The Prostate 35:157–164 (1998)

Morphological and Hormonal Changes in the Ventral and Dorsolateral Prostatic Lobes of Rats Treated With Finasteride, a 5-Alpha Reductase Inhibitor

S. Prahalada,[1]* L. Rhodes,[2] S.J. Grossman,[1] D. Heggan,[1] K.P. Keenan,[1] M.A. Cukierski,[1] C.M. Hoe,[1] C. Berman,[2] and M.J. van Zwieten[1]

[1]*Department of Safety Assessment, Merck Research Laboratory, West Point, Pennsylvania*
[2]*Department of Endocrine Pharmacology, Merck Research Laboratory, Rahway, New Jersey*

BACKGROUND. In rats, the prostate is divided into three distinct lobes, and the lobes are dependent on androgens [testosterone (T) and dihydrotestosterone (DHT)] as trophic hormones. However, the reasons for the difference in the incidence of proliferative changes reported are not well-understood. Administration of finasteride, a 5-alpha reductase (5αR) inhibitor which selectively inhibits the conversion of T to DHT, results in elevated intraprostatic T levels. However, long-term (2 years) administration of finasteride results in no increase in proliferative changes in the ventral lobes of the rat prostate. Therefore, studies were designed to determine the differences in intraprostatic hormonal levels, morphology, and 5αR activity in different lobes of the rat prostate.

METHODS. Sexually mature male Sprague-Dawley rats were used in all studies. Finasteride was administered orally to rats. The methodology included determination of intraprostatic T and DHT levels by radioimmunoassay, qualitative and quantitative evaluation of prostatic morphology, and in vitro determination of 5αR activities in rat prostatic lobes.

RESULTS. A significant amount of 5αR activity was observed in the dorsal, ventral, and lateral lobes of the rat prostate. Both 5αR isozymes (types 1 and 2) were present in all lobes, based on 5αR activities observed at both acidic and neutral pH. Oral administration of finasteride (160 mg/kg/day) for 15 days resulted in significant ($P \leq 0.001$) decreases in intraprostatic DHT levels and increases in T levels; when compared to controls, the mean decrease in DHT levels in the ventral and the dorsolateral lobes was 86% and 94%, respectively, and the mean increase in T levels in the ventral and the dorsolateral lobes was approximately 3 times and 20 times, respectively, higher than in controls. Chronic administration of finasteride (80 mg/kg/day) for 6 months resulted in significant ($P \leq 0.001$) decreases in the weights of the prostatic lobes, which correlated with significant ($P \leq 0.001$) decreases in the total number of epithelial and stromal cells per gland in both the ventral and dorsolateral lobes of the prostate. There were no qualitative differences in prostatic morphology between the control and finasteride-treated groups. A short-term study in control rats exposed to bromodeoxyuridine (Brdu) showed that the number of Brdu-labeled cells in the dorsolateral lobe was significantly ($P \leq 0.05$) greater than in the ventral lobe.

CONCLUSIONS. This first comparative study has highlighted some of the similarities and differences among the prostatic lobes of the rat. Inhibition of conversion of T to DHT with finasteride resulted in a significant increase in intraprostatic T levels and a significant decrease

*Correspondence to: S. Prahalada, Department of Safety Assessment, WP45-232, Merck Research Laboratory, Merck and Co., Inc., Sumneytown Pike, West Point, PA 19486. E-mail: Srinivasa_Prahalada@merck.com

Received 15 April 1997; Accepted 2 October 1997

in DHT levels in rats; despite a significant increase in intraprostatic T levels, the prostate remained atrophic, indicating that DHT alone has a trophic effect on the prostate. *Prostate 35:157–164, 1998.*

KEY WORDS: **5α-reductase; finasteride; rat; prostatic lobes; histomorphology; testosterone; dihydrotestosterone**

INTRODUCTION

In rats, the prostate is divided into distinct ventral, dorsal, and lateral lobes. The coagulating gland closely attached to the seminal vesicles is also referred to as the anterior lobe of the prostate. The ventral lobe is the most commonly evaluated among the prostatic lobes in rats. Although the morphological differences among these lobes have been described in detail [1–4], there have been only limited comparative physiological and pharmacological studies in rats [2,5,6]. In man, the prostate is not divided into distinct lobes, but is divided into zones that appear to have morphological, functional, and pathological significance [7].

