The Soy Effect in the Disease Models of Nonbacterial Prostatitis and Obstructive Voiding

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The goal of this study was to improve the understanding of the potential significance of dietary soy for human health by investigating its effects in the animal models of nonbacterial prostatitis and urethral obstruction. Nonbacterial prostatitis was induced in adult Noble rats with the combined treatment of testosterone and 17β-estradiol. The inflammatory foci categorized into three forms were counted and correlated with expression of an estrogen-responsive gene, progesterone receptor (PR), in the dorsolateral lobes of the rats on soy (+) and soy (−) diets. Development of obstructive voiding after neonatal estrogenization of Noble rats (NeoDES rats) was followed with urodynamic measurements in rats on soy (+) and soy (−) diets. The amounts of genistein and daidzein, two major soy-derived isoflavones, were measured in the urine of Noble rats by the high-performance liquid chromatography–photodiodearray method. Dietary soy decreased the total number of inflammatory foci while no demonstrable effects were seen on the cellular composition of the infiltrates. Soy did not increase the weights of the pituitary gland, testes, or sex accessory glands, but it did increase the number of PR-positive epithelial cells in the dorsolateral prostate. It also decreased the bladder pressures in NeoDES rats but did not increase the flow rates. The soy effects may be mediated by the strong estrogen influence involved in the animal models. Dietary soy had anti-inflammatory effects in the prostate but only marginal effects on the development of obstructive voiding in Noble rats. The anti-inflammatory effects of soy may contribute to the lower prevalence of prostatitis-like symptoms and the historically lower risk of benign prostatic hyperplasia in Japan; however, no evidence was found that regular consumption of soy influences the age-related development of lower urinary tract symptoms or decline of flow rate. Exp Biol Med 232:674–681, 2007

Key words: soy; prostatitis; obstructive voiding; LUTS

Introduction

Chronic nonbacterial prostatitis (CP) has been implicated in the development of human benign prostatic hyperplasia (BPH) (1–3). The prevention of CP reported by Sharma *et al.* (4) in Sprague-Dawley rats on soy diets may be one of the mechanisms through which dietary soy reduces the likelihood of BPH in Asian men, who have a low incidence of BPH (5, 6). The lower prevalence rates of prostatitis-like symptoms (7) may also mean lower prevalence rates of obstructive voiding, which is often found in association with CP (8). There is no confirmatory clinical data to support the idea that regular consumption of soy prevents the development of human CP/chronic pelvic pain syndrome or obstructive voiding. To the best of our knowledge, no studies have been published about the possible effects of dietary soy or its constituents on the voiding of men or laboratory animals. Since there are no known modifiable risk factors for CP or BPH, identifying dietary changes that can reduce the risks is of importance.

It is assumed that dietary soy contains substances, particularly isoflavones, that are capable of modulating the responses of tissues to estrogens selectively. Therefore, two estrogen-related animal models were chosen to demonstrate the possible beneficial effects of dietary soy. The anti-inflammatory action was studied in adult Noble rats with CP induced with the combined treatment of estradiol and testosterone (9). The combined hormone treatment results in decreased testosterone and increased estradiol concentrations in serum that mimics the age-related hormonal changes in men. Neonatal Noble rats were estrogenized with

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diethylstilbestrol (neoDES rats) and were used to test the possible chemopreventive action of dietary soy on the development of obstructive voiding (10).

Materials and Methods

Adult male Noble rats (NBL/Cr), weighing 270–320 g, were obtained from Charles River (Raleigh, NC). The study plan was approved by the Animal Care and Use Committee at the University of Turku. The animals were maintained under standard laboratory conditions under 12:12-hr light:-dark cycle. They had free access to feed pellets and tap water.

Animal Model for CP. CP was induced in Noble rats with a combined treatment of testosterone (0.24 mg/day) and estradiol (0.07 mg/day). Hormones were administered via subcutaneous pellets (17β-estradiol 5 mg/60-day release; testosterone 15 mg/60-day release; Innovative Research of America, Inc., Sarasota, FL). The hormone treatment resulted in elevated estradiol and lowered or normal testosterone concentrations in serum, mimicking the age-related hormonal changes in men (9). Anesthesia for the implantation was induced with xylazine (20 mg/ml; Bayer, Leverkusen, Germany) and ketamine (50 mg/ml; Pfizer Oy, Espoo, Finland).

Quantification of the Inflammatory Foci. Tissue blocks containing the dorsolateral lobes of the prostate (DLP) with a cross-section of proximal urethra were dissected from the rats. Tissues were immediately immersed in 10% buffered formalin for 24 hrs at room temperature. After fixation, the samples were dehydrated in ethanol, cleared in xylene, and embedded in paraffin. At 500-μm intervals, 5-μm sections were cut perpendicular to the longitudinal urethral axis. Then the sections were stained with hematoxylin and eosin. Stained sections were photographed with an Olympus DP-10 camera under an Olympus SZX9 microscope (Olympus Optical Co., Ltd., Tokyo, Japan).

