02	
Free T	ND	0.003	ND	0.01	100	0.04	ND	ND	
DHT	ND	ND	NA	1.90	0.02	100	NA	1.41	ADG 0.19
ADG	ND	ND	NA	ND	ND	ND	ND	ND	
E_1	ND	ND	ND	ND	ND	NA	100	1.25	E3 0.22
E_2	ND	ND	ND	0.0001	0.0033	0.0002	1.77	100	E3 0.47

For explanation of hormone abbreviations see *Subjects and Methods*.
E3, estriol; NA, not available; ND, nondetectable.
[a] Other steroids not mentioned were not relevant to this study and/or had cross-reactivities below 0.01%.

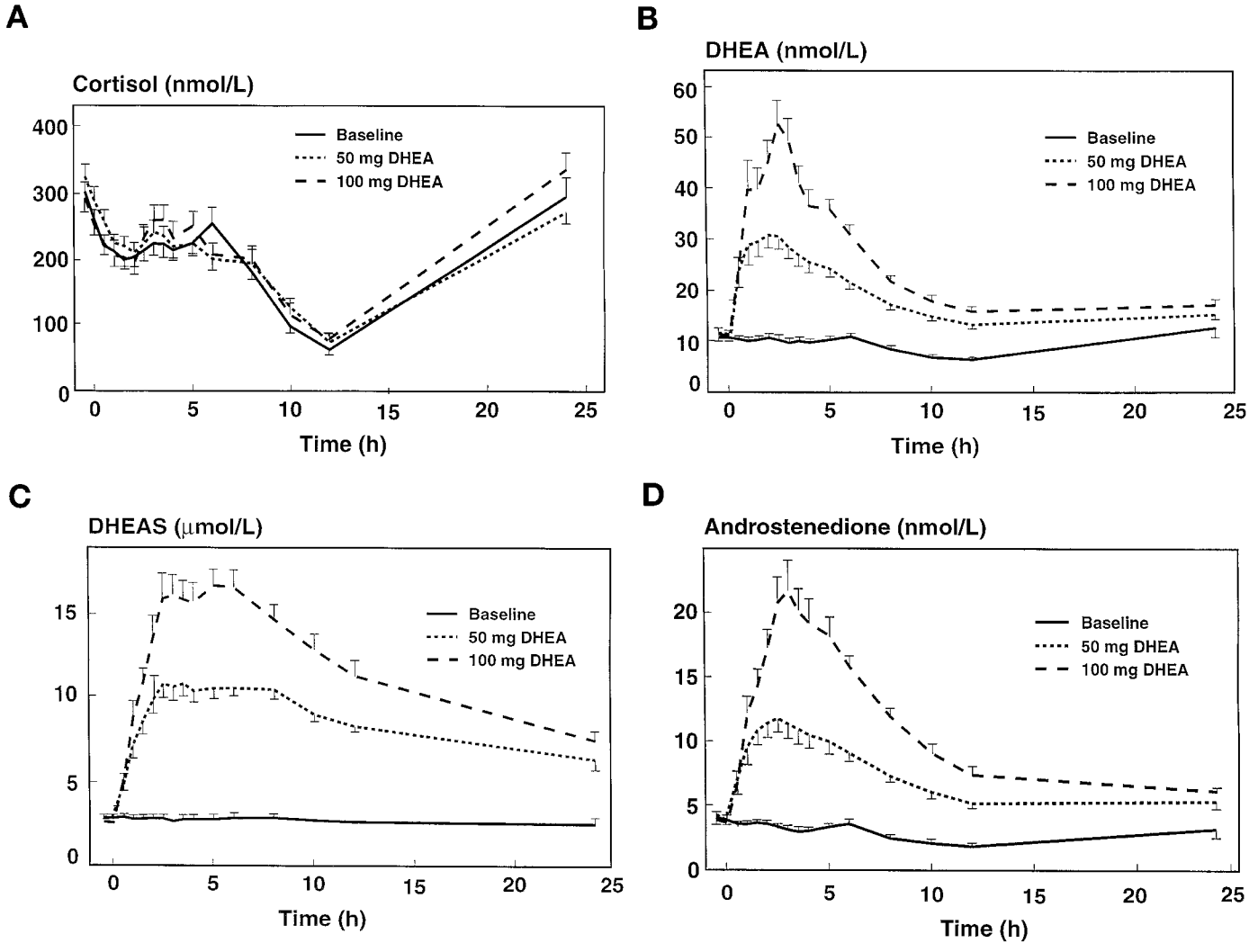

FIG. 1. Serum concentrations of cortisol (A), DHEA (B), DHEAS (C), and androstenedione (D; mean ± SEM) in 14 male volunteers after the ingestion of placebo, 50 mg DHEA, or 100 mg DHEA.

centrations. Detailed data concerning the pharmacokinetics of the two different DHEA doses are given in Table 3.