In rats, the spontaneous and experimentally induced proliferative changes in the prostate have been studied in detail. In aging rats, the incidence of spontaneous focal hyperplasia and neoplasia vary depending on the strain of rat, and the lesions have generally been described to involve the ventral lobe of the prostate; in contrast, in experimentally-induced models, including those where the tumors were induced and/or promoted with high doses of testosterone (T), the dorsolateral lobe seems to be commonly affected [8–12]. Although all three prostatic lobes are dependent on androgen as a trophic hormone, the reason for the difference in the incidence of proliferative lesions in different lobes is unknown. One of the concerns raised based on rat tumor model studies was that the elevated intraprostatic T levels promoted prostate cancer [9]; however, in these studies, the potential contribution of dihydrotestosterone (DHT) alone, a potent prostatic androgen, was not evaluated, e.g., by inhibiting the conversion of intraprostatic T to DHT. Since finasteride, a 5-alpha reductase (5αR) inhibitor, selectively inhibits formation of a potent prostatic androgen (e.g., DHT) without interfering with T function, its use enabled us to study the effect of DHT inhibition on different prostatic lobes in rats. In rats, finasteride inhibits both isozymes of 5αR (types 1 and 2); thus, it was expected to cause maximum inhibition of prostatic DHT production in this species [13]. Long-term treatment of rats (1–2 years) with finasteride has demonstrated that inhibition of conversion of T to DHT resulted in marked decrease in the weight of the ventral lobe of the prostate as well as a significant decrease in prostatic glandular and stromal compartments; there was no increase in proliferative changes in any of the prostatic lobes [14]. To further understand the pharmacological effects of finasteride on rat prostatic lobes, studies were designed with the following objectives: 1) to determine the T and DHT levels in prostatic lobes of control and finasteride-treated rats, 2) to evaluate morphometric changes in ventral and dorsolateral lobes of the prostate following chronic administration of finasteride, and 3) to determine the types of 5αR activity in different prostatic lobes.

MATERIALS AND METHODS

Intact male Sprague-Dawley rats (CRL:CD[SD]BR) were used in all studies. General care and maintenance of animals in this colony were similar to the procedures described in detail earlier [14]. Protocol of the studies was approved by the Merck Institutional Animal Care and Use Committee.

Fifteen-Day Serum and Tissue Testosterone and Dihydrotestosterone Study

A total of 24 sexually mature (101 days old at study initiation) male rats weighing 385–529 g were obtained from Charles River Laboratories (Raleigh, NC) for this study. Rats were randomly divided equally (12 rats/group) into a vehicle control group and a finasteride-treated group. Control rats received the vehicle (0.5% methylcellulose, Dow Chemical Co., Midland, MI). Finasteride was administered at a dose of 160 mg/kg/day as a suspension in 0.5% methylcellulose. Suspensions of drug and vehicle were administered orally at a dosing volume of 5 ml/kg. On day 15 of the study, all rats were euthanized approximately 3–4 hr after the last dose. At necropsy, caval blood samples were taken for determination of serum T and DHT levels. Dorsolateral and ventral lobes of the prostate were removed, weighed, frozen in liquid nitrogen, and stored at –70°C until assayed for T and DHT levels.

Serum and tissue T and DHT levels from a total of 8 rats in each group were determined by radioimmunoassay (RIA), using methods previously described [15]. Briefly, samples were extracted using ethyl acetate, and for tissue samples, extracts were passed over a C8 solid-phase extraction column (Varian Sample Preparation Products, Harbor City, CA) and eluted. HPLC separation of the samples was then per-

formed to separate T and DHT for analysis. For calculations of recoveries for serum and tissue assays, samples of female sheep sera or homogenized rat prostate tissue were spiked with 200 pg of both ^{3}H-T and ^{3}H-DHT, and were run with each assay. Values were corrected for recoveries of ^{3}H-T and ^{3}H-DHT. For serum, mean recoveries (± standard deviation, SD) for T and DHT were 55 ± 4.5% and 44 ± 5.1%, respectively. For tissue samples, the mean (± SD) recoveries for T and DHT were 55 ± 4.3% and 40 ± 10.4%, respectively. The limit of detection of the assay was 8 pg/ml. For serum, the interassay coefficient of variation was 23% (n = 19) and 32% (n = 19) for T and DHT, respectively, while the intraassay coefficient of variation was 8.2% and 11.7% for T and DHT, respectively. For tissue, the interassay coefficient of variation was 26.7% (n = 16) and 13.7% (n = 16) for T and DHT, respectively, while the intraassay coefficient of variation was 16.7% and 8.1% for T and DHT, respectively.

Qualitative and Quantitative Evaluation of Prostatic Histomorphology

In another study, rats (10 rats/group) were treated chronically for approximately 6 months prior to necropsy with either vehicle or 80 mg/kg/day oral finasteride; details of the study design were published elsewhere [16]. Prostatic lobes were fixed and stored in 10% neutral buffered formalin, weighed, embedded in paraffin blocks, cut at 3 μm thickness, and stained with trichrome stain. The tissue sections were examined by light microscopy for qualitative changes, and the differences were quantitated by determination of volume fractions of the prostatic glandular (epithelium and lumen) and stromal (fibrovascular tissue and smooth muscle) compartments as well as the epithelial and stromal cell numbers, using a stereology procedure described previously [14].

Prostatic Cell Proliferation in Control Rats

In a third study, a total of 12 sexually mature male rats was dosed daily with 0.5% methylcellulose for 15 days. Five days prior to euthanasia, rats were anesthetized with ketamine/xylazine mixture and subcutaneously implanted with an Alza osmotic minipump (Alza Corporation, Palo Alto, CA; model 2ml-1) loaded (50 mg/ml) with bromodeoxyuridine (Brdu). The pump was placed via a small dorsal midline skin incision that was closed with surgical staples. Five days later, at necropsy, both ventral and dorsolateral lobes were collected and processed for routine histology and Brdu staining. A total of 2,000 nuclei in each prostatic lobe was counted, and the number of Brdu-labeled cells was expressed as a percent of labeled cells.