The histopathologic classification and counting system of inflammatory infiltrates proposed by Nickel *et al.* (11) was used with some modifications. Inflammatory foci were divided into three different categories: perivascular (inflammatory cells tightly around the blood capillaries), stromal (inflammatory cells in the stroma between the glands), and glandular (inflammatory cells in the epithelium and inside the lumen of the glands). The total number of foci in each category was counted in six histologic sections of DLP of each animal. Sections were screened by two independent observers who worked blindly.

Immunohistochemical Staining of Progesterone Receptor (PR). A PR antibody (DAKO, Glostrup, Denmark) was used as a marker of estrogen action in the prostate (12–14). Slides were dewaxed and rehydrated. After washing in water, sections underwent antigen retrieval in a microwave oven in 10m*M* sodium citrate buffer (pH 6.0) for 15 mins. Endogenic peroxidase activity was blocked with 1% H_2O_2 in phosphate-buffered saline (PBS) for 20 mins. The PR antibody was diluted 1:400 in PBS with 3% bovine serum albumin and 0.05% Tween. The sections were incubated with primary antibodies overnight at 4°C and then with horseradish peroxidase–conjugated antibody for 30 mins using the DAKO Envision+ System. The slides were rinsed with PBS. Color was developed with a diaminobenzidine substrate (DAKO). These sections were then slightly counterstained with Mayer hematoxylin, dehydrated, and mounted. The proportional score of positively stained cells was evaluated and given a score of 0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining, or 4 = intense staining. The proportional score reflected the number of nuclear PR-positive epithelial cells in the acini of DLPs.

Study Protocol and Experimental Diets. To test the possible anti-inflammatory actions of soy, 12-week-old Noble rats (n = 5–6 per group) were maintained on RM3 soy (–) or soy (+) diets (SDS, Witham, UK) for 9 weeks. The rats were maintained on open-formula RM3 soy (–) diet before the experiment and transferred onto the soy (+) diet 2 weeks before hormone implantation. Soy (+) included 7.61% extracted and toasted soy protein and 4.25% soy oil.[1] The open-formula, soy-free diet (soy [–]) that was used as a control diet included maize gluten as the main protein source and corn oil.[2] The animals were sacrificed by CO_2 suffocation followed by neck dislocation at 9 weeks after implantation (11 weeks after the transfer to the experimental soy-containing diet). After sacrifice, body, mean testes, and pituitary gland weights were recorded.

Analysis of Intake and Urinary Excretion of Isoflavones. The intake values were estimated based on isoflavone content of the feed and the amount of feed consumed by the animals. Isoflavone content of soy (+) feed was calculated according to Odum *et al.* (15). Daily excretion of isoflavones in urine was monitored by collecting individual 24-hr urine samples during the last week before sacrifice. There were 120 μl of ascorbic acid (100 mg/ml in H_2O) and 120 μl of sodium azide (10 mg/ml in H_2O) in the collection jars of the metabolic cages for preserving the samples. The volumes of the centrifuged and filtrated urine samples were recorded, and the samples were stored at –20°C.

Urine samples were pretreated as described previously (16) with slight modifications. Briefly, 0.5 ml of urine was buffered with 0.15 *M* sodium acetate (pH 4.0) and incubated

[1]The composition of the RM3 soy (+) diet as reported by the manufacturer is moisture 10.0%, crude oil 4.25%, crude protein 22.39%, crude fiber 4.21%, ash 7.56%, and nitrogen-free extract 51.20%. The protein percentage coming from each raw material is barley 1.2%, fish meal 4.96%, soy 7.61%, wheat 3.29%, wheat feed 3.94%, whey powder 0.30%, yeast powder 0.91%, premix (amino acids) 0.14%, and maize gluten 0.00%.

[2]The composition of the RM3 soy (–) diet as reported by the manufacturer is moisture 10.0%, crude oil 4.72%, crude protein 23.05%, crude fiber 3.25%, ash 7.89%, and nitrogen-free extract 50.66%. The protein percentage coming from each raw material is barley 1.93%, fish meal 6.63%, soy 0.00%, wheat 3.37%, wheat feed 2.37%, whey powder 0.61%, yeast powder 1.15%, premix (amino acids) 0.14%, and maize gluten 6.85%.

overnight at 37°C with *Helix pomatia* to hydrolyze the isoflavone conjugates. Both samples and standards were extracted with methanol using conditioned and equilibrated solid-phase vacuum extraction columns (Sep-Pak Vac 3cc tC18; Waters Ltd., Elstree, UK). Methanol was evaporated in a warm bath with nitrogen gas, and thereafter the residues were redissolved in high-performance liquid chromatography (HPLC) mobile phase.

