

## EFFECT OF DEHYDROEPIANDROSTERONE ON OXALATE METABOLISM IN RATS

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### 1. ABSTRACT

Urinary oxalate plays an important role in the formation of calcium oxalate stone, and endogenous oxalate metabolism mainly occurs in the liver. Since dehydroepiandrosterone (DHEA) is known to have an effect on hepatocellular proliferation and on some hepatic enzymes, we examined the influence of DHEA on the activity of hepatic oxalate-related enzymes and on urinary oxalate excretion in rats. Fourteen male rats were castrated and divided into two groups. The control group was fed a standard diet, while the other rats were fed a diet containing 0.5% DHEA. After 4 weeks, the liver weight and the urinary levels of oxalate, glycolate, and glycine were significantly higher in the DHEA-treated rats than in the controls, while body weight did not differ between the two groups. Hepatic alanine:glyoxylate aminotransferase and glyoxylate reductase showed significantly higher activity in the DHEA-treated rats than in the controls, while glycolate oxidase activity was significantly reduced. Treatment with DHEA induced hyperoxaluria along with hepatocyte proliferation. This hyperoxaluria was probably caused by hepatocyte proliferation, but it could not be explained simply by the changes of hepatic oxalate-related enzymes. Investigation of the modulation of peroxisomal enzymes by peroxisomal proliferators or inhibitors may provide further insights into hepatocyte oxalate metabolism.

### 2. INTRODUCTION

Dehydroepiandrosterone (DHEA) is the main adrenal steroid and is a precursor of androgen and estrogen biosynthesis in humans (1). The production of DHEA peaks in early adulthood (adrenarche) and gradually declines with age, a change that is termed the "adrenopause" (2). In fact, many diseases associated with aging are thought to be correlated with reduced DHEA production, suggesting a potential anti-aging effect of this hormone. Recently, attempts have been made to use DHEA for the prevention of various diseases associated with aging. For example, DHEA acts as a neurosteroid with effects on various neurotransmitter receptors in the brain and thus has a considerable influence on mood, well-being, and sexuality in patients with mood disorders or adrenal insufficiency (3). DHEA has been suggested to be a multifunctional hormone with anticancer,

immunopotentiating, neurotropic, and general anti-aging effects (4), and it significantly reduces the frequency of exacerbation of systemic lupus erythematosus and improves disease activity (5).

DHEA is also known to have an effect on hepatocellular and peroxisomal proliferation (1, 6). Peroxisomes are most abundant in the liver, accounting for about 1 to 2% of the cell volume. Treatment of rats with DHEA caused a 200% increase of liver weight and a more than 5-fold increase of peroxisome density (7, 8), and some peroxisomal enzymes (such as acyl-CoA oxidase and  $\beta$ -oxidase) also showed an increase in activity (9). A number of hepatic enzymes have been suggested to be involved in oxalate metabolism. Oxalate plays an important role in the formation of calcium oxalate stones (9); it is produced from glycolate via glyoxylate by glycolate oxidase (GO) (10), and glyoxylate may be converted back to glycolate by glyoxylate reductase (GR) in the cytosol (11). On the other hand, peroxisomal alanine:glyoxylate aminotransferase (AGT) catalyzes transamination between alanine and glyoxylate to form pyruvate and glycine. Because this enzyme has a high affinity for glyoxylate ( $K_m$ : 10  $\mu$ M), it minimizes oxalate synthesis from glyoxylate by lactate dehydrogenase (LDH) that has a low affinity (higher  $K_m$ ) for glyoxylate (12, 13). If DHEA affects these oxalate metabolism-related enzymes in the liver, treatment with this hormone may alter oxalate metabolism and urinary oxalate excretion.

In the present study, we examined the effect of DHEA on hepatic enzymes and oxalate metabolism in rats.

### 3. MATERIALS AND METHODS

Fourteen male Wistar rats weighing 120-140 g were used in this study. The rats were castrated under 2% halothane anesthesia, and were randomly divided into two equal groups. The control group was fed a standard diet (CE-2, Nihonkurea, Japan), while the other group was fed a diet containing 0.5% DHEA (Sigma, Japan). All rats had free access to tap water. After 4 weeks, the rats were weighed and anesthetized by intraperitoneal injection of urethane (1 g/kg). The urethra was blocked and urine was

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**Table 1.** Body weight and liver weight of control rats and DHEA rats