Characterization of Prostatic 5αR Enzymatic Activity

Tissues were obtained from sexually mature male Sprague-Dawley rats at approximately 14 weeks of age. The animals were euthanized with CO_2. The tissues (ventral, dorsal, and lateral prostatic lobes, epididymis, and hypothalamic region) were removed, carefully dissected, and weighed. Homogenates of the tissue were prepared in 250 mM sucrose, 40 mM phosphate, 25 mM potassium chloride, and 5 mM magnesium sulfate buffer, pH 6.5, and were frozen at –70°C until time of analysis.

To determine pH vs. rate profiles, tissue homogenates (ca. 0.02–0.5 mg protein), 7-^{3}H-testosterone (1 μCi, 100 pmol), and buffer (33 mM succinate, 44 mM imidazole, and 44 mM diethanolamine, pH 4.5–7.5) at a total volume of 0.1 ml were preincubated at 37°C for 4 min. NADPH (50 nmol) was added and the reactions were allowed to proceed for 20 min (10 min for epididymis). The reaction was stopped by extracting the products into 0.3 ml of hexane/ethyl acetate (70:30). Reaction products were assayed by chromatography on a 120 × 4.6 mm silica column with hexane/ethyl acetate (70:30) as the eluant. The radiolabeled products were monitored with an on-line scintillation counter (Beckman Instruments, Fullerton, CA; Beckman 171) that had been calibrated with known amounts of ^{3}H-dihydrotestosterone and ^{3}H-androstanediol (New England Nuclear Research Products, Boston, MA). Reaction rates of 5α reduced metabolite formation (dihydrotestosterone and androstanediol) were normalized for protein concentration (as determined by DC protein assay, Bio-Rad Laboratories, Hercules, CA) and are expressed as pmol/min/mg protein.

Determination of Michaelis Constant (Km)

The determination of Km was performed in a manner similar to that of the assay described above. Less protein was used (0.1 mg/ml) in the presence of variable amounts of ^{3}H-testosterone in a total volume of 0.5 ml. The testosterone concentration range for type 1 5αR activity (pH 6.5) was 200–4,000 nM, while that for type 2 5αR activity (pH 5.0) was 20–400 nM. Reaction velocity as a function of testosterone concentration was computer-fitted to the Michaelis-Menten equation by least squares analysis (Enzfitter, Biosoft, Ferguson, MO).

Statistical Analysis

Prostatic weights from the 15-day study were analyzed for normality using the W statistics of Wilk and Shapiro [17], and for homogeneity using Levene's test [18]; analysis of variance was done by Tukey's trend

test [19]. The serum and tissue hormone data and Brdu labeling data were analyzed by a two-sample *t*-test [20]. Morphometric data were rankit transformed [21] and then compared by a two-sample *t*-test. All *P* values were two-sided and were deemed significant at $P = 0.05$.

RESULTS

Effect of Finasteride on Serum and Prostatic T and DHT Levels

Administration of finasteride (160 mg/kg/day) for 15 days resulted in a significant ($P < 0.001$) decrease in circulating DHT levels; the magnitude of decrease in the mean DHT level was approximately 98% compared to the vehicle-treated group (Fig. 1). In the finasteride-treated rats, there was an associated increase in serum T levels (Fig. 1); however, the observed increase (mean 82%) was not statistically significant ($P > 0.05$). Administration of finasteride resulted in a significant ($P < 0.001$) decrease in prostatic DHT levels, with an associated significant ($P \leqslant 0.001$) increase in T levels (Fig. 2). The magnitude of mean decreases in DHT levels was 86% and 94% in dorsolateral and ventral lobes, respectively. The magnitude of mean increases in prostatic T levels was 279% and 2,004% in the ventral and dorsolateral lobes, respectively (Fig. 2). In this study, the observed decreases in prostatic DHT levels in both prostatic lobes correlated with the observed significant ($P < 0.001$) decreases in the prostatic weights of finasteride-treated rats; the magnitude of mean decreases in weights was 39% and 46% in the dorsolateral and ventral lobes, respectively (Fig. 3).