Androstenedione

The administration of DHEA induced a sharp and dose-dependent increase in serum A'dione concentrations, which peaked after 3 h (t_{max}, 3.0 ± 1.8 and 3.3 ± 1.1 h for 50 and 100 mg DHEA, respectively) followed by a slow decline (Fig. 1D). Compared to placebo, the AUC 0–12 h increased to 263% (50 mg DHEA) and 416% (100 mg DHEA; Table 2). The serum androstenedione concentrations after 50 mg DHEA were equivalent to the upper normal range, while 100 mg DHEA induced supraphysiological concentrations.

Androgens and androgen metabolites

Neither the administration of 50 nor 100 mg DHEA led to an increase in total serum T (Fig. 2A) or DHT concentrations (Fig. 2B), whereas a slight, but significant, increase in free T concentrations to 113% (50 mg DHEA; t_{max}, 1.9 ± 1.4 h) and 115% (100 mg DHEA; t_{max}, 2.9 ± 2.2 h) was observed (Fig. 2C and Table 2).

The administration of DHEA was also followed by a significant increase in serum ADG concentrations (t_{max}, 2.4 ± 1.8 and 3.2 ± 2.5 h for 50 and 100 mg DHEA, respectively; Fig. 2D). The AUC 0–12 h for ADG increased to 168% of baseline after 50 mg DHEA and to 235% after 100 mg DHEA. The serum ADG concentrations after 50 mg DHEA varied within the normal range, whereas 100 mg DHEA led to clearly supraphysiological concentrations.

Estrogens

After DHEA administration, serum E_1 (Fig. 3A) as well as serum E_2 (Fig. 3B) increased significantly in a dose-dependent manner. Peak concentrations for E_1 were measured 30–720 min after DHEA administration (t_{max}, 3.3 ± 2.7 h for 50 mg DHEA and 3.6 ± 2.7 h for 100 mg DHEA). Serum E_2 concentrations also peaked between 60–600 min after DHEA ingestion (t_{max}, 4.4 ± 2.5 h for 50 mg DHEA and 4.7 ± 2.3 h for 100 mg DHEA). The AUC 0–12 h after 50 mg DHEA was

TABLE 2. AUCs of first 12 sampling hours (AUC 0–12) for measured hormones in the healthy male volunteers (n = 14); comparison of AUCs 0–12h by ANOVA after logarithmic transformation of measured values

AUC 0–12	Baseline	50 mg DHEA	100 mg DHEA
Cortisol (nmol/L·h)	2178 ± 291	2260 ± 460 NS ($P = 0.58$)[a]	2270 ± 548 NS ($P = 0.70$)[b] NS ($P = 0.87$)[c]
DHEA (nmol/L·h)	108 ± 22	252 ± 45 $P \leq 0.0001$	349 ± 73 $P \leq 0.0001$ $P \leq 0.0001$
DHEAS (μmol/L·h)	33.2 ± 9.0	113.6 ± 19.3 $P \leq 0.0001$	163.8 ± 36.4 $P \leq 0.0001$ $P \leq 0.0001$
Androstenedione (nmol/L·h)	38.9 ± 8.8	102.4 ± 28.0 $P \leq 0.0001$	161.7 ± 41.4 $P \leq 0.0001$ $P \leq 0.0001$
Androstanediol glucuronide (nmol/L·h)	121 ± 42	202 ± 79 $P \leq 0.0001$	283 ± 110 $P \leq 0.0001$ $P \leq 0.0001$
Free testosterone (pmol/L·h)	449 ± 118	508 ± 127 $P \leq 0.0001$	516 ± 125 $P \leq 0.0001$ NS ($P = 0.64$)
Testosterone (nmol/L·h)	178 ± 29	184 ± 29 NS ($P = 0.27$)	184 ± 21 NS ($P = 0.18$) NS ($P = 0.81$)
Dihydrotestosterone (nmol/L·h)	9.78 ± 2.98	10.04 ± 2.98 NS ($P = 0.62$)	9.88 ± 3.03 NS ($P = 0.85$) NS ($P = 0.76$)
E_2 (pmol/L·h)	510 ± 198	635 ± 156 $P \leq 0.0001$	700 ± 209 $P \leq 0.0001$ NS ($P = 0.11$)
E_1 (pmol/L·h)	1442 ± 269	2537 ± 434 $P \leq 0.0001$	3254 ± 671 $P \leq 0.0001$ $P \leq 0.0001$

