The Prostate 43:49–58 (2000)

Pharmacological Effects of the Lipidosterolic Extract of *Serenoa repens* (Permixon®) on Rat Prostate Hyperplasia Induced by Hyperprolactinemia: Comparison With Finasteride

Fabien Van Coppenolle,[1]* Xuefen Le Bourhis,[2] Françoise Carpentier,[3] Geoffrey Delaby,[1] Henri Cousse,[4] Jean-Pierre Raynaud,[5] Jean-Paul Dupouy,[6] and Natalia Prevarskaya[1]

[1]*Laboratoire de Physiologie Cellulaire, USTL, INSERM EPI 9938, Villeneuve d'Ascq, France*
[2]*Laboratoire de Biologie du Développement, UPRES 1033, USTL, Villeneuve d'Ascq, France*
[3]*Service d'Anatomo-Pathologie, Centre Hospitalier de Roubaix, Roubaix, France*
[4]*Laboratoire Pierre Fabre, La Chartreuse, Castres, France*
[5]*Université Pierre et Marie Curie, Paris, France*
[6]*Laboratorie de Neuroendocrinologie du Développement, USTL, Villeneuve d'Ascq, France*

BACKGROUND. The growth of the prostate gland is mainly dependent on androgens. Other hormones, like prolactin (PRL), also influence prostate development. Our purpose was to analyze and compare the effects of two drugs (5α-reductase inhibitor) used in the therapy of benign prostatic hyperplasia: lipidosterolic extract of *Serenoa repens* (LSESR), and finasteride in an in vivo model of rat prostate hyperplasia induced by hyperprolactinemia.
METHODS. Hyperprolactinemia was induced by 30 daily injections of sulpiride. Wistar rats received daily gavages of LSESR or finasteride. We used the following groups: control, castrated, castrated with a substitute testosterone (T), or 5α-dihydrotestosterone (DHT) implant.
RESULTS. Hyperprolactinemia increases the wet weight and induces hyperplasia in the lateral prostate (LP). Unlike finasteride, LSESR significantly reduced LP growth and hyperplasia in castrated, DHT-implanted, and sulpiride-treated rats.
CONCLUSIONS. Finasteride was only capable of inhibiting the effect of androgens on rat prostate enlargement. LSESR inhibited not only the androgenic but also the trophic effect of PRL in rat LP hyperplasia. *Prostate 43:49–58, 2000.*

KEY WORDS: **rat prostate hyperplasia; prolactin; androgens; LSESR; finasteride**

INTRODUCTION

Benign prostate hyperplasia (BPH) and prostate cancer are very common diseases among elderly men. Fifty percent of men over 50 years old suffer from BPH. Furthermore, prostate cancer is the second leading cause of death by cancer [1].

Prostate development and growth are controlled by androgens [2,3]. Treatments currently used in hor-

Grant sponsor: Pierre Fabre Médicament; Grant sponsor: Association pour la Recherche sur le Cancer; Grant sponsor: Association pour la Recherche sur les Tumews de la Prostate; Grant sponsor: Institut National de la santé de la Recherche Médicale; Grant sponsor: Ligue Nationale contre le Cancer.

*Correspondence to: Fabien Van Coppenolle, Laboratoire de Physiologie Cellulaire, Centre de Biologie Cellulaire, USTL, INSERM EPI 9938, Bâtiment SN3, 59655 Villeneuve d'Ascq Cedex, France. E-mail: fvancopp@pop.univ-lille1.fr

Received 23 August 1999; Accepted 17 November 1999

monotherapy for prostate diseases are only aimed at inhibiting the effect of androgens on prostate cell growth [4]. They are based on reducing androgen levels in the following ways: (1) Drugs such as the lipidosterolic extract of *Serenoa repens* (LSESR) [5] or finasteride [6] are used to inhibit the enzyme 5α-reductase, which converts testosterone (T) to 5α-dihydrotestosterone (DHT), the most active androgen in the stimulation of prostate-cell proliferation [7], in the prostate. (2) Flutamide inhibits the fixation of androgens to their receptors [8]. (3) Another approach, using chronic administrations of GnRH agonists [9,10], is also employed to induce an inhibition of androgenic synthesis.

In men, T levels decrease with age [11,12], while prolactin (PRL) concentrations increase [13,14]. It is becoming increasingly clear that PRL is implicated in prostate growth [15–19]. It has been suggested that PRL acts in synergy with androgens, either by enhancing the T effect [20] or by increasing the number of cytosolic and nuclear androgen receptors [21]. Furthermore, some in vitro experiments have shown that PRL can also act directly on prostate cells [22,23], as they possess PRL receptors [19,24–26]. In addition, Nevalainen et al. [19,20] demonstrated that human and rat prostate cells synthesize PRL. Thus, this hormone may regulate prostate growth in an autocrine/paracrine loop. However, the PRL pathway has not yet been taken into account in hormonotherapy for prostate diseases.

In this work, we studied the effects of LSESR and finasteride on rat prostate hyperplasia induced by hyperprolactinemia. We now report that LSESR inhibits the effects of PRL and androgens on prostate growth. On the other hand, finasteride (a specific 5α-reductase inhibitor) only antagonizes the action of T on rat lateral prostate growth.