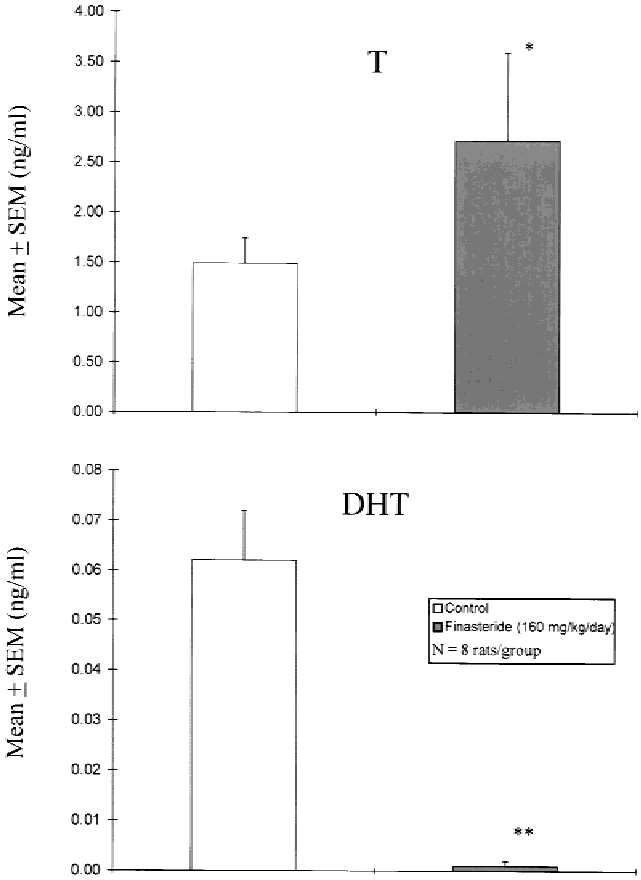

Fig. 1. Serum dihydrotestosterone (DHT) and testosterone (T) levels in rats treated with finasteride (160 mg/kg/day) for 15 days. A significant (**$P < 0.001$) decrease in serum DHT levels and a nonsignificant (*$P > 0.05$) increase in serum T levels occurred, as compared to vehicle control.

Effects of Finasteride on Prostatic Morphology

Oral administration of finasteride (80 mg/kg/day) for 6 months resulted in a significant ($P < 0.001$) decrease in the weight (volume) of both prostatic lobes; the mean decreases were 46% and 67% in dorsolateral and ventral lobes, respectively (Table I). There were no qualitative light microscopic changes in finasteride-treated rats. However, the morphometric analysis showed that the decreased prostatic weights were associated with a corresponding decrease in the total prostatic glandular and stromal compartments. Although the epithelial and stromal cell densities expressed as number of cells per gram of prostate showed no change (ventral lobe) or a slight but statistically significant ($P < 0.05$) increase (dorsolateral lobe), there was a highly significant ($P < 0.001$) decrease in the total number of epithelial and stromal cells per total gland in both the ventral and dorsolateral prostatic lobes of the rats treated chronically with finasteride (Table I).

Brdu-Labeled Cells in Prostatic Lobes of Normal Rats

In all animals, Brdu-stained cells were present in both prostatic lobes. The percent of labeled cells in the ventral lobe ranged from 0.55–2% (mean, 1.23%), and in the dorsolateral lobe it ranged from 1.3–5.85% (mean, 2.98%). The number of Brdu-labeled cells in the dorsolateral lobe was significantly ($P < 0.05$) greater than in the ventral lobe.

Prostatic Isozymes in Rats

The distribution of 5αR isozymes in rats varied with the tissue studied. The two extremes are illustrated in Figure 4 for hypothalamus (type 1) and epididymis (type 2), respectively. Tissue from the hypo-

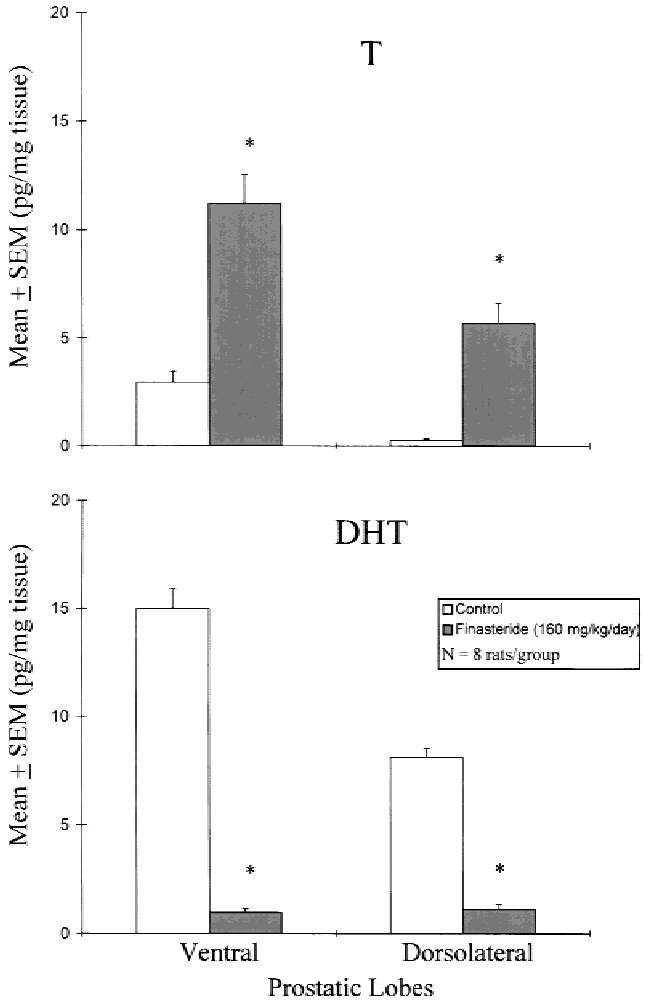

Fig. 2. Prostatic T and DHT levels in rats treated with finasteride (160 mg/kg/day) for 15 days. A significant (*$P \leq 0.001$) decrease in tissue DHT levels and a significant (*$P < 0.001$) increase in tissue T levels were observed in both the ventral and dorsolateral lobes of the prostate.

