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Spontaneous Hyperplasia of the Ventral Lobe of the Prostate in Aging Genetically Hypertensive Rats

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ABSTRACT Recent studies have shown that the prostatic autonomic innervation takes part in its homeostasis and growth. Other works showed that spontaneously hypertensive rats (SHR) show excessive sympathetic activity, accompanied by lower urinary tract symptoms, increased growth capacity of prostatic stromal cells, and increased levels of androgens and their receptors. Furthermore, young SHR were reported to present incipient stages of benign prostatic hyperplasia (BPH). The aim of the present study was to examine whether this strain indeed develops spontaneous BPH with age, and can thus serve as a genuine natural model for this disorder. For this purpose, ventral lobes of prostates of one-year-old, male SHR and their normotensive counterparts, Wistar Kyoto (WKY) rats, were examined histopathologically, and the degree of hyperplasia was evaluated according to a score-chart protocol (histoscore). SHR exhibited severe adenomatous spontaneous BPH, characterized by piling-up of epithelial cells, with papillary formations, accompanied by a mild increase in the amount of fibrocytes and smooth muscle cells in the stroma. This was reflected by histoscore values of 38 ± 2. Thickening of prostatic arterioles also was noted, as well as mild chronic inflammatory exudate. WKY rats did not show any of these features of BPH despite their age (histoscore 17 ± 3, significantly different from that of SHR). We conclude that SHR can serve as a rodent model for the spontaneous development of BPH with age, most probably due to the excessive neuroendocrine activity characteristic of this rat strain.

Key words: Sympathetic nervous system; prostatitis; senescent rats; blood pressure.

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The prostate gland in both man and rat is innervated by fine networks of axonal fibers surrounding the glandular elements, most of which are catecholaminergic (Baumgarten et al, 1968; Elbadawi and Goodmas, 1980; McVary et al, 1998), and contains different subtypes of adrenergic receptors (Lepor et al, 1993; McVary et al, 1998). The potential involvement of the sympathetic nervous system in the pathogenesis of benign prostatic hyperplasia (BPH) has recently attracted scientific interest (McVary et al, 1998). Experimental denervation of the prostate induces atrophic changes of the acini as well as a decrease in their secretory activity (Wang et al, 1991; Martinez-Piñeiro et al, 1993; McVary et al, 1994, 1998). Moreover, α-adrenergic antagonists have been used for the treatment of BPH for many years (Caine, 1986, 1995; Beduschi et al, 1998), and recently doxazosin was shown to induce apoptosis of both prostatic stromal and epithelial cells (Kyprianou et al, 1998). We recently showed, that daily administration of pharmacologic doses of the α-adrenergic agonist phenylephrine for 1 month is sufficient to induce atypical glandular prostatic hyperplasia in rats (Golomb et al, 1998). Taken together, these data suggest that excessive sympathetic activity may contribute to and promote prostatic overgrowth of epithelium and stroma.

There have been epidemiologic reports of association between BPH and hypertension, without the suggestion that such association is necessarily causal (Boyle, 1994). Excessive sympathetic activity is known to play a role in hypertension (Pool, 1994; Julius, 1996; Mancia, 1997), and therefore might constitute a pathogenetic link between BPH and high blood pressure (Pool, 1994).

One of the most studied experimental models of hypertension is the spontaneously hypertensive rat (SHR). Excessive basal and environmentally evoked sympathetic activity is a major feature of these rats, and this activity has a major contribution to their high blood pressure (Magee and Schofield, 1994; Pool, 1994; Julius, 1996). In addition, excessive sympathetic activity in SHR also leads to hyperactive urinary voiding in this rat strain (Clemow et al, 1997; Persson et al, 1998). Another interesting feature of the SHR is an increased proliferation rate of different primary cells (fibroblasts and vascular smooth muscle cells) derived from SHR in culture, compared with its normotensive counterpart, the Wistar-Kyoto rat (WKY: Paquet et al, 1989; Guicheney et al, 1991; Golomb et al,

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1994). To the best of our knowledge, a comparison of the growth rates of epithelial cells of the 2 rat strains has not been reported.

Initial proliferative lesions in prostates of young SHR were reported by Nakamura et al (1991). They also found that this abnormality was inhibited by α-adrenergic blockade (Nakamura and Itakura, 1992). Integrating all these data on SHR led us to inquire whether this strain displays significant spontaneous prostatic hyperplasia progressing with aging, and thus can serve as a new model to study the natural intrinsic evolution of this disease. For this purpose, we examined and characterized the morphologic features of the prostates of aged SHR and compared them with those of the normotensive WKY rats.