Group	Body weight (g)		Liver weight (g)
	Baseline	4 weeks	
Control	131.1 ± 4.2	298.9 ± 30.4	12.7 ± 0.9
DHEA	126.0 ± 6.1	290.4 ± 23.3	17.7 ± 1.3 <sup>1</sup>

mean ± S.D., <sup>1</sup>: p<0.01, comparison with control

**Table 2.** Serum parameters of control rats and DHEA rats after 4 weeks

Group	Creatinine (mg/dl)	ALT (IU/L)	AST (IU/L)
Control	0.34 ± 0.06	78 ± 6	39 ± 3
DHEA	0.33 ± 0.04	82 ± 8	42 ± 6

mean ± S.D

**Table 3.** Urinary parameters of control rats and DHEA rats after 4 weeks

Group	Urinary creatinine (mg/dl)	Oxalate/creatinine ratio (mg/mg)	Glycolate/creatinine ratio (mg/mg)	Glycine/creatinine ratio (mg/mg)	Citrate/creatinine ratio (mg/mg)
Control	25.2 ± 7.2	0.11 ± 0.02	0.06 ± 0.01	0.06 ± 0.01	2.89 ± 0.98
DHEA	31.7 ± 16.3	0.17 ± 0.33 <sup>1</sup>	0.09 ± 0.03 <sup>2</sup>	0.08 ± 0.02 <sup>2</sup>	3.77 ± 2.01

mean ± S.D., <sup>1</sup>: p<0.01, comparison with control; <sup>2</sup>: p<0.05, comparison with control

**Table 4.** Hepatic enzyme activities in control rats and DHEA rats after 4 weeks

Group	AGT activity (μmol of pyruvate/h/mg of protein)	GO activity (μmol of glyoxylate/h/mg of protein)	GR activity (μmol of glycolate/h/mg of protein)
Control	8.05 ± 0.55	2.17 ± 0.19	0.29 ± 0.11
DHEA	9.36 ± 0.66 <sup>2</sup>	0.81 ± 0.46 <sup>1</sup>	0.64 ± 0.13 <sup>1</sup>

mean ± S.D., <sup>1</sup>: p<0.01, comparison with control; <sup>2</sup>: p<0.05, comparison with control

collected by bladder puncture after 2 h. Blood was withdrawn from the *vena cava* and was centrifuged for 10 min at 3,000 rpm to separate serum. In addition, the liver was removed and weighed (14). All specimens were stored at -80°C until assay.

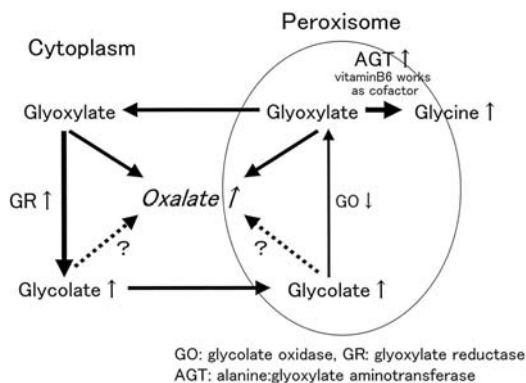
Urinary oxalate and glycine levels were measured by capillary electrophoresis (Hewlett-Packard <sup>3D</sup>CE, Germany) using an HPCE buffer solution (pH 7.7; Fluka, Switzerland) and a basic anion buffer solution (pH 12.1; Agilent Technologies, Germany), respectively (14), while the urinary glycolate, glyoxylate and citrate levels were measured using an organic buffer solution (pH 5.6; Agilent Technologies, Germany) (15). Serum levels of creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), as well as urinary creatinine, were also measured (SRL, Japan). Liver tissue levels of AGT, GO, and GR activity were measured according to the methods of Nishijima et al. and Murthy et al. with some modifications (14, 16). After the reaction was stopped by heating for 5 min at 95°C, and the pyruvate, glyoxylate, or glycolate level in the reaction mixture was measured by capillary electrophoresis. Protein levels in the supernatant were quantified by using an ultraviolet spectrophotometer to read the absorbance at 280 nm with bovine serum albumin as the standard. Hepatic enzyme activity was expressed as the production of pyruvate (AGT), glyoxylate (GO), or glycolate (GR) in μmol/h/mg of protein. Results are reported as the mean ± standard deviation (S.D.). Student's *t*-test for unpaired data was used for statistical analysis, with significance being set at *p* < 0.05.

## 4. RESULTS

The effect of DHEA on body weight and liver weight is shown in Table 1. Body weight increased over time from the baseline level (126.0 ± 6.1 g in the DHEA-treated rats and 131.1 ± 4.2 g in the control rats), and there was no significant difference in weight between the control rats (298.9 ± 30.4 g) and the DHEA-treated rats (290.4 ± 23.3 g) at 4 weeks. However, the liver weight at 4 weeks was significantly greater (139.5%, *p* < 0.001) in the DHEA-treated rats (17.7 ± 1.3 g) than in the control rats (12.7 ± 0.9 g).