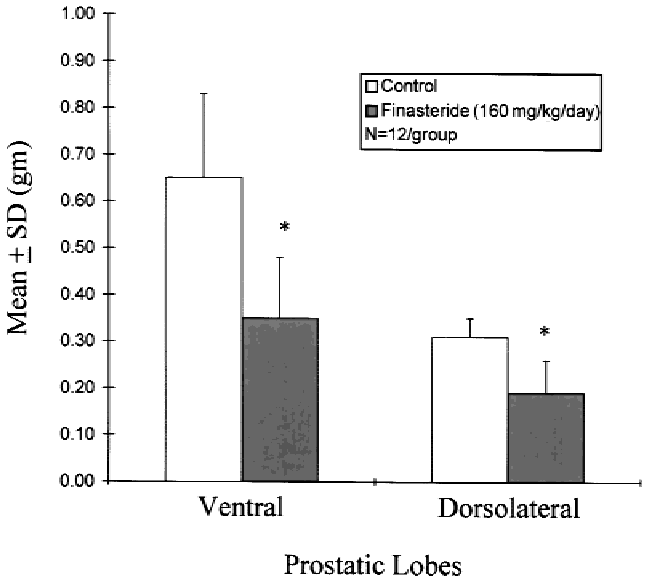

Fig. 3. Prostatic weights in rats treated with finasteride (160 mg/kg/day) for 15 days. A significant (*$P < 0.001$) decrease in the weights of both prostatic lobes (ventral and dorsolateral) was observed in finasteride-treated rats as compared to vehicle control.

thalamic region expressed considerable activity at neutral pH but was relatively devoid of activity at acidic pH. Epididymal tissue was the opposite, with activity primarily at acidic pH consistent with the known distribution of type 2 isozyme in this tissue [22]. The other tissues in this study appeared to contain both enzymes to variable extents, based on measurable activity across the entire pH range that was studied.

In the ventral prostate, both 5αR isozymes appeared to be present, based on the activities observed at both acidic and neutral pH. The pH vs. rate profile for the lateral prostate was similar to that of the ventral prostate (Fig. 4), although the specific activity was somewhat higher in the lateral lobe. The dorsal prostate also appeared to express both 5αR isozymes, based on the analysis of pH vs. rate profiles (Fig. 4). In the dorsal lobe, there appeared to be a greater proportion of activity at neutral pH vs. acidic pH compared to other segments of the prostate (lateral and ventral lobes). The overall specific activity in these three lobes fell in a narrow range of activity (4–11 pmol/min/mg protein) that was intermediate between the low activity (<0.2 pmol/min/mg protein) seen in the hypothalamus (type 1) and the high activity (up to 42 pmol/min/mg protein) in the epididymis (type 2). In summary, significant amounts of 5αR activity were found in all segments of the prostate, and varied subtly in their pH vs. rate profile.

Initial experiments were conducted by adding ^{3}H-testosterone to the reaction (100 μl) in 10 μl of ethanol. This final concentration was subsequently found to be unacceptable, since it inhibited enzyme activity. Using the lateral prostatic lobe, it was found that while the observed activity at pH 4.5 was relatively unaffected by 10% ethanol, approximately 90% of 5αR activity was lost at pH 6.5 (data not shown). The overall effect was to obscure the contribution of type 1 5αR isozyme, with the resultant pH vs. rate profile being similar to that of the epididymis. Thus, all the experiments described in this paper used 1% ethanol as the vehicle for ^{3}H-testosterone.

The Km for 5αR activity in the ventral prostate and epididymis were determined. Type 1 5αR activity of the ventral prostate had an apparent Km of 2 μM. The affinity of type 1 5αR activity was virtually independent of protein concentration (0.1–5.5 mg/ml) and the

TABLE I. Finasteride: Morphometric Evaluation of Ventral and Dorsolateral Lobes of the Rat Prostate

	Ventral lobe (mean ± SE)		Dorsolateral lobe (mean ± SE)	
Prostatic measurements	Control	Finasteride	Control	Finasteride
Total weight (g)	0.61 ± 0.06	0.20 ± 0.02**	0.52 ± 0.02	0.28 ± 0.01**
Glandular compartment (cc)	0.48 ± 0.05	0.14 ± 0.01**	0.40 ± 0.02	0.13 ± 0.01**
Stromal compartment (cc)	0.13 ± 0.01	0.06 ± 0.01**	0.12 ± 0.01	0.05 ± 0.00**
Volume fraction (vv%)				
Glandular compartment (%)	78.1 ± 1.25	69.3 ± 1.46*	76.9 ± 1.55	73.1 ± 0.90*
Stromal compartment (%)	22.0 ± 1.25	30.7 ± 1.46*	23.1 ± 1.55	26.9 ± 0.90*
Cell density ($Nv^a \times 10^7$/g)				
Epithelial cells	7.56 ± 0.73	8.27 ± 0.52	3.98 ± 0.25	5.71 ± 0.29*
Stromal cells	1.13 ± 0.16	1.40 ± 0.11	0.68 ± 0.06	0.92 ± 0.07*
Cells/gland ($N \times 10^7$)				
Epithelial cells	4.46 ± 0.53	1.60 ± 0.09**	2.03 ± 0.12	0.99 ± 0.07**
Stromal cells	0.65 ± 0.07	0.27 ± 0.03**	0.35 ± 0.03	0.16 ± 0.01**

*$P \leq 0.05$.
**$P < 0.001$.
[a]Nv; Cell number.