HPLC (2695 separation module; Waters Ltd.) coupled to a photodiodearray (PDA) detector (2996 PDA detector) was used for quantifying the isoflavone contents in urine. Symmetry C_{18} columns (4.5 × 75 mm with 3.5-μm particles) were used. The mobile phase consisted of two eluents: A (50 m*M* sodium acetate buffer [pH 5.0]/methanol/acetonitrile, 40/40/20) and B (50 m*M* sodium acetate buffer [pH 5.0]/methanol, 80/20). The separation of daidzein and genistein was performed at room temperature in a gradient run as previously described (17). The flow rate was 0.60 ml/min and injection volume was 50 μl. The retention times were approximately 16.0 mins for daidzein and 19.9 mins for genistein.

Animal Model for Urethral Dyssynergia. Male Noble rats were treated neonatally with 10 μg of DES (Sigma-Aldrich, St. Louis, MO) dissolved in rapeseed oil (Raisio Co., Raisio, Finland). Forty microliters of the solution was administered subcutaneously daily on Days 1–5 of postnatal life. Neonatal exposure to DES estrogenizes male rats and predisposes them to reversible urethral dyssynergia (10, 18). By definition, urethral dyssynergia means inappropriate contraction or failure of complete relaxation of the urethral musculature during the detrusor contraction. Maximal and mean flow rates were decreased significantly in neoDES rats which is consistent with a failure in the opening mechanisms of the urethra. These animals had increased bladder pressure, determined by the maximal and mean bladder pressures. Voiding was still possible but often micturition consisted of several voidings, which resulted in significantly increased micturition time. Neonatal estrogenization also caused extensive inflammation covering the whole prostate. The counting of the individual inflammatory foci was not feasible.

The initial diet for all animals was soy (–). Half of the dams were transferred onto soy (+) 2 weeks before fertilization, and the second half continued with the original soy (–) diet. Afterwards the pups continued with either soy (–) or soy (+) diets, until measurements, which were performed at 5–6.5 months.

Urodynamic Recordings. The urodynamics of the rats were recorded under anesthesia. Intraperitoneal injection of chloral hydrate (0.9 g/kg; Sigma-Aldrich) was used as a basic anesthesia. Anesthesia was maintained with intravenous urethane (0.32 g/kg; Sigma-Aldrich), if needed. Body temperature was kept constant at 36°C–38°C by means of a thermostatically controlled animal blanket (Harvard Apparatus Ltd., Edgenbridge, UK) and heating lamp, if needed. The bladder and distal urethra were exposed by a midline incision of the lower abdomen. To measure the bladder pressure, a 20-gauge intravenous cannula was inserted through the bladder apex into the lumen (19). The cannula was connected to an infusion pump (SP 100i Syringe Pump; World Precision Instruments, Inc., Sarasota, FL) and pressure transducer (P23XL; Statham Instruments, Hato Ray, Puerto Rico). The pressure transducer was connected to an amplifier (Grass Instruments, Quincy, MA). The whole system was filled with 37°C saline (0.9% NaCl). Micturition was physiologically evoked by continuous infusion (0.185 ml/min) of saline into the bladder after an equilibration period (10 mins).

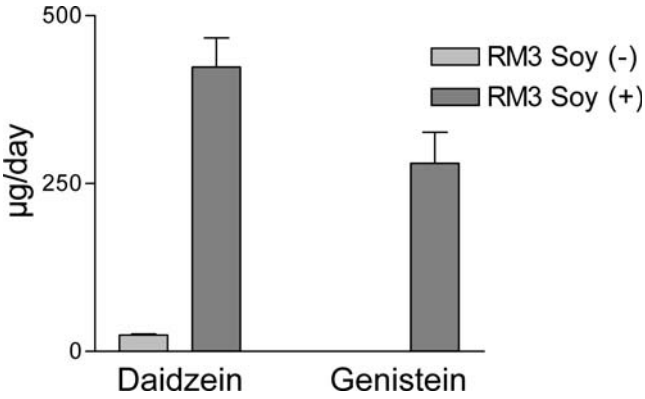

Figure 1. The total amounts of daidzein and genistein excreted daily in the urine of hormone-treated rats maintained on soy (–) and soy (+) diets for 2 plus 9 weeks. The daily urine was collected in metabolic chambers. Isoflavones and genistein contents (g/day) were analyzed with HPLC-PDA.

The urine flow rate was measured by using an ultrasonic flow probe (Transonic Systems, Inc., Ithaca, NY). The probe was placed around the distal urethra and connected to a flow meter (Transonic Systems, Inc.) (10, 20). Continuous urodynamics were recorded by Acq Knowledge 3.5.3 (MP100 Manager; BIOPAC Systems, Inc., Goleta, CA).

Statistical Analysis. Statistical analyses were conducted with GraphPad Prism 3.02 (GraphPad Software, San Diego, CA). Data was assessed by using the Kolmogorov-Smirnov normality test for normal distribution. In normally distributed data, one-way analysis of variance (ANOVA) and Tukey's multiple comparison test were used to compare statistical differences among the groups. The unpaired *t* test was used for comparison of perivascular, stromal, and glandular inflammation categories. All data were represented as group means ± SD. Values of $P < 0.05$ were considered statistically significant.