There were no significant differences of urinary creatinine, serum creatinine, serum ALT, and serum AST between the control rats and the DHEA-treated rats (Tables 2 and 3). The urinary oxalate/creatinine, glycolate/creatinine, and glycine/creatinine ratios were all significantly higher (oxalate/creatinine: 150.7%, *p* = 0.001, glycolate/creatinine: 149.1%, *p* = 0.026, and glycine/creatinine: 145.2%, *p* = 0.027) in the DHEA-treated rats than in the control rats, while citrate/creatinine ratio did not differ between the groups.

Regarding hepatic enzymes, the total AGT activity (measured as the rate of pyruvate production from glyoxylate and alanine) and the GR activity (the rate of glycolate production from glyoxylate incubated with liver extract) were significantly higher (AGT activity: 116.3%, *p* = 0.023, and GR activity: 216.7%, *p* = 0.007) in the DHEA-treated rats than in the control rats (Table 4). On the other hand, GO activity (the rate of glyoxylate production from glycolate) was significantly lower (37.4%, *p* = 0.005) in the DHEA-treated (Table 4).



**Figure 1.** Diagram of putative hepatic oxalate metabolism in DHEA- treated rats (24). Urinary glycine, glycolate, and oxalate excretion were all increased in DHEA-treated compared with control rats; hepatic AGT and GR activity were also higher, but GO activity was lower. This decrease of GO activity along with the increase of hepatic AGT and GR activity in DHEA-treated rats led to relative hyperoxaluria

## 5. DISCUSSION

Dehydroepiandrosterone (DHEA) is a C-19 adrenal steroid precursor of the gonadal steroids. In humans, circulating levels of DHEA (as its sulfated conjugate) are high at puberty and throughout early adulthood, but subsequently decline with age. Dietary supplementation to maintain high levels of DHEA has been claimed to show beneficial effects on memory, the immune system, and fat and carbohydrate metabolism (17). DHEA-sulfate (DHEA-S), but not DHEA itself, activates peroxisome proliferator-activated receptor alpha (PPAR alpha) in the liver, an intracellular receptor belonging to the steroid receptor superfamily. Thus, DHEA-S may be a physiological modulator of hepatic fatty acid metabolism and peroxisomal enzyme expression, and may thus contribute to the anticancer and chemoprotective properties of this intriguing class of endogenous steroids (18). Numerous animal experiments have shown that DHEA is a multifunctional hormone with immunoenhancing, antidiabetic, antiobesity, anticancer, neurotropic, memory-enhancing, and anti-aging effects (19).

Recently, various effects of DHEA on the liver have attracted attention. A wide variety of mechanisms have been postulated to explain the chemopreventive effect of DHEA, including an influence on liver weight, hepatocellular proliferation, and peroxisomal proliferation (6-9). It was reported that rats feeding a 0.45% DHEA diet caused a marked (200%) increase of liver weight and a more than 5-fold increase of peroxisome density (7, 8). In the present study, the liver weight of DHEA-treated rats increased by about 50%, and this increase of liver weight was slightly lower than in the previous report (7). We used male Wistar rats weighing 120-140 g that were fed a special powder diet containing 0.5% DHEA in this study, while rats weighing 90-100 g and fed the usual solid diet were used in the other study. Therefore, these differences in conditions appear to have some influence on the growth of the rats and the increase of liver weight. Yamada et al. also