MATERIALS AND METHODS

Animals

One hundred forty-five male Wistar rats (200–220 g) from Dépré Breeding Center (Saint Doulchard, France) were used. These animals were conditioned for 1 week prior to experimentation. Rats were randomized and housed 5 per cage on a 12-hr light-12-hr dark cycle. They were provided ad libitum with water and standard laboratory chow.

During this work, all animal studies were conducted in accordance with the European Communities Council ruling of November 24, 1986 (86/609/EEC).

Surgical Procedures

All surgeries were performed on day 1 under ether anesthesia and strict sanitized conditions. The operated animals were treated with antibiotics (penicillin) to prevent infections.

Castrations were performed on day 1 via the scrotal route by removing epididymal fat pads with the testes. Operated animals were then sutured, and the injured areas were disinfected with betadine solution and sprayed with aluspray (Vetoquinol, France).

In order to add the desired quantity of exogenous androgens for comparison with control animals, we implanted silastic medical-grade silicone tubing (0.078 i.d. × 0.125 o.d., Dow Corning Corp., Midland, MI) (1 cm length), filled with either testosterone (Sigma, France) or 5α-dihydrotestosterone (Sigma), subcutaneously over the scapula. One end of the tubing was sealed with adhesive (Silastic Medical Adhesive, Dow Corning Corp.) according to Robaire *et al.* [28]. After loading with the hormone, the unsealed end was sealed with adhesive. After the adhesive had hardened, the implants were stored overnight in distilled water. It has been found that a 2.5-cm implant mimics the physiological testosterone level [29]. The choice of a 1-cm implant was to produce a subnormal testosterone release.

The implants were inserted on day 8, in pockets formed over the dorsal area of the scapula. The incised area was disinfected, and then sutured.

Hyperprolactinemia Induction

Hyperprolactinemia was induced by daily intraperitoneal injections of a 40 mg/kg aqueous sulpiride solution (± sulpiride, Sigma).

LSESR (Permixon®) Gavages

The lipidosterolic extract of *Serenoa repens* (batch numbers 708 and 712) was from Pierre Fabre Médicament (Labège, France). The animals received daily gavages of LSESR plus carrier (2.5% ethanol) or carrier alone. The doses used were: 100 mg/kg/day; 320 mg/kg/day; or 640 mg/kg/day.

Finasteride Gavages (Chibro-Proscar®)

Finasteride (Merck, Whitehouse Station, NJ) compounds were dissolved in 2.5% ethanol. The animals received daily gavages of 5 mg/kg of finasteride (batch number 974214) or carrier alone.

Sampling

Since previous reports [30–32] indicated an increase in PRL during stress, sham castrated, solvent-injected groups and animals receiving carrier alone (2.5% ethanol in aqueous solution) were also evaluated. It was

TABLE I. Scheme of Experimental Procedures for 30 Days of Sulpiride, Permixon, and Finasteride Treatment

Experimental groups	Surgery on day 1	Surgery on day 8	Treatments from day 8 to sacrifice day
I, control			
II, control + sulpiride			Sulpiride
III, control + LSESR 100			LSESR 100 mg/kg
IV, control + LSESR 320			LSESR 320 mg/kg
V, control + Fin5			Finasteride 5 mg/kg
VI, control + sulpiride + LSESR 100			Sulpiride + LSESR 100 mg/kg
VII, control + sulpiride + LSESR 320			Sulpiride + LSESR 320 mg/kg
VIII, control + sulpiride + Fin5			Sulpiride + Finasteride 5 mg/kg
IX, castrated	Castration		
X, castrated + T	Castration	T implant	
XI, castrated + T + LSESR 100	Castration	T implant	LSESR 100 mg/kg
XII, castrated + T + LSESR 320	Castration	T implant	LSESR 320 mg/kg
XIII, castrated + T + Fin5	Castration	T implant	Finasteride 5 mg/kg
XIV, castrated + DHT	Castration	DHT implant	
XV, castrated + DHT + LSESR 100	Castration	DHT implant	LSESR 100 mg/kg
XVI, castrated + DHT + LSESR 320	Castration	DHT implant	LSESR 320 mg/kg
XVII, castrated + DHT + Fin5	Castration	DHT implant	Finasteride 5 mg/kg
XVIII, castrated + T + sulpiride	Castration	T implant	Sulpiride
XIX, castrated + T + sulpiride + LSESR 100	Castration	T implant	Sulpiride + LSESR 100 mg/kg
XX, castrated + T + sulpiride + LSESR 320	Castration	T implant	Sulpiride + LSESR 320 mg/kg
XXI, castrated + T + sulpiride + LSESR 640	Castration	DHT implant	Sulpiride + LSESR 640 mg/kg
XXII, castrated + T + sulpiride + Fin5	Castration	DHT implant	Sulpiride + Finasteride 5 mg/kg
XXIII, castrated + DHT + sulpiride	Castration	DHT implant	Sulpiride
XXIV, castrated + DHT + sulpiride + LSESR 100	Castration	DHT implant	Sulpiride + LSESR 100 mg/kg
XXV, castrated + DHT + sulpiride + LSESR 320	Castration	DHT implant	Sulpiride + LSESR 320 mg/kg
XXVI, castrated + DHT + sulpiride + Fin5	Castration	DHT implant	Sulpiride + Finasteride 5 mg/kg
XXVII, sham castrated	Sham-castration		
XXVIII, solvent-injected			NaCl 0.9%
XXIX, carrier-gavaged			2.5% ethanol in aqueous solution

previously shown that empty tubing implants have no effect on rat prostate growth [28,33,34].