Materials and Methods

Animals

One-year-old male SHR (n = 9) and WKY rats (n = 10) were used. The rats were housed in rooms with controlled temperature and a 12-hour, light-dark cycle, and had free access to standard rat chow pellets and tap water. Systolic blood pressure was recorded periodically by the tail cuff method (IITC, Woodland Hills, Calif).

The animals were euthanized by intraperitoneal lethal dose of chloral hydrate, the prostate was excised, and the ventral lobes were separated and fixed for 5 hours in Stieve's solution: 76% vol/vol saturated $HgCl_2$ (Sigma, St Louis, Mo), 20% vol/vol formaldehyde 37% (Merck, Darmstadt, Germany), and 4% glacial acetic acid (Merck; Lillie, 1965). Thereafter, the tissue was thoroughly rinsed with water, routinely dehydrated in ethanol and xylene, paraffin embedded, and cut into 5-μm thick sections. Following rehydration steps, in order to remove remnants of mercury salts, the sections were bleached with Lugol's solution for 10 minutes, washed with water for 5 minutes, immersed in 5% sodium thiosulfate solution, and washed again (Lillie, 1965). Then, they were stained by Harris' hematoxylin-eosin, according to standard procedures.

Histopathologic Examination of Slides and Histoscore

To ensure a thorough and uniform pathologic examination that can be analyzed by standard spreadsheets, a semiquantitative assessment of the main histopathologic findings from SHR and WKY rats was used. We recorded the histopathologic examination of each specimen with a score-chart protocol, ''histoscore,'' which was previously developed and modified in our laboratory (Scolnik et al, 1994; Golomb et al, 1998). This approach takes into account the various histologic changes of the glandular epithelium, such as acinar regularity, presence of intraluminal villosities or papillary projections and cribriform patterns, as well as loss of cellular polarity with focal hyperplastic nodules (piling-up), or extrusion (budding-out) of epithelial cells into the stroma. The examination, description, and scoring of the slides were performed in a blinded manner, so that the examiners of all the slides were unaware of the rat strain as they were examining the specimens.

Table 1. *Comparison of basic data of 1-year-old Wistar Kyoto (WKY) rats versus spontaneously hypertensive rats (SHR)**

Variable	WKY (n = 9)	SHR (n = 10)
Body weight (g)	295 ± 12	307 ± 6
Systolic blood pressure (mm Hg)	136 ± 8	232 ± 18†
Heart weight (g)	1.12 ± 0.07	1.72 ± 0.31†
Prostate histoscore (arbitrary units)	17 ± 3	38 ± 2†

* Data are expressed as mean ± SEM.
† Significantly different from WKY, $P < .05$.