Values are the mean ± SEM.
[a] Baseline *vs.* 50 mg DHEA.
[b] Baseline *vs.* 100 mg DHEA.
[c] 50 mg DHEA *vs.* 100 mg DHEA.

TABLE 3. Pharmacokinetic data (calculated after baseline correction) of DHEA and DHEAS after oral administration of 50 mg DHEA and 100 mg DHEA, respectively

	Serum DHEA (after 50 mg DHEA)	Serum DHEA (after 100 mg DHEA)	Serum DHEAS (after 50 mg DHEA)	Serum DHEAS (after 100 mg DHEA)
AUC 0–12 h (DHEA: nmol/L·h; DHEAS: μmol/L·h)	176.1 ± 21.2 $P < 0.001$[a]	317.6 ± 35.3 $P < 0.001$[a] $P < 0.001$[b]	113.6 ± 19.3 $P < 0.001$[a]	163.8 ± 36.4 $P < 0.001$[a] $P < 0.001$[b]
C_{max} (DHEA; nmol/L; DHEAS; μmol/L)	36.7 ± 9.69 $P < 0.001$[a]	58.7 ± 15.2 $P < 0.001$[a] $P < 0.001$[b]	12.4 ± 2.3 $P < 0.001$[a]	18.8 ± 4.2 $P < 0.001$[a] NS ($P = 0.5$)[b]
T_{max} (h)	2.64 ± 2.02 NS ($P = 0.07$)[c]	2.54 ± 1.23 NS ($P = 0.05$)[c] NS ($P = 0.21$)[d]	4.11 ± 2.00 NS ($P = 0.09$)[c]	3.64 ± 1.29 NS ($P = 0.07$)[c] NS ($P = 0.57$)[d]
l (L/h)	0.14 ± 0.04	0.18 ± 0.04	0.065 ± 0.03	0.07 ± 0.02
$t_{½}$ (h)	5.35 ± 2.16	4.04 ± 1.02	12.66 ± 5.02	10.63 ± 4.30

[a] Comparison of placebo *vs.* 50 mg DHEA or 100 mg DHEA, by ANOVA.
[b] Comparison of 50 mg DHEA *vs.* 100 mg DHEA, by ANOVA.
[c] Comparison of placebo *vs.* 50 mg DHEA or 100 mg DHEA, by Wilcoxon signed rank test.
[d] Comparison of 50 mg DHEA *vs.* 100 mg DHEA, by Wilcoxon signed rank test.

equivalent to 176% (E_1) and 124% (E_2) of baseline values, whereas 100 mg DHEA induced increase to 226% (E_1) and 137% (E_2) of baseline values (Table 2). The maximum concentrations measured for serum E_1 and E_2 were still within the normal range for men.

Discussion

The major finding of our study is that in elderly men a dose of 50 mg DHEA, which restores serum DHEA and DHEAS to youthful levels in healthy men, induces significant increases in serum E_1 and E_2 concentrations, whereas total T and DHT, the main circulating androgens in men, remain unaffected. This contrasts with the results of our previous study on the pharmacokinetics and bioconversion of DHEA in women showing a significant increase in serum androgens but only a slight increase in serum E_1 and no change in serum E_2 after oral DHEA administration (17). Thus, oral administration of DHEA