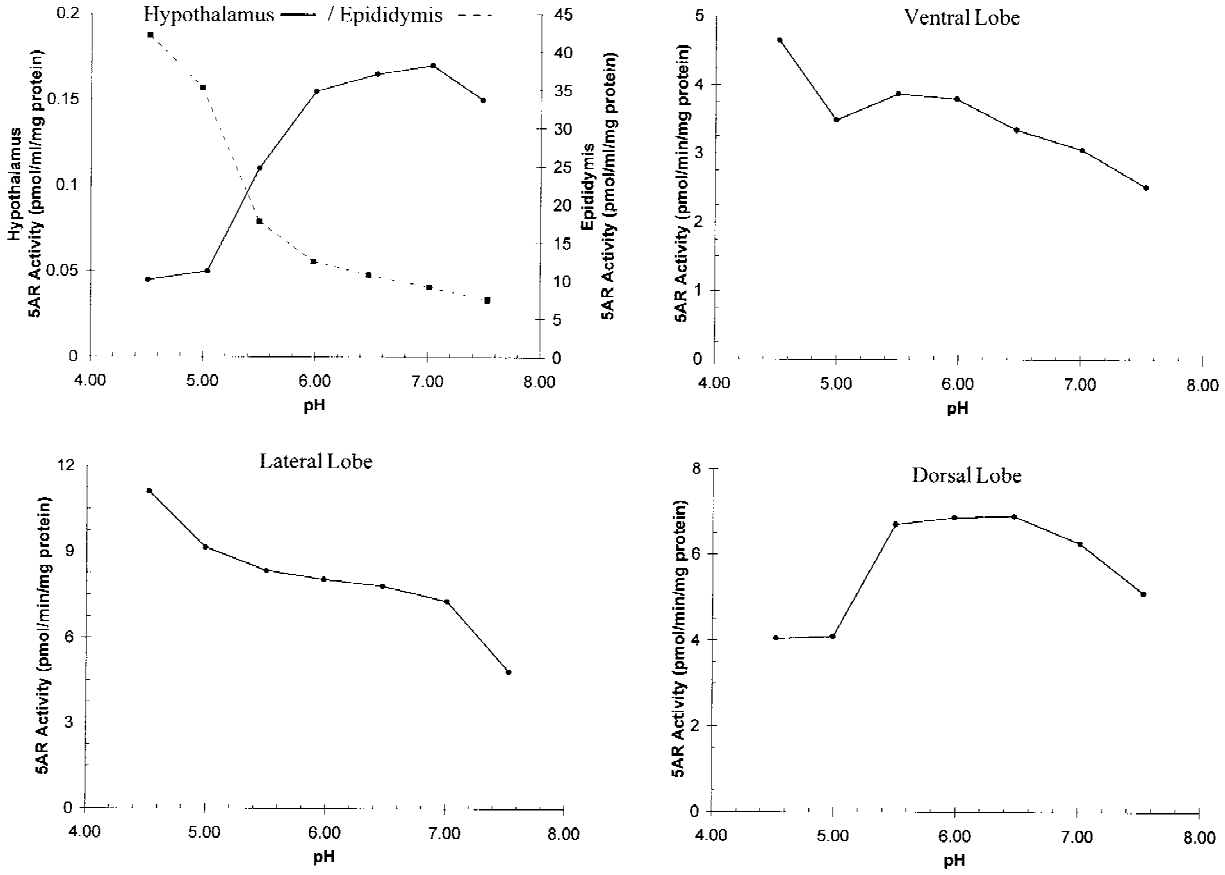

Fig. 4. Distribution of 5αR activity in different prostatic lobes of the rat. For purposes of comparison, the hypothalamus and epididymis, with 5αR activity at neutral pH and acidic pH, respectively, are shown.

testosterone concentration range chosen (20–4,000 nM). The affinity of ventral prostate type 2 5αR activity was higher (550 nM) than that of type 1 5αR. Relatively high affinities could only be obtained with low protein concentrations (0.1 mg/ml). The kinetic characteristics of type 2 activity in the epididymis were similar to those of type 2 5αR isozyme in ventral prostate (Km 400 nM).

DISCUSSION

Determination of 5αR activity has suggested that both 5αR isozymes (types 1 and 2) are present in all three lobes of the rat prostate. This is consistent with earlier observations in the ventral lobe of the rat prostate [13]. In addition, it has been shown using Northern blot analysis that the ventral prostate contains mRNA for both isozymes [22]. The pH vs. rate profile of 5αR activity in the ventral prostate was virtually identical to that reported by Normington and Russell [22]. That both prostatic lobes are dependent on DHT as a trophic hormone is evident by the observed decrease in weight following finasteride treatment (Fig. 3). Determination of prostatic androgen (T and DHT) levels showed that the administration of finasteride resulted in a significant decrease in intraprostatic DHT levels and a significant increase in intraprostatic T levels in both lobes. Despite this significant increase in intraprostatic T levels, T could not restore prostatic weight, indicating that DHT alone has a stimulating effect on the prostate. This is consistent with the described changes in T and DHT levels in the ventral prostates of rats treated with finasteride [23–25].