Presentation of Data

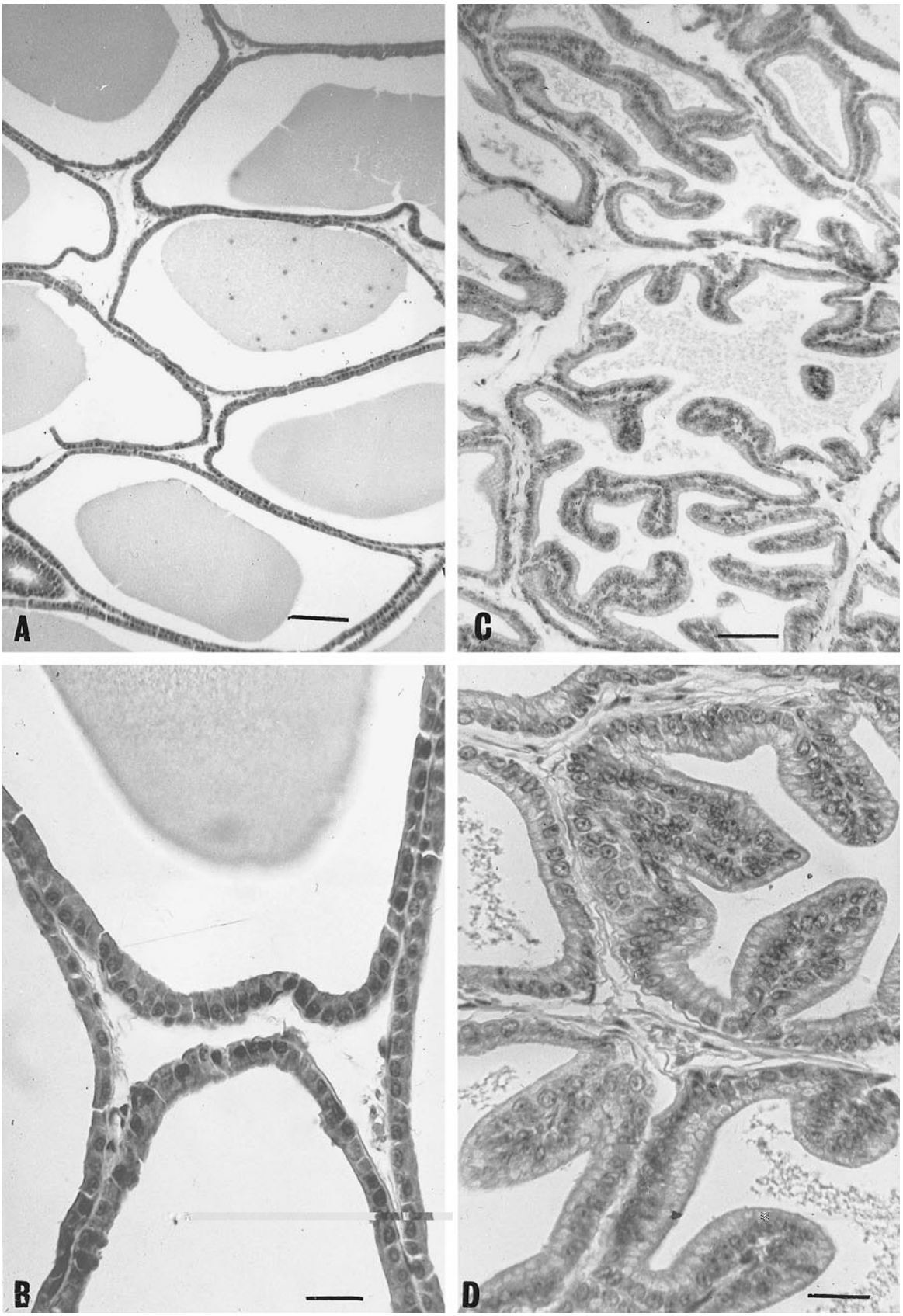
Histoscores were expressed in arbitrary units, and were obtained from a thorough examination of 3 different sections, from 3 different levels, for each animal. Data were expressed as means ± SEM. Student's *t* test was used to analyze differences between the strains.

Results

Systolic blood pressure and heart weight were significantly different in one-year-old SHR and WKY rats, whereas their body weight was similar (Table 1). The histopathologic examination of the ventral portions of the prostates of SHR revealed definite lesions of benign adenomatous hyperplasia, in contrast to the normotensive rats, which showed a normal morphologic pattern (Figures 1 and 2; Table 2).

Prostates of WKY rats were characterized by regular, unfolded closely packed acini (Figure 1A) tapered by low cuboidal cells showing a uniform monolayered arrangement (Figure 1B). Their acinar lumen was filled with a proteinaceous granular eosinophilic material. A delicate fibrous stroma with thin-walled blood vessels was intermingled between the acini (Figures 1B and 2A). The histoscore value of these normal features was of 17 ± 3 units (Table 2).