For the urodynamic data, the normal distribution was checked with Shapiro-Wilk's *W* normality test. If the data was normally distributed, one-way ANOVA and Tukey's HSD test were used to compare the statistical differences among the groups. If the data was not normally distributed, the Kruskall-Wallis test was used with Mann-Whitney *U* test as a post hoc test (Statistica 5.1; StatSoft, Inc., Tulsa, OK).

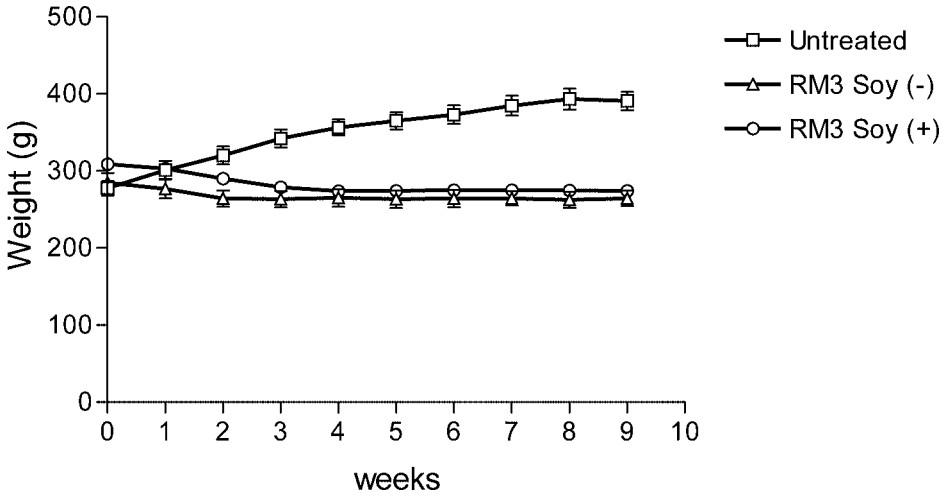

Figure 2. Body weights of nontreated and hormone-treated Noble rats maintained on soy (–) and soy (+) diets for 9 weeks. No significant differences were found between the soy (–) and soy (+) groups.

Results

Effects of Soy Diet in an Animal Model for CP. *Daily Intake and Urinary Excretion of Isoflavones.* As expected, animals on the soy (+) diet excreted significant amounts of isoflavones (Fig. 1). The relative amounts of genistein and daidzein in the urine of animals on the soy-containing diet corresponded approximately to their contents in the soy-containing feed. In all animals, the urinary excretion of daidzein was greater than that of genistein. Animals on the soy (–) diet excreted only trace amounts of daidzein in the urine. The daily doses of genistein and daidzein in the soy (+) diet were calculated to be 1.1 mg/day and 1.8 mg/day, respectively, when the daily intake of feed was 17.3 g/day. These amounts considerably exceed the consumption of soy protein (more than a 10-fold difference) or isoflavones (more than double) by Asian populations (21).

Body and Organ Weights. Hormone implantation retarded the growth of the rats (Fig. 2). No differences in weight gain were seen between the animals on the soy (–) and soy (+) diets (Table 1). Hormone treatments *via* implants increased the relative weights of the pituitary glands (Table 1). A decrease was observed in the absolute and relative weights of the testes (Table 1) and accessory sex glands (data not shown). Dietary soy further decreased the relative weights of the testes but had no statistically significant effect on the weights of the pituitary glands (Table 1) or accessory sex glands (data not shown).

Anti-Inflammatory Effects of Dietary Soy. The development of nonbacterial inflammation in the DLP has been described in detail elsewhere (9). In summary, inflammation developed from perivascular (Fig. 3b) to stromal (Fig. 3c) and finally to glandular form (Fig. 3d) in 3–9 weeks. Immunocytochemical stainings confirmed that the lymphocytes were T cells. The cells found in perivascular and periglandular spaces and stroma were predominantly CD3+ cells. CD8+ cells were mostly found intraepithelially. Leukocytes were observed in the glandular lumina. A few scattered infiltrates of lymphocytes were seen in untreated animals (Fig. 3a). The total number of inflammatory foci was reduced in hormone-treated rats on the soy (+) diet (Fig. 4a). The number of foci was significantly decreased (Fig. 4b) in each category (perivascular, stromal, and glandular inflammation). Dietary soy had no demonstrable effects on cellular composition of the infiltrates.

