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Effect of castration and finasteride on urinary oxalate excretion in male rats

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Abstract We investigated the effects of castration and finasteride administration on urinary oxalate (Ox) excretion in a rat ethylene glycol (EG) model of urolithiasis. Male adult SD rats were divided into six groups. Group 1 were normal, untreated rats. The other five groups, all treated with 0.75% EG for 4 weeks; were as follows: group 2, non-castrated (intact) rats; group 3, castrated rats; group 4, castrated rats with a 4-cm testosterone implant; group 5, intact rats treated with high-dose finasteride (7.5 mg%); and group 6, intact rats treated with low-dose finasteride (0.75 mg%). Urinary Ox excretion increased 12.8-fold after 4 weeks of EG treatment (group 2 vs group 1). Both castration (group 3) and finasteride administration (groups 5 and 6) significantly decreased urinary Ox excretion compared with intact rats (group 2). We conclude that dihydrotestosterone is partially responsible for the exaggerated hyperoxaluria observed in the rat EG model of urolithiasis.

Key words Testosterone · Dihydrotestosterone · Finasteride · Urinary oxalate

Introduction

It is well known that urolithiasis is a male-predominant disease. The incidence of idiopathic calcium oxalate (CaOx) stone disease in men has been reported to be 3 times that in women [16, 17]. The peak age of onset of idiopathic CaOx stone disease occurs in the third and fourth decades of life [4], when the level of serum testosterone is also the highest [2]. This association between serum testosterone and urolithiasis has as yet received only limited attention.

Lyon et al. [10] were first to note, in an experimental ethylene glycol ingestion model of urolithiasis, that male rats were more prone to develop kidney crystal deposition than female rats. This observation has recently been confirmed by Lee et al. [7, 8], who reported that testosterone can promote CaOx kidney crystal deposition in rats given 0.5% EG in their drinking water. Castration in male rats dramatically reduced the development of crystal deposition. Exogenous testoterone administered to castrated male and female rats (but not intact female rats) restored crystal deposition. Lee et al. [8] concluded that testosterone promotes and estrogens inhibit urolithiasis. The precise mechanisms by which sex hormones affect kidney crystal deposition are unclear. Testosterone is know to increase the hepatic levels of glycolate oxidase (GAO), an important enzyme in the metabolic pathway for Ox synthesis [15]. Testosterone thus may lead to an increase in hepatic Ox synthesis, resulting in hyperoxaluria. Hyperoxaluria in turn may be responsible for the increased predisposition to CaOx urolithiasis.

It is unknown whether the lithogenic effects of male hormones result from testosterone or dihydrotestosterone (DHT). DHT is the biologically more active male hormone converted from testosterone by the cytosolic enzyme, 5α-reductase. Finasteride (Proscar), an inhibitor of 5α-reductase [14, 22], has been used for the treatment of benign prostatic hypertrophy (BPH) in doses from 5 mg to 100 mg, without significant side effects [12, 18].

The purpose of the present study was to evaluate systematically the effects of castration and finasteride administration on urinary Ox excretion and kidney crystal deposition in a rat EG urolithiasis model.

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Material and methods

Animal study groups

All the animal experimental protocols were approved by the Animal Research Committee of the University of Colorado. Adult male Sprague-Dawley rats, weighing 250–275 g, were used for the study. Ethylene glycol (EG) was used to induce hyperoxaluria and kidney CaOx crystal deposition. The rats were divided into six groups: group 1, normal, non-castrated (intact) rats used as controls; group 2, intact rats treated with 0.75% EG for 4 weeks; group 3, castrated rats treated with 0.75% EG for 4 weeks; group 4, castrated rats treated with a 4-cm testosterone implant and 0.75% EG for 4 weeks; group 5, intact rats treated with 0.75% EG and 7.5 mg% (high-dose) finasteride for 4 weeks; and group 6, intact rats treated with 0.75% EG and 0.75 mg% (low-dose) finasteride for 4 weeks. There were six rats in each study group. Both EG and finasteride were mixed in the rat drinking water, access to which was allowed ad libitum. Finasteride powder was kindly supplied by Merck (West Point, Pa.). All rats were fed an Agway R-M-H 3000 diet (Agway, C.G., N.Y.) for the entire length of the study. This diet contained 22.5% protein, 0.97% calcium, 0.85% phosphorus, 0.21% magnesium, 0.44% sodium, 0.95% potassium, vitamin A 20 229 IU and vitamin D_3 1045 IU per 100 g diet. Water consumption by each rat was determined twice weekly. All rats were weighed at the beginning and end of the study period.