The ventral lobes of the prostates of SHR showed irregular acini with many intraluminal projections protruding into the acini to a variable extent (Figure 1C), together with a decrease in the amount of prostatic secretions (Figure 1C and D). Their epithelial cells were taller in shape, with irregularities in their nuclear arrangement (apolarity; Figure 1D), and even focal conglomerates of cells piling-up were noted (Figure 2B). The stroma of these rats was characterized by severe periarterial fibrosis, mild fibrosis in other interacinar areas, along with hypertrophy of the smooth muscle cells (Figures 1D and 2B). These lesions were reflected by a histoscore value of 38 ± 2 units (Table 2). In some cases a slight inflammatory exudate consisting of mononuclear leukocytes also was noted (Figure 2B). The prostatic arterioles of SHR had a thick wall with narrowed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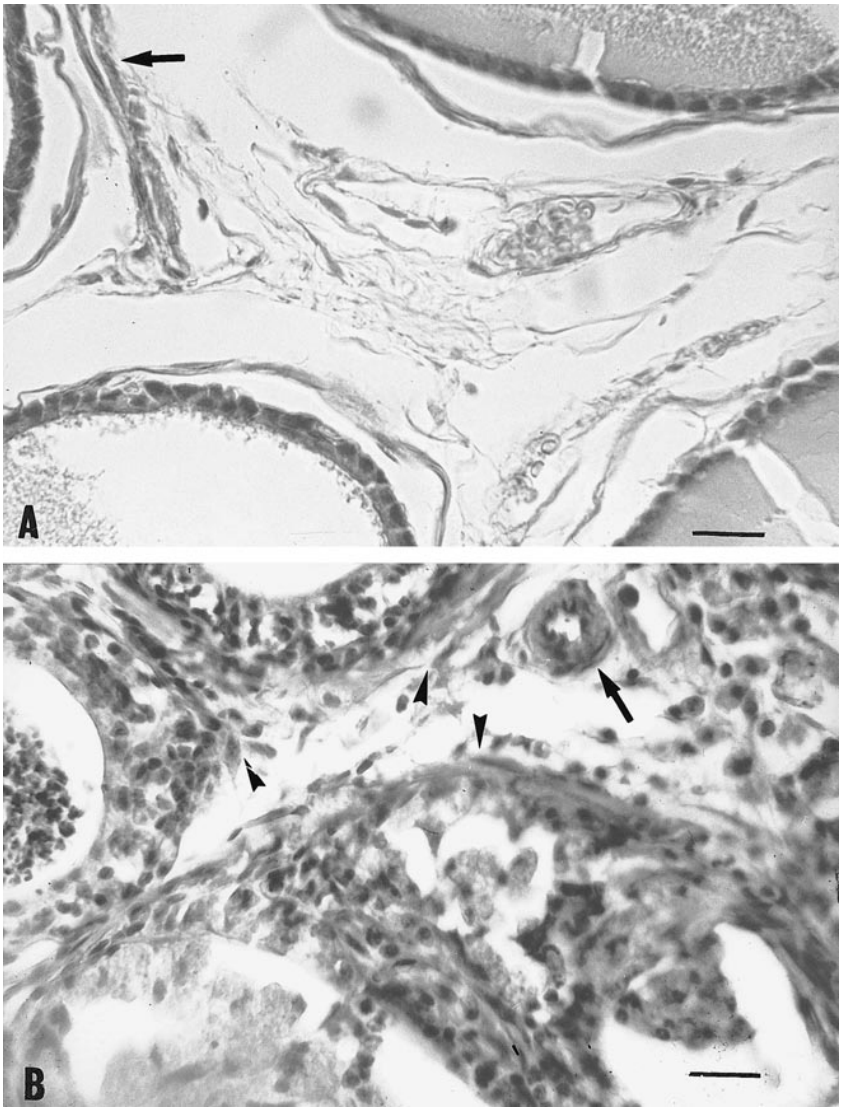

Figure 2. Comparative prostatic stromal features of one-year-old normotensive WKY rats **(A)**, and spontaneously hypertensive rats **(B)** are shown. Slightly edematous delicate stroma, with few fibrocytes are observed in the normotensive rat prostate **(A)**. Arrowheads indicate interacinar fibrosis, with hypertrophy of periacinar smooth muscle cells and a mild mononuclear leukocyte exudate in SHR **(B)**; arrows, the difference in arteriolar wall thickness between the 2 strains. Scale bar = 25μm. Hematoxylin–eosin stain.

lumina (Figure 2B) due to vascular smooth muscle hypertrophy resulting from hypertension.

Discussion

In this study, we found that the ventral prostate gland of old SHR show definite features of benign adenomatous hyperplasia.

Different laboratories have invested a lot of effort to provide adequate experimental models for BPH. Most of the studies concerning prostatic disorders in rodents, especially in rats, deal with the effect of sex hormones on the prostatic microenvironment or with the induction of growth by different chemical substances (Scolnik et al, 1994; Ho et al, 1995). In this study, we show that the genetically hypertensive rat strain, SHR, also develops

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Figure 1. Ventral prostate acini of one-year-old normotensive Wistar Kyoto (WKY rats) **(A**, **B)**, and spontaneously hypertensive rats (SHR) **(C**, **D)** are shown. Note the densely packed regular acini, filled with a proteinaceous material **(A)**, tapered with a monolayer of cuboidal cells, and surrounded by a delicate fibrovascular stroma **(B)**. Irregular, rather empty acini with intraluminal projections **(C)**, consisting of columnar cells, some of which lost their polar arrangement **(D)** are found in SHR. The stroma is fibrous and relatively dense **(D)**. Scale bar = 60 μm in A and C, and scale bar = 25 μm in B and D. Hematoxylin–eosin stain.