Table I lists the surgical events (castrations and implants) and treatments (daily intraperitoneal injections of sulpiride and gavages of LSESR or finasteride) for the various experimental groups.

Immediately after sacrifice, the prostate lobes were dissected, weighed, and treated for light microscopy, as described below.

Histology

Tissue pieces were fixed in 10% neutral-buffered formalin and embedded in paraffin. Histological analyses were performed on serial sections obtained from prostatic samples stained with hematoxylin-erythrosin-saffron (HES).

Hormonal Assays

Plasma levels of PRL were measured by radioimmunoassay (RIA) with materials supplied by the NIDDK rat pituitary hormone distribution program (NIDDK, Torrance, CA), using rat RP3-PRL in reference preparations. In our experiments, the rats were sacrificed on the day after the last sulpiride injection, so that the prolactinemia measured represented the chronic PRL level after 30 days of treatment with sulpiride.

Statistical Analysis

We expressed the prostate weight relative to the body weight according to Robinette [33]. The Tukey test was used to establish the presence of significant differences. Significance was established at levels of $P < 0.05$, $P < 0.01$, and $P < 0.001$.

RESULTS

After 30 days of treatment, the rats were sacrificed. Rat prostates consist of three parts: ventral lobes, lat-

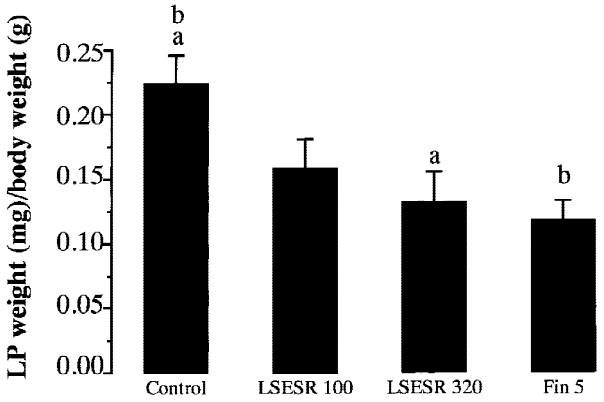

Fig. 1. Histogram showing total lateral prostate weight (mg) divided by total body weight (g). Animals received treatment as described in Table I. Values are means, and bars indicate SEM; n = 5. The values of the following treatments were significantly different: $P < 0.05$, a, b. Control, control animals; LSESR 100, animals receiving LSESR at 100 mg/kg/day *per os*; LSESR 320, animals receiving LSESR at 320 mg/kg/day *per os*; Fin 5, animals receiving finasteride at 5 mg/kg/day *per os*.

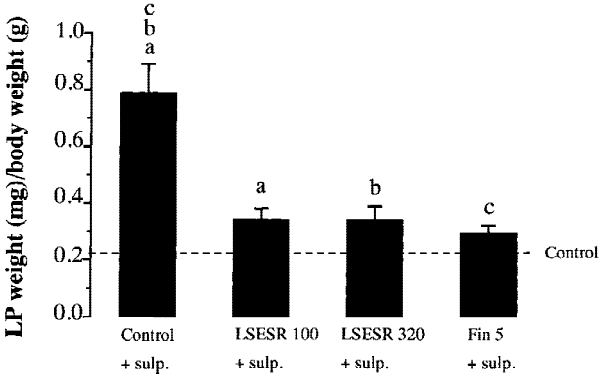

Fig. 2. Histogram showing total lateral prostate weight (mg) divided by total body weight (g). Animals received treatment as described in Table I. Values are means, and bars indicate SEM; n = 5. The values of the following treatments were significantly different: $P < 0.01$, a, b, c. Control, control animals; sulp., animals receiving intraperitoneal sulpiride injections (40 mg/kg/day); LSESR 100, animals receiving LSESR at 100 mg/kg/day *per os*; LSESR 320, animals receiving LSESR at 320 mg/kg/day *per os*; Fin 5, animals receiving finasteride at 5 mg/kg/day *per os*.

eral lobes, and dorsal lobes. Each lobe was dissected and weighed separately.

Only the lateral prostate (LP) is sensitive to hyperprolactinemia (data not shown). For this reason, only changes in the wet weight of the lateral lobes were analyzed in order to define the effects of LSESR and finasteride on LP enlargement induced by hyperprolactinemia.

Effects of LSESR and Finasteride on the Wet Weight of the LP

LSESR and finasteride were tolerated by all animals, and no side effects were observed. Sulpiride injections did not modify the weight of LP in castrated and in castrated-adrenalectomized rats (data not shown) after 30 days. LSESR and finasteride did not reduce the weight of these LP (sulpiride-treated or not; data not shown).

Figure 1 illustrates the wet weight of the LP in intact animals after 30 days of treatment.

LSESR at 100 mg/kg daily was ineffective, as the LP weight was not significantly reduced. On the contrary, LSESR at 320 mg/kg and finasteride at 5 mg/kg induced a significant decrease of 41% and 47%, respectively.