Testosterone implants

The testosterone implants were prepared by filling testosterone into a 4-cm section of Dow-Corning (Midland, Mich.) silastic medical-grade tubing (inner diameter, 1.98 mm; outer diameter, 3.18 mm) which was then sealed with silastic adhesive A (Dow Corning) according to a method described previously [13]. The estimated release rate of testosterone was 30 μg/cm per day [19]. Awoniyi et al. [1] have shown that the serum testosterone concentration obtained with the subcutaneous implantation of a 4-cm testosterone tube is 75–80% higher than that in the normal intact male rat. The implantation of the testosterone tube was done under light metofane anesthesia. A 0.5-cm incision was made over the lower back of the rat, followed by the creation of a small subcutaneous pocket (4 cm long) using blunt dissection and insertion of the silastic implant. The rats in group 4 started their EG treatment 1 week after receiving their testosterone implant.

Urine collection and analysis

Twenty-four hour urine was collected from each rat 1 day before the animal was killed, using a metabolic cage at room temperature with thymol as preservative. Urinary pH was measured by an Accumet 1003 pH meter (Fisher Scientific, Penn.) immediately after collection. The urine was then filtered with a Whatman #1 filter and stored at −20°C until further analysis. A portion of the urine was acidified with concentrated HCl to pH < 3.0 for the Ox assay. Urinary calcium (Ca), phosphate (PO_4), uric acid (Ua), magnesium (Mg) and creatinine (Cr) were measured in the University Hospital Laboratory using a Hitachi 747 autoanalyzer; Ox and citrate (Cit) were measured in our Urolithiasis Research Laboratory using enzymatic methods (Sigma, St. Louis, Mo.).

Serum creatinine and hormone assay

Blood samples from each rat were taken using a heart puncture technique on the day the animal was killed. All blood samples were obtained between 0900 hours and 1200 hours to avoid the influence of circadian rhythmic secretion of sex hormones. Serum Cr was measured in the Hospital Laboratory using a Hitachi 747 autoanalyzer. Cr clearance was calculated based on serum Cr, urine Cr and urine volume. Serum testosterone and DHT were determined using a radioimmunoassay (RIA) kit (Amersham Life Science, Arlington Heights, Ill.).

Kidney crystal deposition and tissue chemical composition

At the end of the study, all rats were killed in a 100% CO_2 chamber and both kidneys were removed and placed in crushed ice immediately. After the kidneys had been weighed, the right kidney was fixed with 10% buffered formalin, embedded in paraffin, cut into 5-μm section for slides, and stained with hematoxylin and eosin. The slides were examined with a polarizing light microscope for crystal deposits. The type of crystal deposits was determined by X-ray diffraction. The left kidney was used for wet kidney tissue Ca, Ox and PO_4 analysis. The kidney tissue was homogenized by a Sonifier II Cell Disrupter (Branson Ultrasonics, Conn.) and dissolved in 1 M HCl overnight at 4°C. After centrifugation, the supernatant was removed and neutralized with 1 M NaOH. Tissue Ca, Ox and PO_4 were determined by methods described for urinary chemical analysis.

Statistical analyses

The Kruskal-Wallis method was used for the statistical analyses among the various study groups.

Results

All rats gained weight during the 4 weeks of treatment. The highest daily body weight gain occurred in group 1 rats (Table 1). This weight gain was significantly more than that in the EG-treated rats (groups 2 to 6). The average daily water consumption was 27–39 ml. The average intakes of finasteride for the high- and low-dose treatment rats (group 5 and 6) were 6.72 and 0.80 mg/kg body weight per day, respectively.

Serum testosterone level in castrated rats (group 3) was < 0.5% that of intact rats (group 2). Testosterone implantation in castrated rats (group 4) increased the serum testosterone level to 1.76 times that of intact rats (Table 2). Finasteride administration did not significantly alter serum testosterone concentrations. As expected, the serum DHT concentrations in rats treated with high or low doses of finasteride were significantly lower than in the normal controls, indicating an effective

Table 1 Rat daily body weight gain and ethylene glycol (*EG*) ingestion results (mean ± SE)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Daily body weight gain (g)	5.79 ± 0.51	3.39 ± 0.27[a]	3.39 ± 0.22[a]	2.21 ± 0.26[a,b,c]	2.16 ± 0.08[a,b,c]	3.07 ± 0.19[a]
EG ingestion (mg/24 h)	269 ± 28	250 ± 8	291 ± 19	258 ± 7	202 ± 13	241 ± 11

[a] $P < 0.05$ vs group 1; [b] $P < 0.05$ vs group 2; [c] $P < 0.05$ vs group 3

inhibition of 5α-reductase in the transformation of testosterone to DHT (Table 2).