Table 1. Body,[a] Relative Pituitary Gland, and Testes Weights[b]

	Untreated soy (–)	*n*	Treated with T + E_2 soy (–)[c]	*n*	Treated with T + E_2 soy (+)[c]	*n*	*P* untreated versus soy (–) and soy (+)	*P* soy (–) and soy (+)
Body weight (g)	390.8 ± 29.04	6	264.5 ± 24.71	6	274.5 ± 7.34	6	<0.001	NS
Relative pituitary weight	3.299 ± 0.15	5	10.24 ± 0.77	5	11.66 ± 3.65	5	<0.001	NS
Absolute testes weight (g)	1.716 ± 0.07	6	0.427 ± 0.02	6	0.347 ± 0.01	6	<0.001	<0.05
Relative testes weight	4.402 ± 0.21	6	1.631 ± 0.18	6	1.263 ± 0.08	6	<0.001	<0.01

[a] Body weights (g) at the end of the treatment period. Significant decrease in body weight of T + E_2–treated Noble rats.
[b] Pituitary gland and mean testes weights were divided by body weights and multiplied by 1000 and 100,000, respectively. Significant differences were found between soy (–) and soy (+) groups compared with controls ($P < 0.001$). The soy (–) group showed significantly higher absolute ($P < 0.01$) and relative ($P < 0.05$) testes weights compared with the soy (+) group. Values are means ± SD.
[c] E_2, estradiol; T, testosterone.

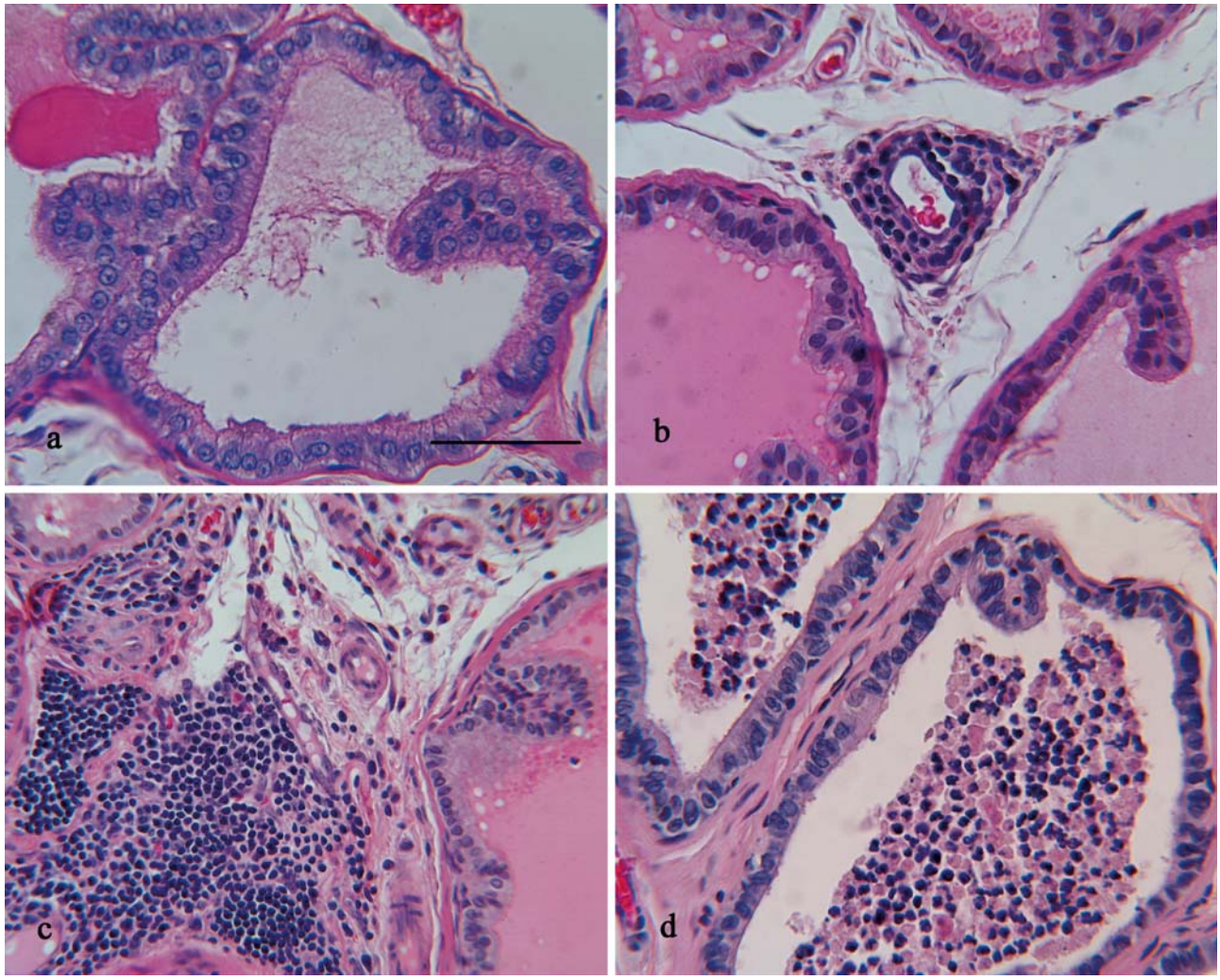

Figure 3. Representative sections of inflammatory changes from the prostates of Noble rats on the soy (–) diet. No significant inflammatory changes were seen in untreated animals (a) on the soy (–) diet. Perivascular (b), stromal (c), and glandular (d) inflammation in the DLPs of Noble rats treated with testosterone plus estradiol and fed with the soy (–) diet. Similar types of inflammatory foci were also observed in the DLPs of rats on the soy (+) diet, but the number of foci was significantly lower (see Fig. 3a and b). Bar, 50 μm.