As shown in Figure 2, sulpiride induced a 3.5-fold increase in lateral lobe weight. In control animals treated with sulpiride, we noticed a significant decrease in LP weight with LSESR at 100 mg/kg (–56%), LSESR at 320 mg/kg (–57%), and finasteride at 5 mg/kg (–63%).

As shown in Figure 3, castration induced an 83% decrease in LP weight. T implants restored 78% of the LP weight in castrated animals. Gavages with LSESR (at 100 and 320 mg/kg) were ineffective in inducing a decrease in LP weight. On the contrary, finasteride at 5 mg/kg induced a decrease (–41%) in the LP weight in castrated, T-implanted rats compared to untreated castrated, T-implanted rats.

In Figure 4, as shown previously, castration decreased the LP weight. DHT implants restored 82% of the LP weight compared to noncastrated animals. In castrated rats implanted with DHT, neither LSESR at 100 and 320 mg/kg nor finasteride at 5 mg/kg reduced LP wet weight compared to castrated, DHT-implanted rats.

As shown in Figure 5, in castrated, T-implanted animals, sulpiride induced a 2.4-fold increase in lateral lobe weight compared with noninjected rats. LSESR at 100 mg/kg and at 320 mg/kg did not decrease the LP weight. On the contrary, LSESR at 640 mg/kg and finasteride at 5 mg/kg decreased the wet weight of the lateral lobes by 59% and 67%, respectively, under these experimental conditions.

As shown in Figure 6, daily sulpiride injections induced an 87% increase in LP weight in castrated and DHT-implanted rats. LSESR at 100 mg/kg did not reduce the LP weight in castrated, DHT-implanted, and sulpiride-treated animals. On the other hand, LSESR at 320 mg/kg significantly inhibited LP growth by 40%. However, finasteride at 5 mg/kg did not reduce the wet weight of the LP.

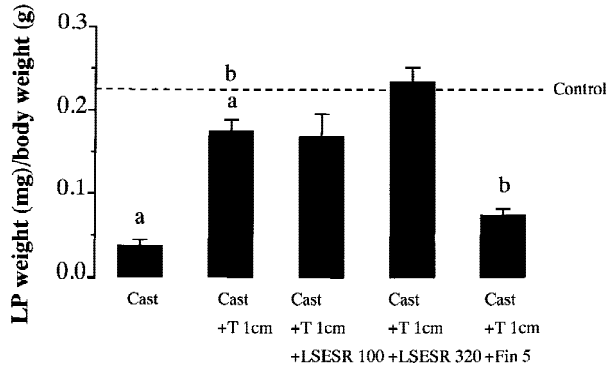

Fig. 3. Histogram showing total lateral prostate weight (mg) divided by total body weight (g). Animals received treatment as described in Table I. Values are means, and bars indicate SEM; n = 5. The values of the following treatments were significantly different: $P < 0.001$, a; $P < 0.01$, b. Cast, castrated animals; T 1 cm, animals receiving 1 cm subcutaneous T implant; LSESR 100, animals receiving LSESR at 100 mg/kg/day *per os*; LSESR 320, animals receiving LSESR at 320 mg/kg/day *per os*; Fin 5, animals receiving finasteride at 5 mg/kg/day *per os*.

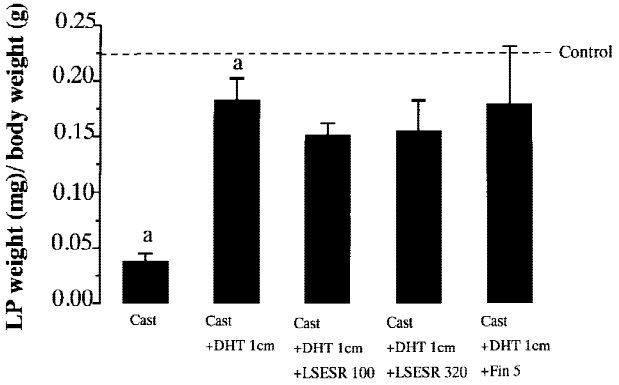

Fig. 4. Histogram showing total lateral prostate weight (mg) divided by total body weight (g). Animals received treatment as described in Table I. Values are means, and bars indicate SEM; n = 5. The values of the following treatments were significantly different: $P < 0.001$, a. Cast, castrated animals; DHT 1 cm, animals receiving 1 cm subcutaneous DHT implant; LSESR 100, animals receiving LSESR at 100 mg/kg/day *per os*; LSESR 320, animals receiving LSESR at 320 mg/kg/day *per os*; Fin 5, animals receiving finasteride at 5 mg/kg/day *per os*.