Since T has been shown to be a prostate cancer promoter in rodents [9,26], it was important to rule out any direct adverse effect of elevated intraprostatic T levels in rats. Qualitative and quantitative morphological evaluations of the prostate from long-term studies (1–2 years) in rats treated with a high oral dose (160 mg/kg/day) of finasteride demonstrated no adverse effects [14]. To confirm that the pharmacological effect of finasteride was maintained following chronic dosing (~6 months) in rats, quantitative morphometric evaluation of both ventral and dorsolateral lobes was done in the present study. In both prostatic lobes there was a significant decrease in the number of epithelial and stromal cells/gland in the finasteride-treated group compared to control. The relevance of the above findings in rats for risk assessment is also supported by an initiation-promotion assay described in rats [26]; in this study, rats were given the carcinogen 3,2,dimethyl (DMAB) as a tumor initiator and testosterone (T) as a promoter, which resulted in increased incidence of prostatic hyperplasia and carcinoma. In contrast, coadministration of finasteride with T to a group of rats exposed to the carcinogen prevented the development of prostatic lesions.

There are several spontaneous and experimentally induced models described using rats to study the pathogenesis, treatment, and prevention of prostate cancer; however, the incidence of prostate cancer in rats varies with the strain, age, and affected lobes [9]. In man, the incidence of prostate cancer is age-dependent and primarily involves the peripheral zone of the prostate, which is embryologically homologous to the dorsolateral lobe in rats [3]. The ventral lobe of the rat prostate does not appear to have a comparable prostatic zone in man [3].

Although both ventral and dorsolateral prostatic lobes are dependent on DHT, there appear to be some morphological and physiological differences between these lobes. Comparison of androgen levels (expressed as pg/mg tissue) in the prostatic lobes of control rats showed that the T and DHT levels were markedly higher in the ventral lobe than those measured in the dorsolateral lobe. However, the mean ratio of DHT to T levels in the dorsolateral lobe was six times greater than in the ventral lobe of control rat prostates. In control rats, the cell density as well as the number of cells/gland was greater in the ventral lobe than in the dorsolateral lobe of the prostate. This difference was due to a greater number of both epithelial and stromal cells in the ventral lobe than in the dorsolateral lobe. However, a cell turnover study using Brdu labeling indicated that there is an increased cell turnover in the dorsolateral lobe compared to the ventral lobe of control rat prostate. This observation is consistent with the findings in a rat study, which indicated that the Brdu-labeled cells in the ventral lobe of the prostate comprised approximately 1% of the total as compared to 7% in the dorsolateral lobe of control rats at initiation of the study; administration of testosterone propionate resulted in a minimal increase over control in the Brdu-labeled cells in the ventral lobe, whereas a doubling in Brdu labeling in the dorsolateral lobe was apparent, although it was seen only over a brief period of treatment [27].

Based on a 2-week study in rats, Yamashita et al. [28] concluded that there is heterogeneity in the response of prostatic lobes to androgen deprivation following treatment with diethylstilbestrol, gonadotropin-releasing hormone analog, finasteride, or castration; it was observed that the treatment-related decreases in prostatic weight, prostatic DNA, and protein levels, as well as decreases in zinc content, varied with the prostatic lobe studied. These physiological and morphological differences in the prostatic lobes of rats may partly explain the differences in the susceptibility of the prostatic lobes to altered endocrine milieu.

Since the important trophic hormone (i.e., DHT) was markedly inhibited in the finasteride-treated rats, the observed increase in intraprostatic T levels has had no adverse effect on prostatic morphology in long-term studies in rats. This is in contrast to rat models where higher T levels were achieved without inhibiting the conversion of T to DHT, making it difficult to evaluate the relative contributions of each of these androgens to the observed pathology [9].