Urine chemistries and renal functional results are summarized in Table 3. After 4 weeks of EG treatment, urinary Ox excretion increased to 2.5 to 18.2 times that of group 1 rats: the highest increase occurred in intact rats (group 2) whereas the lowest increase in Ox excretion occurred in castrated rats (group 3) (Fig. 1). Compared with normal rats, all increases in urinary Ox excretion were statistically significant except for that in castrated rats (group 3). Urinary Ox excretion in castrated rats (group 3) and finasteride-treated rats (group 5 and 6) was only 20%, 40% and 53%, respectively, that in intact rats (group 2) after EG treatment. Urinary Ca and Cit concentrations decreased significantly in all EG-treated rats except for the castrated rats (group 3). Both urinary Cr excretion and creatinine clearance were normal and not statistically different among the six study groups.

Kidney tissue microscopy showed that one rat in group 2 had extensive crystal deposits and one rat in group 3 had only a few crystal deposits. These crystals had an X-ray diffraction pattern similar to CaOx but not to calcium phosphate (CaP) crystals. The remainder of the kidneys were free of CaOx crystal deposits. Tissue Ca, Ox and PO_4 analysis results are shown in Table 4. The mean tissue Ca and Ox concentrations in group 2 rats were much higher because of the extremely high tissue Ca and Ox concentrations in the rat that had

Table 2 Rat serum testosterone and dihydrotestosterone (*DHT*) results (means ± SE). There were no DHT measurements done in group 4 rats because of an inadequate plasma sample

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Serum testosterone (ng/ml)	2.218 ± 0.685	2.350 ± 0.889	0.104 ± 0.040[a,b]	3.907 ± 0.547[c]	2.369 ± 0.333[c,d]	1.382 ± 0.444[c,d]
Serum DHT (ng/ml)	0.458 ± 0.161	0.712 ± 0.217	0.114 ± 0.013[a,b]		0.199 ± 0.026[b,c]	0.120 ± 0.046[a,b]

[a] $P < 0.05$ vs group 1; [b] $P < 0.05$ vs group 2; [c] $P < 0.05$ vs group 3; [d] $P < 0.05$ vs group 4

Table 3 Rat urinary chemistries and creatinine clearance (mean ± SE)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Volume (ml/24 h)	10.1 ± 2.4	15.9 ± 5.0	13.4 ± 1.9	9.6 ± 1.5	6.2 ± 0.9	9.7 ± 1.5
pH	6.68 ± 0.18	6.90 ± 0.39	5.83 ± 0.06	6.47 ± 0.22	6.88 ± 0.35	6.59 ± 0.16
Creatinine (mg/24 h)	9.8 ± 0.7	11.3 ± 1.0	10.9 ± 0.5	9.9 ± 0.6	9.4 ± 0.5	10.3 ± 0.4
Calcium (μmol/24 h)	22.7 ± 7.9	7.9 ± 1.2[a]	20.3 ± 4.0[b]	7.4 ± 1.5[a,c]	7.0 ± 1.3[a,c]	5.2 ± 0.3[a,c]
Phosphate (μmol/24 h)	572 ± 106	421 ± 47	505 ± 35	453 ± 55	401 ± 27	475 ± 31
Uric acid (μmol/24 h)	11.3 ± 0.9	11.3 ± 2.5	8.4 ± 0.8	7.1 ± 0.4	7.7 ± 0.7	7.9 ± 0.3
Citrate (μmol/24 h)	51.5 ± 10.2	31.2 ± 2.8[a]	44.2 ± 5.5	23.8 ± 4.5[a,c]	20.1 ± 3.9[a,c]	17.3 ± 2.8[a,b,c]
Magnesium (μmol/24 h)	71.9 ± 34.0	128.5 ± 41.4	159.4 ± 32.4	97.8 ± 26.8	44.3 ± 19.4	48.1 ± 9.3
Creatinine clearance (ml/min)	1.249 ± 0.128	1.278 ± 0.044	1.248 ± 0.098	1.563 ± 0.298	1.191 ± 0.123	1.524 ± 0.101