LP Histology Following Different Treatments

The LP of castrated, T-implanted rats contained similar proportions of small and large glands (Fig. 7A). In castrated, T-implanted, and sulpiride-treated rats, volumes of LP glands were generally larger than those of castrated, T-implanted rats, with the presence of very large glands (Fig. 7B). In castrated, T-implant, sulpiride- and LSESR-treated rats (Fig. 7C), gland volume was smaller than in castrated, T-implanted, and

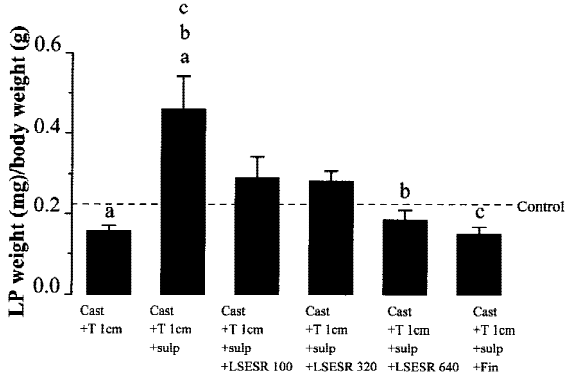

Fig. 5. Histogram showing total lateral prostate weight (mg) divided by total body weight (g). Animals received treatment as described in Table I. Values are means, and bars indicate SEM; n = 5. The values of the following treatments were significantly different: $P < 0.001$, a, c; $P < 0.01$, b. Cast, castrated animals; sulp., animals receiving intraperitoneal sulpiride injections (40 mg/kg/day); T 1 cm, animals receiving 1 cm subcutaneous T implant; LSESR 100, animals receiving LSESR at 100 mg/kg/day *per os*; LSESR 320, animals receiving LSESR at 320 mg/kg/day *per os*; LSESR 640, animals receiving LSESR at 640 mg/kg/day *per os*; Fin 5, animals receiving finasteride at 5 mg/kg/day *per os*.

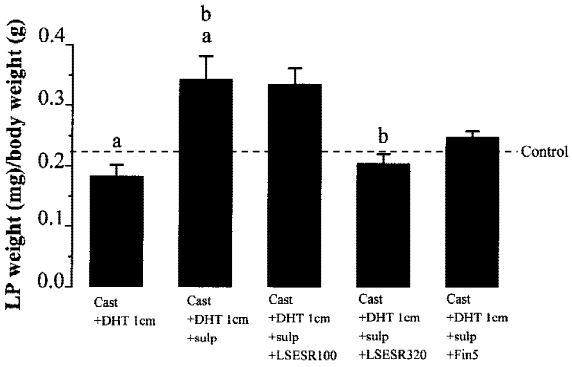

Fig. 6. Histogram showing total lateral prostate weight (mg) divided by total body weight (g). Animals received treatment as described in Table I. Values are means, and bars indicate SEM; n = 5. The values of the following treatments were significantly different: $P < 0.001$, a; $P < 0.01$, b. Cast, castrated animals; sulp., animals receiving intraperitoneal sulpiride injections (40 mg/kg/day); DHT 1 cm, animals receiving 1 cm subcutaneous DHT implant; LSESR 100, animals receiving LSESR at 100 mg/kg/day *per os*; LSESR 320, animals receiving LSESR at 320 mg/kg/day *per os*; Fin 5, animals receiving finasteride at 5 mg/kg/day *per os*.

sulpiride-treated rats. In castrated, T-implanted, sulpiride- and finasteride-treated rats (Fig. 7D), gland volume was similar to that of castrated and T-implanted rats, with neutrophil infiltration in some glands.

In castrated and DHT-implanted rats, the lateral prostate contained a similar proportion of small and large glands (Fig. 8A). In castrated, DHT-implanted, and sulpiride-treated rats, LP gland volume was gen-