Number of PR-Positive Cells. No PR-positive cells were found in the DLPs of untreated control animals (Fig. 5a). Hormone treatment induced the expression of this estrogen-responsive gene in both the inflamed and non-inflamed acini of DLPs. PR-positive cells were located solely in the epithelium. Since the staining intensities in the nuclei of epithelial cells were similar for PR staining in different treatment groups, the proportional scores of PR were evaluated. The soy (+) diet increased ($P < 0.01$) the expression of PR (Figs. 5b and c and 6).

Effects of Soy Diet on Voiding. The maximal and mean bladder pressures, as well as the urine flow rates, were recorded during the second phase of micturition (22) in NeoDES rats. During this second phase bladder pressure oscillations, typically seen in rat micturition, are associated with multiple urine flow peaks. As shown earlier (10) and in the present study, the maximal and mean bladder pressures were increased, maximal and mean urine flow rates were decreased, and micturition time was prolonged in NeoDES rats in comparison with nonestrogenized control rats. However, due to high variation, the maximal urine flow rates were not significantly decreased in NeoDES rats in the present study, even though the NeoDES rats had 10 ml/min lower urine flow rates on average (Table 2). In NeoDES rats on the soy (+) diet, the maximal and mean bladder pressures were decreased, compared with rats on the soy (–) diet. No significant changes were seen in maximal and mean flow rates or in the duration of micturition time (Table 2).

Discussion

Dietary soy reduced the number of lymphocyte infiltrates and subsequently had an anti-inflammatory effect in the DLPs of Noble rats. If applicable to man, this anti-inflammatory effect may contribute to the lower prevalence rates of the prostatitis-like symptoms (7, 23) and historically smaller risk of BPH as seen in Japanese men (5, 6). Among

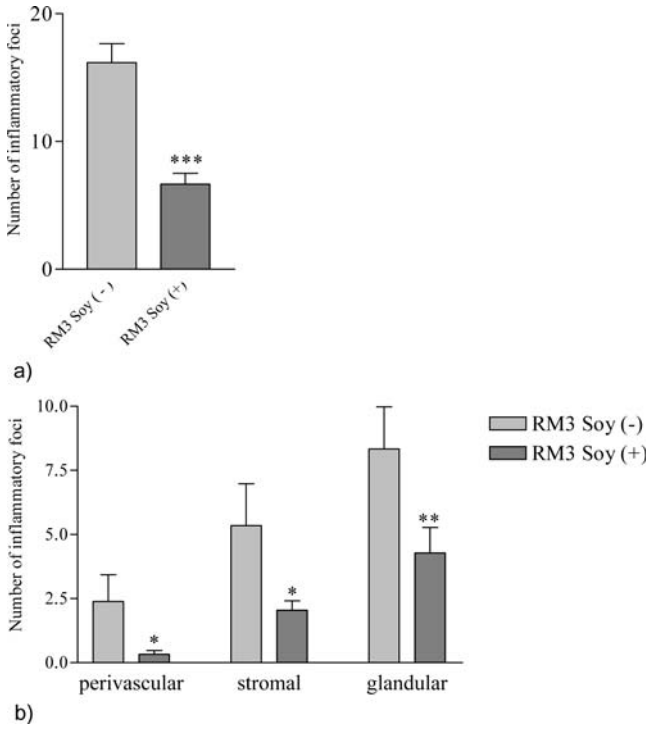

Figure 4. Total number (a) and distribution into different categories of inflammatory foci (b) in the DLPs of Noble rats maintained on soy (–) and soy (+) diets. The total number of inflammatory foci decreased significantly (***$P < 0.001$) in Noble rats maintained on the soy (+) diet. Significant decreases in the number of perivascular and stromal infiltrates (*$P < 0.05$) as well as in the number of inflamed glands (**$P < 0.01$) of Noble rats on the soy (+) diet were also detected.

the putative anti-inflammatory substances present in soy, isoflavones have received the most attention. These weak estrogenic compounds are considered to act as selective estrogen receptor modulators. In breast cancer cells, high isoflavone concentrations are considered to antagonize estrogen action (24). However, it is unlikely that the anti-inflammatory effects of a soy diet are due to the anti-estrogenic action of any soy-derived compounds. It is known that estrogen increases dose-dependent prolactin secretion, which results in an increased prolactin concentration in serum. When males are treated with estradiol, pituitary-enlarging prolactinomas will develop, which is seen as an increase of the glandular size. In the present study, the weight increase of the pituitary gland, due to hormonal manipulation, was not significantly affected in rats after exposure to dietary soy for 9 weeks. In agreement with this, no increase was seen in the weights of the testes either. If soy had been anti-estrogenic, the pituitary gland weights would not have increased and luteinizing hormone and testosterone concentrations and concomitantly testes size would not have decreased. No evidence to support the anti-estrogenicity of soy was obtained from the studies of rats with urethral obstruction either. Life-long exposure to soy had only marginal effects in neoDES rats prone to develop urethral obstructions. Soy treatment decreased