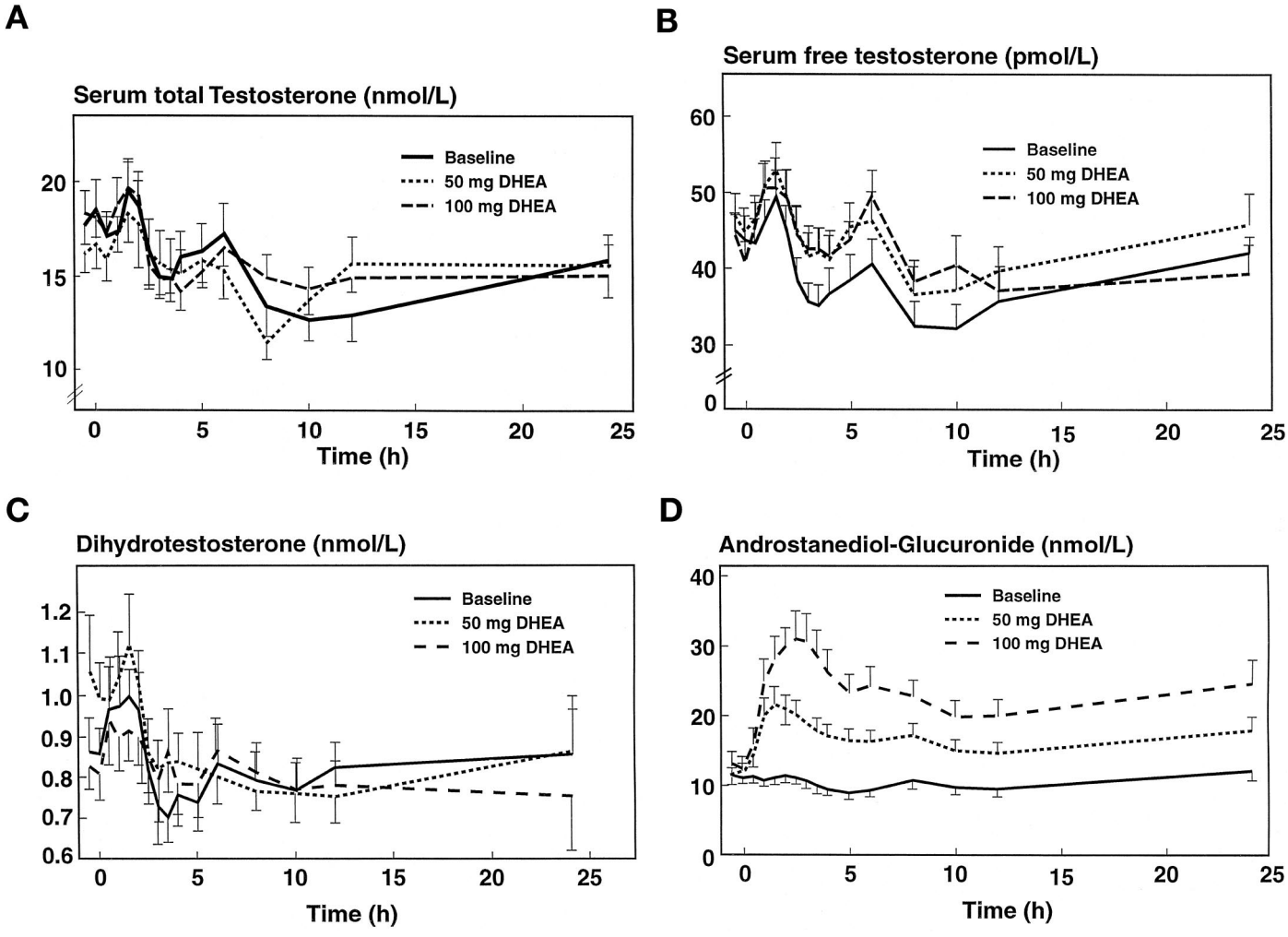

FIG. 2. Serum concentrations of total T (A), free T (B), DHT (C), and androstane-3α,17β-diol-17-glucuronide (D; mean ± SEM) in 14 male volunteers after ingestion of placebo, 50 mg DHEA, or 100 mg DHEA.

influences the androgen/estrogen ratio in both genders in opposite directions.

There are only four previous studies on the bioconversion of DHEA in men, and none of them presented detailed pharmacokinetic data concerning serum estrogens. Yen *et al.* (13) performed frequent sampling over a period of 8 h in eight men after ingestion of a single dose of 50 mg DHEA. They found significant increases in serum DHEA, DHEAS, and A'dione, whereas there was no change in serum T and DHT. However, serum estrogen concentrations were not reported (13).

In accordance with the results of our study, Young *et al.* (18) described a significant and dose-dependent increase in serum estrogens after the administration of 50 and 200 mg DHEA in four men and six women with panhypopituitarism. As in our study, the serum estrogen concentrations after DHEA were still within the normal range for men and started to decline 3–4 h after DHEA administration (18). Unfortunately, no gender-specific analysis was performed, preventing a comparison of sex-related differences in serum estrogen increases.