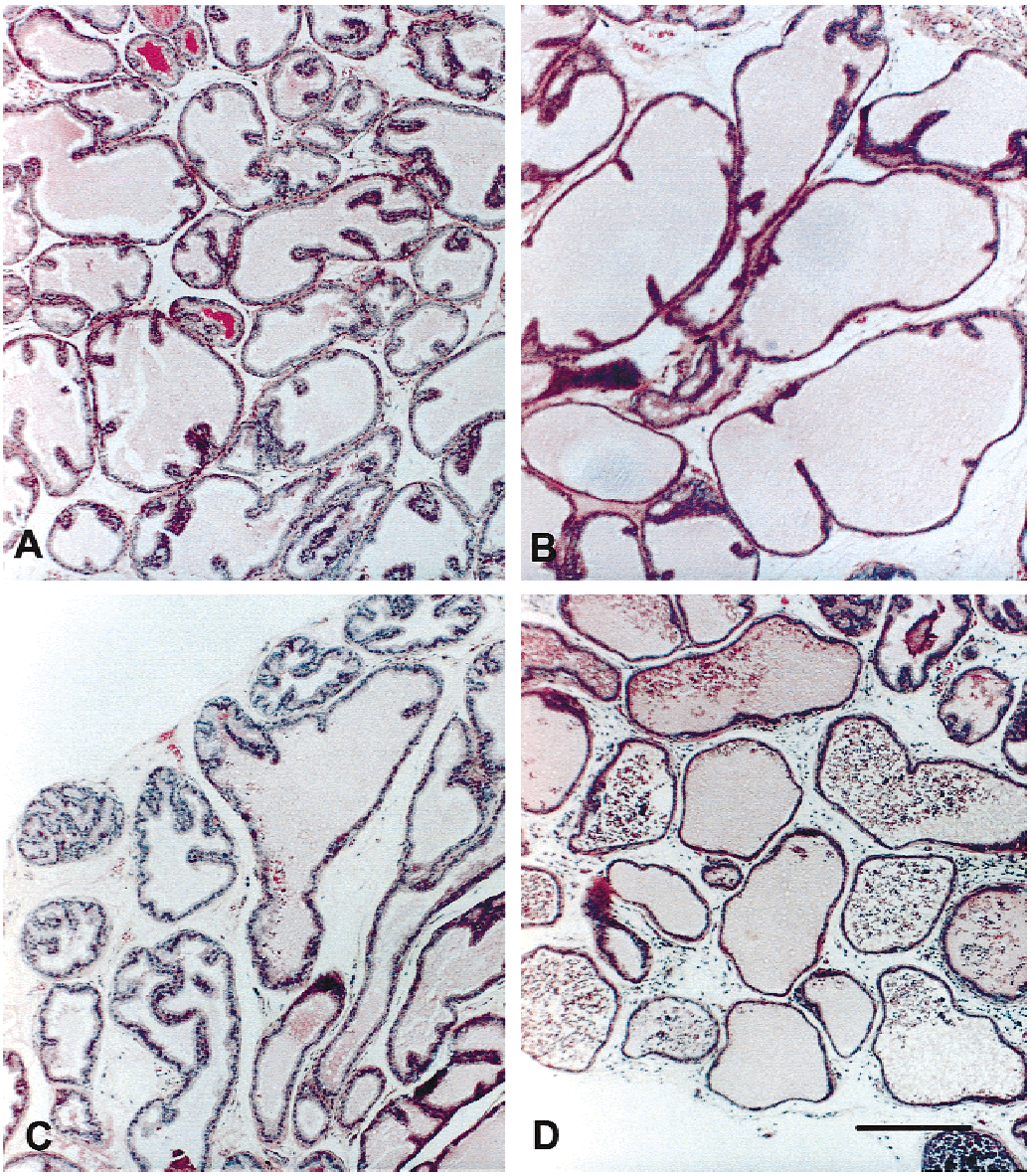

Fig. 7. Histological details of lateral prostate of castrated and T-implanted rats. Castrated and T-implanted animals received additional treatments for 30 days, as described in Table I. **A:** Castrated and T-implanted rat. Note the admixture of small and large glands. **B:** Castrated, T-implanted, and sulpiride-treated rat. Presence of very large glands. **C:** Castrated, T-implanted, sulpiride- and LSESR-treated rat. Glands are smaller than those of castrated, T-implanted, and sulpiride-treated rat. **D:** Castrated, T-implanted, sulpiride- and finasteride-treated rat. Gland volumes are similar to those of castrated and T-implanted rats, with neutrophil infiltration in some glands. Bar, 500 μm.

erally larger than in castrated, DHT-implanted rats. Moreover, some glands contained numerous neutrophils (Fig. 8B). In castrated, DHT-implanted, sulpiride- and LSESR-treated rats, the histological findings were similar to those from castrated and DHT-implanted rats, with similar proportions of small and large glands but no neutrophil infiltration (Fig. 8C). On the other hand, in castrated, DHT-implanted, sulpiride- and finasteride-treated rats, the histological findings were similar to those from castrated, DHT-implanted, and sulpiride-treated rats, with the presence of very large glands, some of which contained numerous neutrophils (Fig. 8D).

DISCUSSION

The purpose of this study was to examine and compare the effects of LSESR and finasteride in an animal model: rat prostate hyperplasia induced by hyperprolactinemia. LSESR is extracted from saw palmetto fruit (*Serenoa repens*). This extract is a mixture of many fatty acids (mainly palmitic, oleic, lauric, and myristic ac-