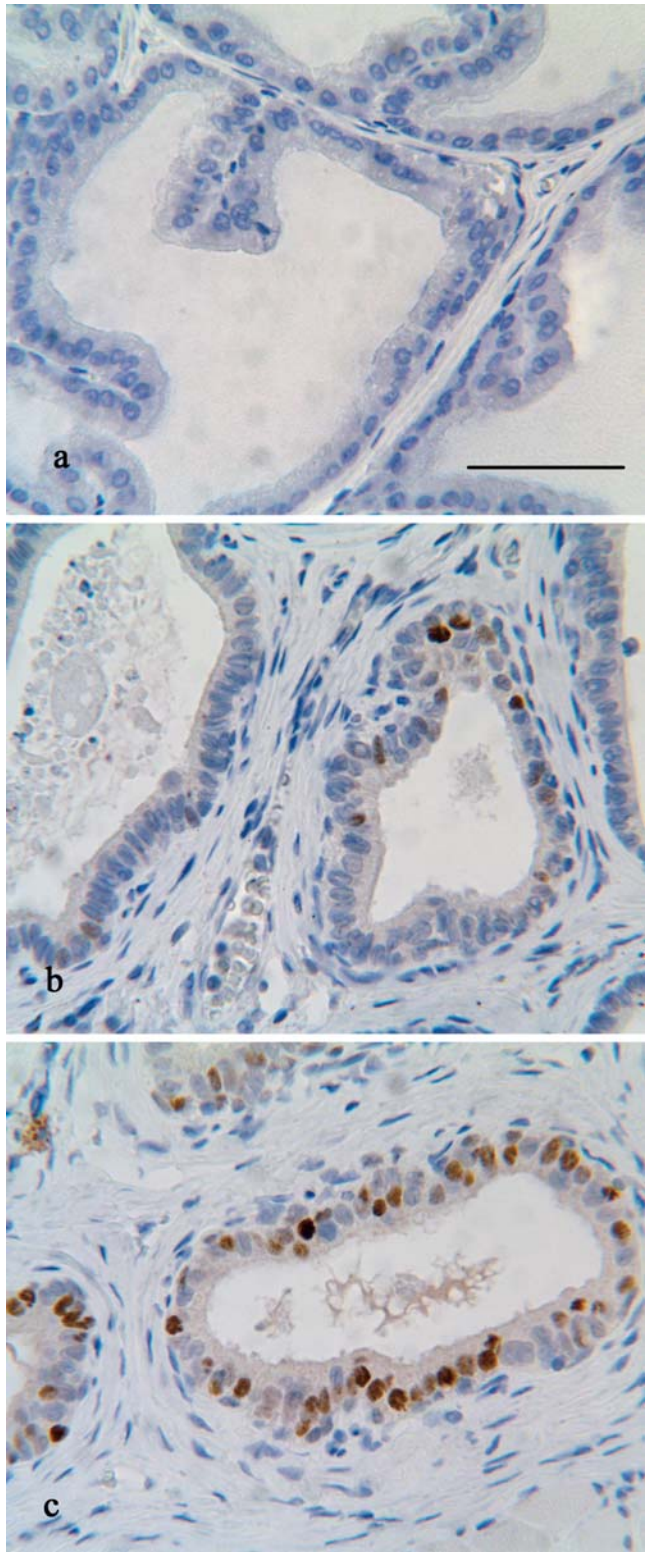

Figure 5. Immunoexpression of PR in the DLPs of Noble rats. No PR-positive cells were observed in untreated animals (a) whereas an increase in PR-expressing epithelial cells in rats on the soy (+) diet (c) was detected compared with rats on the soy (–) diet. Bar, 50 μm.

Table 2. Effects of Soy (–) and Soy (+) Diets on Urodynamic Parameters[a,b]

	Control soy (–)	NeoDES soy (–)	NeoDES soy (+)	*P* control soy (–) versus NeoDES soy (–)	*P* NeoDES soy (–) versus soy (+)
Max BP	37.8 ± 4.77	45.8 ± 6.28	39.2 ± 7.88	0.002 (M)	0.02 (M)
Mean BP	27.9 ± 3.40	35.5 ± 3.52	26.9 ± 3.75	0.0002 (M)	0.003 (M)
Max FR	30.8 ± 12.03	20.5 ± 7.20	23.4 ± 13.39	0.12 (A)	0.85 (M)
Mean FR	4.9 ± 1.91	2.71 ± 1.06	3.1 ± 1.36	0.007 (M)	0.53 (M)
MT	6.9 ± 2.83	10.5 ± 4.42	10.1 ± 2.77	0.03 (M)	0.93 (M)

[a] Values are means ± SD; $n = 8–10$.
[b] BP, bladder pressure (mm Hg); M, Mann-Whitney *U* test; FR, flow rate (ml/min); A, ANOVA; MT, micturition time (secs).

bladder pressures to some extent, but it did not increase flow rates or shorten micturition time. Therefore, soy lacked the typical anti-estrogenic characteristic demonstrated earlier by aromatase inhibitors in neoDES rats (18).