In contrast to the findings of our study, Morales *et al.* (12) found no increases in serum E_1 and E_2 in 13 men treated with a daily dose of 50 mg DHEA for 3 months. This is probably due to the selection of time points for the hormone determinations, as in their study blood for hormone measurements was drawn 12–16 h after the last preceding administration of DHEA (12). At this time, E_2 levels in our patients were no longer significantly different from baseline values, and E_1 levels were on the decline, although still above baseline. Compared to placebo, Young *et al.* (18) found significant increases in serum E_1 and E_2 after 50 mg DHEA, but there was no longer a significant difference 8 h after administration. Thus, in the men studied by Morales *et al.* (12), a transient increase in bioavailable serum estrogens may have been missed due to hormone measurements near the nadir.

Labrie *et al.* (19) administered a 20% DHEA cream in a daily dose of 10 mL for 14 days to a total of eight elderly men and women and found no significant increase in serum estrogen levels in either gender. These results differ from the findings of our study and those of Young *et al.* (18), but may be explained by the route of DHEA administration. As previously reported for transvaginal (20) and sublingual (13) administration of DHEA, Labrie *et al.* (18) also described an

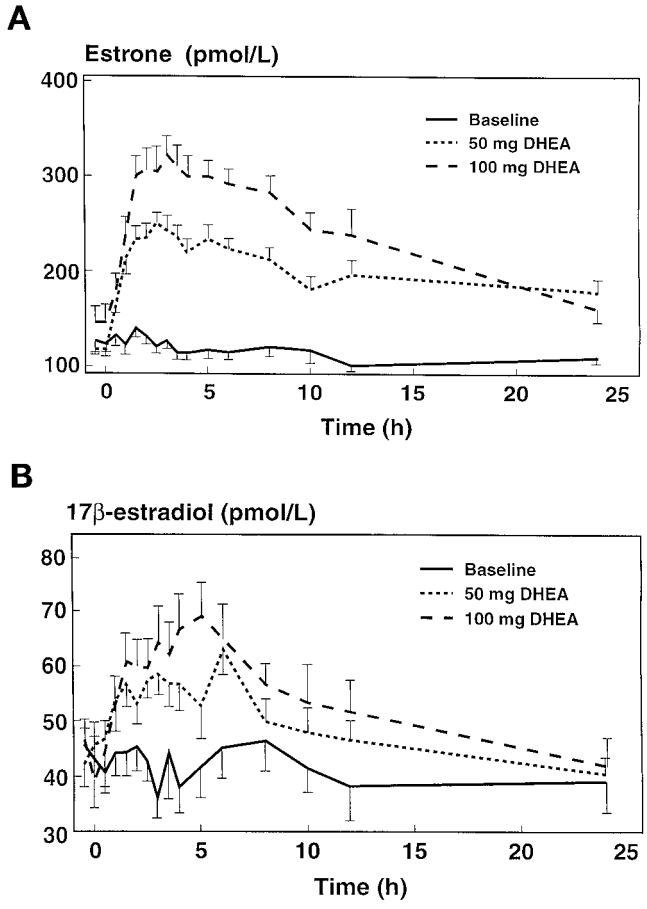

FIG. 3. Serum concentrations of E_1 (A) and E_2 (B; mean ± SEM) in 14 male volunteers after ingestion of placebo, 50 mg DHEA, or 100 mg DHEA.

increased DHEA/DHEAS ratio after percutaneous DHEA administration compared to oral ingestion. Although many tissues contain sulfotransferases (21, 22) and may contribute to the peripheral conversion of DHEA to DHEAS, the hepatic sulfotransferase activity seems to be of predominant importance and is bypassed by nonoral DHEA administration due to avoidance of the hepatic first pass effect. An increased DHEA/DHEAS ratio may lead to a reduced conversion of DHEA to androgens and/or estrogens inside peripheral target cells, as DHEAS has a much longer half-life than DHEA, and it can be continuously converted back to DHEA by widespread tissue sulfatase activity (23–26) followed by further bioconversion. Furthermore, avoidance of the first pass effect by nonoral administration of DHEA also leads to avoidance of hepatic aromatase and 5α-reductase activities. This may explain a lack of conversion to estrogens in men as well as the reduced conversion to androgens in women after percutaneous DHEA administration (19). This view is supported by the data of Casson *et al.* (20), who found an increase in DHEA, but not in DHEAS and T, after transvaginal DHEA administration. Serum estrogen levels were not reported in this study (20).