[a] $P < 0.05$ vs group 1; [b] $P < 0.05$ vs group 2; [c] $P < 0.05$ vs group 3

Table 4 Rat kidney analysis results (mean ± SE)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Weight (g)	2.63 ± 0.09	2.48 ± 0.15	2.29 ± 0.05	2.61 ± 0.09	2.38 ± 0.07	2.58 ± 0.07
Calcium (mmol/kg tissue)	2.23 ± 0.18	2.70 ± 1.9	1.59 ± 0.11	1.85 ± 0.19	1.82 ± 0.08	1.61 ± 0.04
Oxalate (mmol/kg tissue)	0.46 ± 0.02	4.85 ± 4.52	0.18 ± 0.06	0.37 ± 0.08	0.35 ± 0.04	0.40 ± 0.02
Phosphate (mmol/kg tissue)	11.84 ± 0.32	11.46 ± 0.51	11.58 ± 0.25	11.04 ± 0.33	10.70 ± 0.36	11.13 ± 0.28

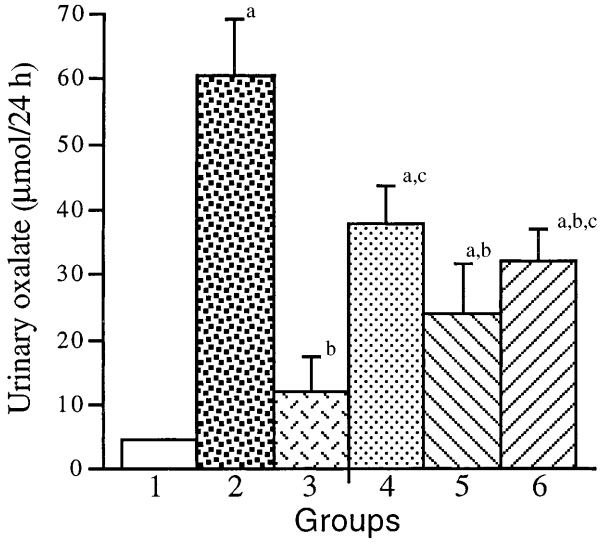

Fig. 1 Urinary oxalate excretion after 4 weeks of ethylene glycol treatment. [a] $P < 0.05$ vs group 1; [b] $P < 0.05$ vs group 2; [c] $P < 0.05$ vs group 3

extensive CaOx crystal deposits (8.58 and 27.5 mmol/kg tissue, respectively). Tissue PO_4 concentrations were similar among the various groups.

Discussion

Urolithiasis is a male-predominant disease, with the incidence of kidney stones in men reported to be 3 times higher than in women [16, 17]. The cause of this male predisposition to urolithiasis is currently unknown. Two possibilities are that male hormones may promote while female hormones may inhibit kidney stone formation. Although clinical proof for this hypothesis is lacking, there is some initial experimental evidence to implicate sex hormones in the pathophysiology of stone disease.

Recently, Lee et al. [7, 8] have shown in a rat experimental urolithiasis model that testosterone promotes and estrogens inhibit urinary Ox excretion and kidney CaOx crystal deposition. Their results showed that the incidence of kidney stones in castrated male rats treated with EG for 4 weeks decreased from 71% to 14% compared with intact male rats. Exogenous testosterone implantation restored CaOx stone formation in castrated, EG-treated male rats and castrated female rats, but not in intact EG-treated female rats. The urinary excretion of Ox appeared to be the primary factor responsible for differences in stone formation observed among the various study groups. Our findings are consistent with the results reported by Lee et al. [6].

The mechanisms by which sex hormones may influence urinary Ox excretion, and thus kidney stone formation, are unclear. Testosterone is known to increase the hepatic level of GAO, an important enzyme in the metabolic pathway for Ox synthesis [15]. This increase in hepatic GAO activity has been proposed to increase endogenous Ox production and thereby urinary Ox excretion. Recently, Lu et al. [9] reported that renal organic anion transporting polypeptide (oatp) mRNA expression is under strong testosterone control and perhaps weaker estrogen control. Possibly other tubular organic anion transporters such as sulfate-oxalate exchanger located on the basolateral side of renal proximal tubular cells [11, 21] may also be under androgen control and alter renal transport of oxalate. Thus, male hormones may promote urinary Ox excretion by increasing hepatic synthesis of Ox and/or increasing renal tubular secretion of Ox.