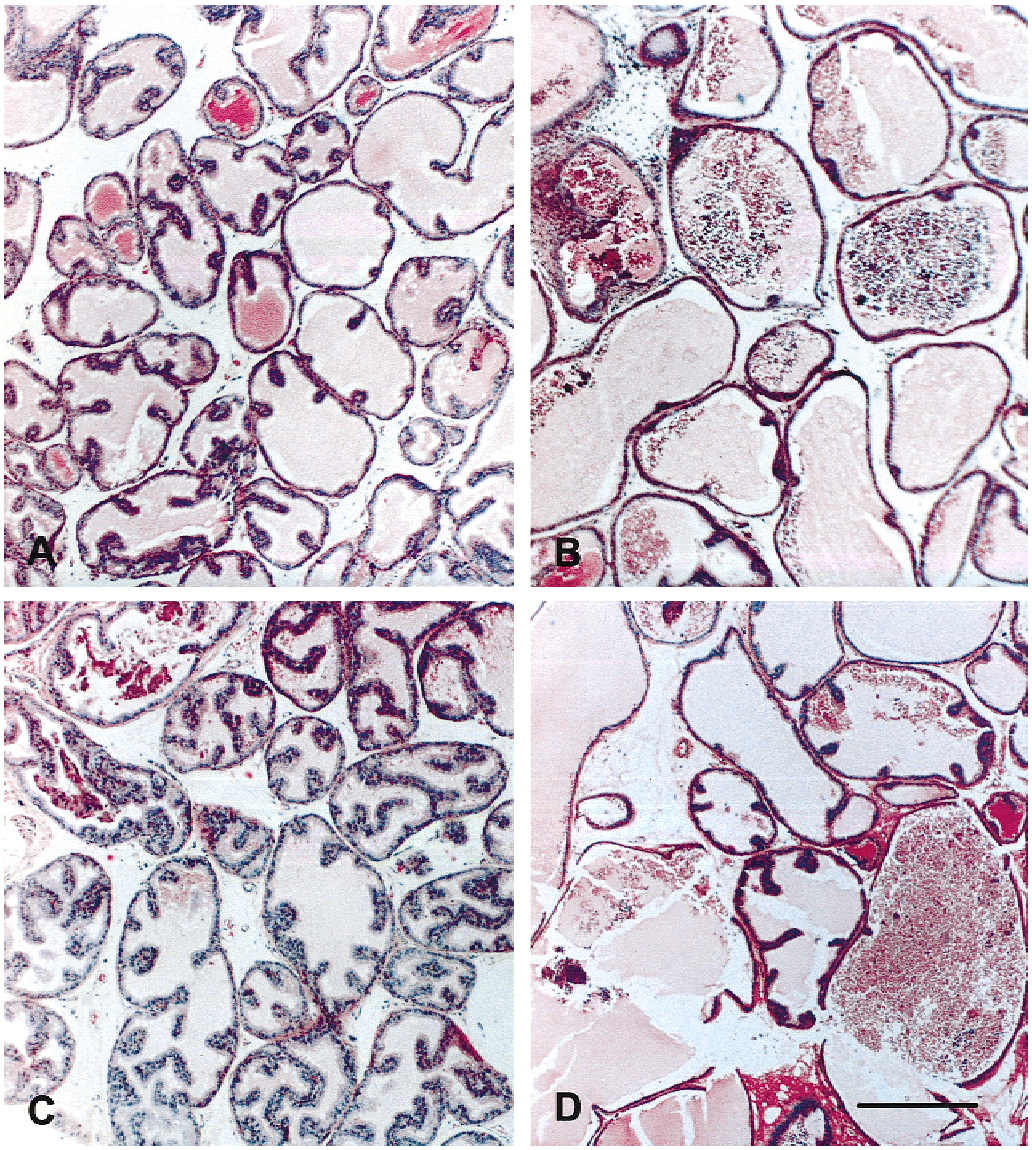

Fig. 8. Histological details of lateral prostate of castrated and DHT-implanted rats. Castrated and DHT-implanted animals received additional treatments for 30 days, as described in Table I. **A:** Castrated and DHT-implanted rat. Note mixture of small and large glands. **B:** Castrated, DHT-implanted, and sulpiride-treated rat. Presence of very large glands, some containing numerous neutrophils. **C:** Castrated, DHT-implanted, sulpiride- and LSESR-treated rat. Histological aspects are similar to those of castrated and DHT-implanted rats, with a mixture of large and small glands and no neutrophil infiltration. **D:** Castrated, DHT-implanted, sulpiride- and finasteride-treated rats, with the presence of very large glands, some containing numerous neutrophils. Bar, 500 μm.

ids) [35]. Thus, LSESR may have a pleiotropic action on prostate growth, first via its inhibition of 5α-reductase isoforms [35–37], and second, through its direct antiandrogenic activity [38]. LSESR therefore exerts an antiproliferative [35] and antiinflammatory [34,39] effect, but is unable to modify T secretion [40]. In this study, we demonstrated the antiprolactinic activity of LSESR for the first time. Finasteride is a specific inhibitor of the type-II 5α-reductase isoform. It was shown to inhibit LP hyperplasia and to reduce the wet weight of the LP under all conditions, except in castrated, DHT-implanted animals, irrespective of whether they were treated with sulpiride. Unlike LSESR, finasteride did not show any antiprolactinic activity. We have shown that among the three rat prostate lobes (ventral, lateral, and dorsal), only the LP is sensitive to hyperprolactinemia. In humans, the dosage of LSESR is 320 mg per day (2 doses of 160 mg) *per os.* The dosage of finasteride is 5 mg daily *per os.* In pharmacological studies [34,41], such as this work, the doses used are usually based on the human dosage per 1 kg of rat. This is why the animals received daily

gavages of 320 mg/kg of LSESR (or alternatively, 100 mg/kg and 640 mg/kg) or 5 mg/kg of finasteride. This *in vivo* model of prostate hyperplasia may be important for pharmacological studies because the LP is considered to be homologous to the transitional zone where human benign prostate hyperplasia occurs [42].

In our study, the animals received 30 daily injections of sulpiride in order to induce chronic hyperprolactinemia [43,44]. Sulpiride is a specific dopamine type-2 receptor inhibitor known to stimulate PRL secretion from the pituitary gland. This molecule affects PRL levels in two ways. Firstly, sulpiride induces a peak of prolactinemia after 30 min (up to 26 times the initial level). Secondly, the PRL concentration decreases over the next 2 hr, but still remains six times higher than the basal values [43]. In our experiments, we measured a 615% increase in PRL levels in control animals treated with sulpiride. Both LSESR (100 and 320 mg/kg) and finasteride (5 mg/kg/day) caused a significant decrease in LP weight in noncastrated animals. These results were mainly due to androgenic inhibition. Finasteride is known to be a specific inhibitor of 5α-reductase isoforms (especially the type-II isoform [45]) and to induce apoptosis in the rat ventral prostate [46]. On the contrary, as LSESR is a mixture of many fatty acids [33], it may interfere with other mechanisms that stimulate rat prostate growth. In control animals treated with sulpiride, PRL induced a significant increase in LP weight. This rise in LP weight was abolished by both LSESR (100 and 320 mg/kg/day) and finasteride (5 mg/kg/day). Thus, under hyperprolactinemia conditions, these two drugs may act by inhibiting the action of androgen. They may also diminish the direct or indirect effect of PRL on LP enlargement.