In agreement with our results, Labrie *et al.* (19) and Morales *et al.* (12) found no significant changes in serum T and DHT in their elderly male volunteers, whereas Young *et al.* (18) in their patients with hypopituitarism (including six men with unreplaced secondary hypogonadism) reported a slight, but significant, increase in serum androgens still below the normal range for men even after the administration of 200 mg DHEA. However, although total T and DHT remained unaffected in our male volunteers, a small, but significant, increase in serum free T was observed. This may be explained by transient interference of DHEA and DHEAS with binding proteins (*e.g.* competitive binding of DHEA and free T to SHBG or albumin) rather than by changes in binding protein concentrations. Both DHEA and T bind to SHBG and albumin (27, 28), and the rapid increase in DHEA as well as in DHEAS after oral ingestion of DHEA may be sufficient to displace a significant percentage of the protein-bound fraction of T. However, the increase in free T was short-lived and is most likely of minor importance.

Additionally, in our male volunteers a significant increase in serum ADG, a major metabolite of DHT and also of androstenedione, was observed. This may indicate an enhanced conversion of DHEA to androgens inside peripheral target cells that is not reflected by circulating androgen concentrations. A DHEA-induced increase in androgenic capacity in men may be supported by the findings of Yen *et al.* (13), who described increased muscular strength and decreased body fat mass in men after 6 months of treatment with a daily dose of 100 mg DHEA, but this may also be a consequence of the reported increase in insulin-like growth factor I (13).

In accordance with previous results both in men (12, 19) and women (12, 13, 17, 19, 29), DHEA administration to our male volunteers also led to a significant increase in serum androstenedione. Thus, DHEA induces a significant increase in serum androstenedione in both sexes, but the direction of further bioconversion may differ depending on the surrounding hormonal background, which may affect peripheral 17β-hydroxysteroid dehydrogenase, 5α-reductase, and aromatase activities.

In contrast to our finding that DHEA administration to elderly men induced no change in androgens, in women receiving DHEA pronounced increases in serum androgens have been described by us and other investigators (12, 13, 17, 19, 20, 29, 30). Serum estrogen levels in women were reported to be either unaffected by DHEA administration (12, 19, 30) or increased only slightly (17, 29).

These observations support the concept of a gender-specific bioconversion pattern of DHEA depending on baseline concentrations (high androgens in men, high estrogens in premenopausal women) with differential changes in the ratio of serum androgen to estrogen concentrations. A small increase in serum T of 1.5 nmol/L in both genders is equivalent to an increase of 100% in women, but to an increase of less than 10% in men. *Vice versa*, small absolute increases in estrogens, as observed in our study, are of potential biological significance in men, whereas they may be of little importance in premenopausal women with high ovarian estrogen secretion. Thus, DHEA may function as a sexually dimorphic hormone.

Such a concept of estrogen-like or androgen-like effects of DHEA depending on the hormonal milieu has previously been proposed by Ebeling and Koivisto (31). It also may explain the gender-specific differences found in some epi-

demiological studies that described an inverse correlation between serum DHEAS and the incidence of cardiovascular morbidity (4, 7) as well as short term mortality (8) in elderly men, but not in elderly women. Similarly, in a study of very old subjects (>90 yr of age), good functional status was positively correlated with serum DHEAS in males only (9).

In addition to its peripheral bioconversion to estrogens, the estrogenic action of DHEA may be mediated by its metabolite androstenediol, which was not measured by us but has previously been shown to significantly increase after DHEA administration (18, 19) and is known to bind to the estrogen receptor (32, 33). Furthermore, DHEA may also directly exert an estrogenic action, as in a recent *in vitro* study DHEA was shown to stimulate the estrogen-responsive element (34).

In conclusion, our study clearly demonstrates a significant increase in circulating serum estrogens after the administration of 50 mg DHEA to elderly men, which restores low endogenous serum DHEAS to youthful levels; on the other hand, in women a lasting increase in serum androgens after the same dose of DHEA has been previously reported (12, 13, 17). This DHEA-induced increase in estrogenic activity may contribute to beneficial effects of DHEA in men. Our data support the view of DHEA as a sexually dimorphic hormone that changes the circulating androgen/estrogen ratio in a gender-dependent fashion. Thus, both pharmacokinetic and clinical studies should take the gender specificity of DHEA into account.

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