reported that treatment of rats with DHEA (300 mg/kg orally for 2 weeks) markedly increased the number of peroxisomes and the activity of some enzymes (carnitine acetyltransferase, microsomal laurate 12-hydroxylase, cytosolic palmitoyl-CoA hydrolase, malic enzyme, etc.) in the liver (9). In addition, hepatic beta-oxidation enzymes were induced over 30-fold by di-2-ethylhexyl phthalate (DEHP), while catalase was induced about 2-fold (20). Clofibrate is another peroxisome proliferator that shows similar effects (21). Peroxisomal AGT mRNA was reported to be increased by peroxisome proliferators (clofibrate and DEHP) and by triiodothyronine (T3) (22). Clofibrate was shown to induce hyperoxaluria in rats along with an increase of hepatic LDH activity (23). In the present study, urinary creatinine-corrected glycine, glycolate, and oxalate excretion were all increased in the DHEA-treated rats; their hepatic AGT and GR activities were also increased, but GO activity was decreased. Although hepatic AGT activity was expected to increase in the DHEA-treated rats, hyperoxaluria occurred despite the decline of GO activity (Figure 1) (24). DHEA is the primary steroid precursor of androstenedione, and it is eventually converted into testosterone (1, 6). The sex hormones also seem to have an influence on urolithiasis because its incidence is higher in males than in females (a difference of approximately 2:1 to 3:1) (25), while the composition of upper urinary tract stones differs between women of reproductive age and postmenopausal women (26). Enzymes involved in the hepatic synthesis of oxalate, including glycolate oxidase, glycolate dehydrogenase, and LDH are reported to be testosterone-dependent (27, 23), and orchidectomy decreases the hepatic synthesis of oxalate, whereas ovariectomy increases it by 10% (28). In addition, estradiol administration decreases hepatic GO levels in both normal and pyridoxine-deficient animals (29). Furthermore, testosterone promotes and estrogen inhibits urinary oxalate excretion in ethylene glycol-treated rats (30). Yoshihara et al. reported that GO activity was higher in male rats and testosterone-treated rats, while it was lower in female rats and castrated male rats. Also, SPT/AGT activity was higher in female rats (intact, castrated, testosterone-treated, and estradiol-treated). However, urinary oxalate excretion did not differ between male and female rats (intact, castrated, testosterone-treated, and estradiol-treated). They concluded that GO activity is dependent on testosterone and that it has no physiological effect but may alter urinary oxalate excretion after loading with oxalate precursors. (31) Fan et al. studied a rat EG model of urolithiasis and concluded that androgens and dihydrotestosterone increase (while estrogens decrease) urinary oxalate excretion, plasma oxalate levels, and calcium oxalate crystal deposition in the kidneys (32, 33).

DHEA can modulate peroxisomal gene expression and the expression of 16 genes (11 peroxisomal) was reported to be altered. Pex 11, acyl-CoA oxidase, L- and D-multifunctional enzyme, thiolase 1, phytanoyl-CoA hydroxylase, 70 kDa peroxisomal membrane protein (PMP 70), and very-long-chain (VLC) acyl-CoA synthetase were upregulated, while 3 other genes were downregulated. In addition, vitamin D is a naturally occurring substance that may possibly influence peroxisome maturation and activity,

since it was reported to cause the downregulation of six genes (peroxin 12, pristanoyl-CoA oxidase, acyl-CoA: dihydroxy acetone phosphate acyltransferase, racemase, mevalonate kinase, and glutaryl-CoA oxidase) (34). The nuclear receptor for vitamin D (VDR) belongs to the family involved in the control of peroxisome proliferation, including peroxisome proliferators activated receptors (PPAR $\alpha$ ), retinoic acid receptor (RAR), and thyroid hormone receptor (THR) (35). Davis et al. have demonstrated peroxisomal proliferation due to vitamin D in the chicken liver and induction of beta-oxidation by vitamin D in the rat liver (34). Halabe et al. recently reported that 1- $\alpha$ -D3 (together with ethylene glycol) caused a significant increase of urinary glycolate without a parallel rise of urinary oxalate excretion, in ethylene glycol-fed rats. They concluded that this increase in urinary glycolate was due to the synergistic effect of both agents (36). Although further study is needed, it may have been due to downregulation of peroxisomal enzymes.

In light of these previous results, the downregulation of GO by DHEA (along with upregulation of AGT and GR) in our study does not completely explain the occurrence of hyperoxaluria and hyperglycolic aciduria. Total AGT activity usually does not correspond with peroxisomal AGT, but is the sum of AGT1 (SPT) + AGT2 + GGT (glutamate glyoxylate aminotransferase) activity (37). Therefore, to clarify the actual influence of DHEA on oxalate metabolism and to investigate the potential effects of other peroxisomal modulators on hyperoxaluria, further animal studies on loading with oxalate precursors may be warranted.

AGT and GR activity showed a significant increase in the DHEA-treated rats compared with the control rats, while GO activity was significantly decreased. AGT and GR convert glyoxylate to other substances and act to minimize oxalate production (10, 11). Glycolate is converted to glyoxylate by GO, so upregulation of GO facilitates oxalate production (12). The direct pathway from glycolate to oxalate was proposed by Fry and Richardson (38), who showed that glyoxylate was not formed from glycolate and that glycolate was converted to oxalate in human liver homogenates using the <sup>14</sup>C-labeled substances. Holmes and Assimos also recently found that oxalate was synthesized from glycolate without oxidation to glyoxylate by GO when Hep G2 cells (a human hepatoma cell line) were incubated with glycolate (24). Therefore, the present finding of hyperoxaluria and hyperglycolic aciduria without an increase of urinary glyoxylate in DHEA-treated rats despite downregulation of GO also suggests the direct synthesis of oxalate from glycolate or other potential sources. We also think it is necessary to study in vitro liver cell culture models in order to clarify the effect of DEAE on hepatic oxalate metabolism in the near future.

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