In order to distinguish between the antiandrogenic and antiprolactinic effects of LSESR and finasteride, we carried out experiments with castrated rats receiving a substitute androgen treatment via subcutaneous implants 1 cm long filled with T or DHT. A 1-cm T implant supplies half the normal T level [28,29]. Hyperprolactinemia did not enhance LP weight in castrated and in castrated-adrenalectomized rats (data not shown). In castrated rats, T implants partly restored LP weight, as compared to control animals. LSESR did not reduce the weight of the lateral lobes. This phenomenon was probably due to the low T level. Thus the ability of LSESR to inhibit 5α-reductase is less clear. Finasteride, however, clearly decreased LP weight in castrated, T-implanted animals. Finasteride acts by inhibiting 5α-reductase. Unlike LSESR, finasteride had a significant effect under these experimental conditions. Both LSESR and finasteride were ineffective in castrated, DHT-implanted rats, because inhibition of 5α-reductase had no effect on the exogenous contribution of the implant to DHT levels. In castrated and T-implanted animals, 30 days of sulpiride injections enhanced the weight of the LP. In such animals, LSESR at 100 and 320 mg/kg/day induced a nonsignificant tendency towards a decrease in lateral lobe weight. Nevertheless, both LSESR at 640 mg/kg/day and finasteride (5 mg/kg/day) significantly reduced LP weight, suggesting that they may inhibit 5α-reductase activity as well as the effects of PRL. However, unlike finasteride, LSESR reduced the weight of the lateral prostate of castrated, DHT-implanted and sulpiride-treated animals. Under these conditions, LSESR had no effect on the DHT delivered by the implant. These results indicate that, in addition to its antiandrogenic activity, LSESR also inhibits the effects of hyperprolactinemia.

A large double-blind comparative study was realized with LSESR and finasteride [4]. This work demonstrated that these two drugs produced similar improvements in BPH symptoms. Nevertheless, finasteride is more efficient than LSESR in inhibiting 5α-reductase activity [47]. This implies that LSESR could also act via other pathways in BPH, such as inhibition of inflammation [34] and PRL action, as demonstrated in the present study. According to these results, we characterized two types of LSESR action: inhibition of androgen stimulation and inhibition of the hyperprolactinemia-induced effects. Finasteride only inhibits the effect of androgen on LP growth, which corresponds to its known inhibiting effect on the type-II 5α-reductase isoform [45].

The mechanisms of PRL action on the prostate are not well-known, apart from the fact that PRL potentiates androgen actions [21,22]. Nevertheless, some in vitro studies identified a direct effect of PRL in prostate cells [24]. Human and rat prostate cells possess PRL receptors. They also synthesize PRL, which may act via PRL receptors, mainly localized on the apical side of the epithelial cells of acini [19]. The mechanisms by which LSESR affects this process are unknown. LSESR may inhibit PRL transduction or modify the activity of PRL receptors, as shown by Vacher *et al.* in CHO cells transfected with PRL receptors [48]. In these cells, LSESR interferes with PRL receptors and signal transduction. Estrogens are implicated in the enhancement of PRL secretion [49,50] and in rat prostate growth, probably via PRL action [17,18,33]. LSESR has antiestrogenic activity [34,51], which may explain its antiprolactinic action on rat prostate enlargement. Furthermore, Lane et al. [17] and Tangbanluekal and Robinette [18] demonstrated that bromocriptine (a type-2 dopamine receptor agonist, which inhibits PRL secretion from the pituitary gland) antagonizes the dorsolateral rat prostate dysplasia and inflammation induced by T and estradiol

implants. LSESR also inhibits the rat prostate enlargement caused by the same cotreatment [34]. As shown in Figure 8, LSESR also appears to display an antiinflammatory action which is consistent with an antiprolactinic effect. LSESR may decrease the PRL secretion mediated by estrogens and/or inhibit the direct effect of hyperprolactinemia (induced by sulpiride) on LP enlargement and inflammation. However, the exact mechanisms by which LSESR inhibits PRL action require further investigations.

As shown by Yatani et al. [52], elevated PRL levels are associated with prostate cancer in humans. Some clinical studies demonstrated the beneficial effects of bromocriptine (an agonist of the type-2 dopamine receptor which inhibits pituitary PRL secretion) in prostate cancer [53–55] and in BPH [56,57]. Thus, using antiprolactinic molecules or extracts, in addition to antiandrogen therapies, could be beneficial in BPH and especially in the androgeno-independent forms of prostate cancer in humans.

CONCLUSIONS

This study demonstrates that LSESR inhibits the lateral rat prostate hyperplasia induced by hyperprolactinemia. Finasteride, a specific 5α-reductase inhibitor, is ineffective in antagonizing PRL action. Further experiments are required to identify the actions of different subfractions of LSESR in this in vivo model of prostate hyperplasia in order to determine which active component inhibits this PRL-induced hyperplasia.

The pleiotropic effects of LSESR partly explain the effectiveness of this drug in treating human benign prostate hyperplasia.

ACKNOWLEDGMENTS

We thank Ariane Bouteillier, Claudine Carbon, and Christelle Milluy for carrying out the histological technical procedures.

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