DHT is a biologically more active male hormone converted from testosterone by the cytosolic enzyme, 5α-reductase. It is unknown whether the lithogenic effects of male hormones in this experimental model of urolithiasis result from testosterone or DHT. In this study, a 5α-reductase blocker, finasteride, was used to address this question. The most significant finding of our study is the alternations in urinary Ox excretion among the various groups. We found both castration and finasteride administration to significantly lower urinary Ox excretion in EG-treated male rats. This effect was most pronounced in castrated rats. These results suggest that the lithogenic effect of male hormones, by increasing urinary Ox excretion, manifest partially from the effects of DHT.

Urinary calcium excretion decreased in all EG-treated groups except the castrated rats (group 3), with a seemingly negative correlation between urinary Ca and urinary Ox excretion. To determine whether urinary Ca concentration may be lowered in treated rats by retention of Ca salts or by Ca binding to other urinary macromolecules by the Whatman #1 filter, we compared three urine pre-treatment methods before urinary ion concentration measurements in 16 additional rats (unpublished data) (1) direct acidification of the unfiltered urine (pH < 2.0) (2) urine filtered with Whatman #1 filter; and (3) urine filtered with a 0.45 μm pore size Millipore filter. We found no significant differences in Ox or PO_4 concentrations between the three methods. The most significant difference noted was in urinary soluble Ca concentration (6.0 mmol/l in method 1 vs approximately 2.0 mmol/l in methods 2 and 3). These results suggest that some of the urinary CaOx crystals, single or aggregated, were retained by the Whatman #1 filter in our study. We chose to filter the urine before sample analysis to minimize the contamination with food and possibly feces that can occasionally occur with the use of metabolic cages. Most commercial rat diets contain 0.5–1.0% of calcium (about 2–4 times the normal rat urinary calcium concentration). Thus, a small dietary contamination of the urine may significantly increase urinary Ca concentration, such as with direct acidification (method 1). However, the total calcium excretion (soluble + sediment retained by the filter, or by direct acidification) was still lower after EG administration than controls, although the mechanisms involved remain unclear.

The daily EG ingestion, urine volume and animal weight gain in group 5 (high-dose finasteride) were the lowest among all study groups. Although one may postulate that the decrease in urinary Ox excretion may be secondary, in part, to decreased EG ingestion in this group, we believe the effect of finasteride is real. This is because a significant decrease in urinary Ox excretion was also noted in rats given low-dose finasteride (group 6 vs group 2).

In the 0.75% EG-treated rat experimental model used in this study, no significant kidney crystal deposition was found. Only two of the 30 EG-treated rats (7%) developed CaOx crystal deposits in the kidneys. Whole kidney tissue Ca, Ox and PO_4 concentrations remained unchanged unless microscopic detectable crystal deposition also occurred. The reason for the low kidney crystal deposition rate might be because of the higher magnesium concentration in the Agway 3000 diet. To investigate the effect of finasteride on kidney crystal deposition, a different rat urolithiasis model would be necessary. The use of a rat diet with a lower magnesium content, such as the AIN-76 diet, may be more suitable for that purpose [7].

Tiselius et al. [20] have reported that orchiectomy or estrogen treatment in male prostate cancer patients does not alter urinary Ox excretion. However, their study was performed in a patient population with an average age greater than 70 years; serum testosterone levels are known to decline after age 70 [3]. As pre-orchiectomy serum testosterone was not measured in these patients and the dietary Ox uncontrolled, the effect of sex hormones on human urinary Ox excretion remains unclear. Another possibility is that the effect of sex hormones on Ox metabolism may only become clinically significant under conditions of high Ox load, such as with increased gastrointestinal absorption of Ox.

In conclusion, castration or finasteride administration blunts the hyperoxaluria response of EG administration to male rats. Thus, DHT appears to be partially involved in increased hepatic Ox synthesis and/or enhanced tubular Ox secretion in this experimental model of urolithiasis. The precise mechanisms by which the male hormones affect urinary Ox excretion need to be further investigated. Furthermore, clinical testing of finasteride for the prevention of recurrent CaOx urolithiasis may be justified based on the result of this study.

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