REFERENCES

1. Jesik CJ, Holland JM, Lee C: An anatomic and histologic study of the rat prostate. Prostate 1982;3:81–97.
2. Lee C, Holland JM: Anatomy, histology and ultrastructure (correlation with function), prostate, rat. In Jones TC, Mohr U, Hunt RD (eds): ''Genital System: Monographs on Pathology of Laboratory Animals,'' New York: Springer-Verlag, 1987:239–251.
3. Price D: Comparative aspects of development and structure in the prostate. Monogr Natl Cancer Inst 1963;12:1–25.
4. Price D, Williams-Ashman HG: The accessory reproductive glands of mammals. In Young WC (ed): ''Sex and Internal Secretions,'' Baltimore: Williams and Wilkins, 1961:366–448.
5. Cunha GR, Donjacour AA, Cooke PS, Mee S, Bigsby RM, Higgins SJ, Sugimura Y: The endocrinology and developmental biology of the prostate. Endocr Rev 1987;8:338–362.
6. Fjosne HE, Haug E, Sunde A: Androgen metabolism in the different lobes of the prostate gland of intact, gonadectomized or hypophysectomized rats with or without androgen substitution. Scand J Clin Lab Invest 1994;54:83–93.
7. McNeal JE: Anatomy of the prostate: A historical survey of divergent views. Prostate 1980;1:3–13.
8. Bosland MC: Hyperplasia, adenoma, adenocarcinoma, prostate, rat. In Jones TC, Mohr U, Hunt RD (eds): ''Genital System: Monographs on Pathology of Laboratory Animals,'' New York: Springer-Verlag, 1987:252–272.
9. Bosland MC: Animal models for the study of prostate carcinogenesis. J Cell Biochem [Suppl] 1992;16:89–98.
10. Isaacs JT: Development and Characteristics of the Available Animal Model Systems for the Study of Prostatic Cancer. In Coffey DS, Gardner WA Jr, Bruchovsky N, Resnick MI, Karr JP (eds): ''Current Concepts and Approaches to the Study of Prostate Cancer.'' New York: Alan R. Liss, Inc., 1987:513–576.
11. Isaacs JT, Coffey DS: Animal model systems for the study of prostatic cancer. In Chisholm GD, Fair WR (eds): ''Scientific Foundations of Urology,'' 3rd ed. Chicago, Yearbook, Inc., 1990, pp 613–620.
12. Leav I, Ho S-M, Ofner P, Merk FB, Kwan PW-L, Damassa D: Biochemical alterations in sex hormone-induced hyperplasia and dysplasia of the dorsolateral prostates of Noble rats. J Natl Cancer Inst 1988;80:1045–1053.
13. Azzolina B, Ellsworth KP, Andersson S, Geissler W, Bull H, Harris G: Inhibition of the rat 5α-reductase by finasteride: Evidence for isozyme differences in the mechanism of inhibition. J Steroid Biochem Mol Biol 1997;61:55–64.
14. Prahalada S, Peter CP, Keenan KP, Soper KA, Hertzog PR, van Zwieten MJ, Gordon LR, Bokelman DL: Qualitative and quantitative evaluation of prostatic histomorphology in rats following chronic treatment with finasteride, a 5-α reductase inhibitor. Urology 1994;43:680–685.
15. Dallob AL, Sadick NS, Unger W, Lipert S, Geissler LA, Gregoire SL, Nguyen HH, Moore EC, Tanaka WK: The effect of finasteride, a 5α-reductase inhibitor, on scalp skin testosterone and dihydrotestosterone concentrations in patients with male pattern baldness. J Clin Endocrinol Metab 1994;79:703–706.
16. Cukierski MA, Sina JL, Prahalada S, Wise LD, Antonello JM, MacDonald JS, Robertson RT: Decreased fertility in male rats administered the 5α-reductase inhibitor, finasteride, is due to deficits in copulatory plug formation. Reprod Toxicol 1991;5: 353–362.
17. Wilk MB, Shapiro SS: The joint assessment of normality of several independent samples. Technometrics 1968;10:825–839.
18. Snedecor GW, Cochran WG: Levene's test for variance homogeneity. In ''Statistical Methods,'' 8th ed. Iowa State University Press, 1989:252–253.
19. Tukey JW, Ciminera JL, Heyse JF: Testing the statistical certainty of a response to increasing doses of a drug. Biometrics 1985;41:295–301.
20. Snedecor GW, Cochran WG: Two-sampled *t*-test. In: ''Statistical Methods,'' 8th ed. Iowa State University Press, 1989:83–93.
21. Harter HL: Expected values of normal order statistics. Biometrika 1961;48:151–165.
22. Normington K, Russel DW: Tissue distribution and kinetic characteristics of rat steroid 5α-reductase isozymes. J Biol Chem 1992;267:19548–19554.
23. Rittmaster RS, Mager KE, Manning AP, Norman RW, Lazier CB: Differential effect of 5α-reductase inhibition and castration on androgen-regulated gene expression in rat prostate. Mol Endocrinol 1991;5:1023–1029.
24. Rittmaster RS, Manning AP, Wright AS, Thomas LN, Whitefield S, Norman RW, Lazier CB, Rowden G: Evidence for atrophy and apoptosis in the ventral prostate of rats given the 5α-reductase inhibitor finasteride. Endocrinology 1995;136:741–748.
25. Shao TC, Kong A, Marafelia P, Cunningham GR: Effects of finasteride on the rat ventral prostate. J Androl 1993;14:79–86.
26. Tsukamoto S, Akaza H, Imada S, Koiso K, Shirai T, Ideyama Y, Kudo M: Chemoprevention of rat prostate carcinogenesis by use of finasteride or Casodex. J Natl Cancer Inst 1995;87:842–843.
27. Ito N, Shirai T, Masui T, Ogewa K, Kato T, Takahaski S: Mechanistic analysis of multistage carcinogenesis in the rat prostate. In Harris CC, Hirohashi S, Ito N, Pitot HC, Sugimura T, Terada M, Yokota J (eds): ''Multistage Carcinogenesis,'' Tokyo: Japan Scientific Societies Press, 1992:125–133.
28. Yamashita A, Hayashi N, Sugimura Y, Cunha GR, Kawamura J: Influence of diethylstilbestrol, leuprorelin (a luteinizing hormone-releasing hormone analog), finasteride (a 5-alpha reductase inhibitor), and castration on the lobar subdivisions of the rat prostate. Prostate 1996;29:1–14.