When given in pharmacologic doses (50–500 mg/kg body wt *per os*), extracted isoflavones caused severe stromal and glandular inflammation in rat prostates (25, 26). This indicates that isoflavones in high doses may be estrogenic in the prostate. However, in the present study, the effects of isoflavone-containing dietary soy (increase of PR staining in the prostate, decreased weight of testes but no increase in pituitary weights, no increase in bladder pressure, and no decrease in flow rate) do not provide unequivocal evidence for an estrogen-agonistic effect of dietary soy either. Rather, the hormonal changes were minimal. This is in agreement with the clinical findings of the effects of isoflavones or isoflavone-rich soy products in men (28–32). However, caution should be exercised when drawing conclusions from the findings in the present study. Models based on the administration of 17β-estradiol in doses resulting in highly elevated concentrations in serum compared with controls or with newborns at the estrogen-sensitive stage may not provide optimal conditions for testing of selective estrogenic or anti-estrogenic actions of soy.

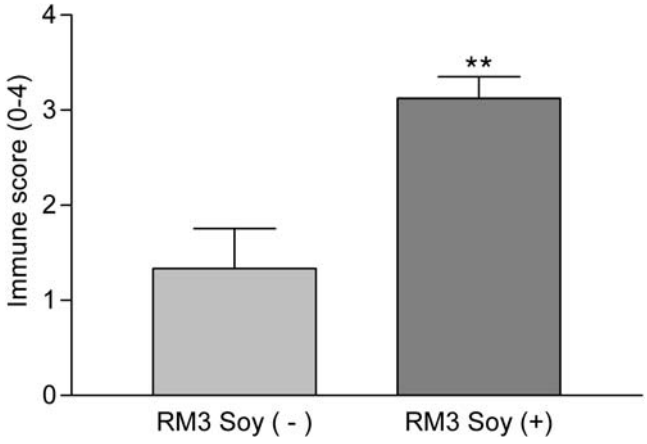

Figure 6. Expression of PR in the prostate of Noble rats. DLPs were examined for nuclear PR positive epithelial cells in the acini. The proportional score of positively stained cells was evaluated and given a score of 0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining, or 4 = intense staining. The PR score was significantly higher (**$P < 0.01$) in the soy (+) group.

Soy was shown earlier to prevent the development of spontaneous prostatitis in rats (4). Neither 4-hydroxyandrostenedione, an aromatase inhibitor, nor tamoxifen, an anti-estrogen, altered the incidence of spontaneous prostatitis, suggesting that estrogen action is not critical for the development of spontaneous prostatitis in rats (33). There appears to be a clear difference in the hormonal responses of spontaneously developing and hormonally induced CP, but in both cases soy had an anti-inflammatory effect. The differences in the soy diets may explain why there was only a partial anti-inflammatory effect in Noble rats. The soy-containing diet in the study of Sharma *et al.* (4) contained 17% soy protein, which is more than double the amount (7.61%) used in the present study. On the other hand, the isoflavone content was much higher in the present study. In both cases, the relative amount of soy protein far exceeds the daily intake of soy protein (25 g) by the top 10% of soy consumers in the Asian population (21). The intake of isoflavones from the soy (+) diet in the present study (~10 mg/kg body wt) also exceeds the typical isoflavone intake in the Asian population (~0.5 mg/kg body wt) (21). The anti-inflammatory effects of soy may also be due to peptides present in soy. Anti-inflammatory peptides present in soy may reduce the bioactivity of pro-inflammatory cytokines such as interleukin 6 or inhibit activation of NF-κB (34, 35).

Soy had marginal effects on voiding in neoDES rats. There were only minor decreases in the bladder pressures during voiding, and the urinary flow rates were not improved at all. The validity of this estrogen-related model for human obstructive voiding has not been confirmed primarily because the role of estrogens in the development of obstructive voiding has not been established. However, this is the only model used so far for testing the effects of soy on voiding dysfunction. This model does not provide any evidence that regular consumption of soy influences the age-related development of lower urinary tract symptoms (LUTS) or the age-related decline in flow rates. These negative results are in agreement with the high prevalence of LUTS and the greater age-related decrease in flow rates of Japanese men compared with American men (5, 36).

In conclusion, dietary soy has been tested for prevention

of the development of prostate inflammation and obstructive voiding in two animal models. Although soy did not appear to beneficially affect voiding in rats neonatally treated with DES, it did have anti-inflammatory activity in the prostates of rats treated with testosterone and estradiol.

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