Table 2. *Histoscore results in WKY rats and SHR**

Variable (score values)	WKY	SHR
Low power magnification		
Luminal shape: regular (1), villous (3), papillary (4), cribriform (5)	1.0 ± 0	4.5 ± 0.2†
Acinar shape: tubular (1), branched (3), irregular (5)	1.7 ± 0.3	4.0 ± 0.4†
Interacinar space: large or moderate (1), back-to-back glands (5)	2.0 ± 0.7	3.8 ± 0.6
Stroma: fine (1), abundant (3), fibrosis/severe SM hyperplasia (5)	1.2 ± 0.2	1.8 ± 0.4
High power magnification		
Epithelial shape: flattened (1), cuboidal (1), cylindrical (3), hexagonal (5)	2.0 ± 0.4	2.8 ± 0.2
Number of layers: mono (1); oligo, 2–4 (3); pluri, >5 (5)	1.6 ± 0.3	2.6 ± 0.3†
If >1, add: focal (3), diffuse (5)	0.9 ± 0.5	1.6 ± 0.4
Alignment: polar (1), apolar (3)	1.0 ± 0	3.0 ± 0†
If there is piling up of epithelial cells add 3	0	2.4 ± 0.4†
If there is budding out of epithelial cells into stroma add 5	0	0
If periacinar clusters of epithelial cells are found add 3	0	0
If isolated clusters of epithelial cells are found outside acini add 5	0	0
Lesion distribution (for apolar or budding out cells, no lesion = 0): unilobar; isolated (2), multiple (6). bilobar; isolated (4), multiple (8)	0	4.8 ± 0.7†
Nuclear shape: round, regular (1); irregular (5)	1.0 ± 0	1.0 ± 0
Nuclear size: small (2), large (2), small and large in the same acinus (4)	2.2 ± 0.2	3.4 ± 1.0
Mitoses per field: absent (0); isolated, 1–2 (2); abundant, 3–5 (5); excessive, >5 (10)	0	0
Basement membrane:		
intact (1); interrupted (5)	1.0 ± 0	1.0 ± 0
thin (1); thick (5)	1.0 ± 0	1.0 ± 0
Total score (arbitrary units)	17 ± 3	38 ± 2*

* Data are expressed as mean ± SEM.
† Significantly different from WKY, $P < .05$.

BPH-like features with aging, mainly of the glandular type, in the absence of any inductive exogenous agents. WKY rats, like rats of other strains such as Sprague-Dawley or Fischer rats, do not spontaneously develop prostatic hyperplasia with advancing age (Scolnik et al, 1994). However, the appearance of the dorsal and lateral prostate lobes is more variable between individual animals, and we did not observe obvious differences between the strains.

The precise mechanism that associates BPH with lower urinary tract symptoms (LUTS) is yet unclear. However, the poor correlation between the degree of BPH and LUTS (Andersson, 1996; Teillac, 1998) implies that LUTS do not directly derive from mechanical benign prostatic obstruction (BPO) caused by the BPH mass volume. The effect of the sympathetic nervous system on both prostatic growth and urinary voiding may be the link between these factors (Andersson, 1996). SHR are known to exhibit excessive basal and environmentally evoked sympathetic activity (Magee and Schofield, 1994), as well as LUTS (Clemow et al, 1997, 1998). LUTS in SHR occurs in young females, as well as males (Clemow et al, 1998). The finding that this rat strain also exhibits BPH lesions supports the role of the sympathetic nervous system in this disorder.

SHR were originally bred according to their high blood pressure, by brother and sister mating of hypertensive rats, and this strain is considered one of the best experimental models of hypertension (Frohlich et al, 1991). Extensive research has been performed to elucidate mechanisms that contribute to their high blood pressure. Many differences, in various physiologic systems and basic cellular functions have been found between SHR and their normotensive controls, the WKY rats, that could account for spontaneous hypertension. Some of the following differences might be relevant to the finding that these rats also exhibit BPH: 1) It was shown that primary fibroblast and smooth muscle cells derived from SHR grow faster than those derived from WKY, or other strains of normotensive rats (Paquet et al, 1989; Golomb et al, 1994). Overgrowth of cells could obviously lead to BPH directly and through local mesenchymal-epithelial interactions (Cunha, 1994). 2) SHR show excessive basal and environmentally evoked sympathetic activity, and this activity has a major contribution to their high blood pressure (Magee and Schofield, 1994; Pool, 1994, Julius, 1996). The direct contribution of neural factors to high blood pressure in these rats was proven by the finding that implantation of the hypothalamic tissue of SHR embryos into the periventricular area of WKY adult rats renders them hypertensive, whereas implantation of WKY hypothalamic tissue does not have such an effect (Eilam et al, 1991). Data are accumulating that the neural factors also play a role in the development of BPH (McVary et al, 1998). 3) In some blood vessels, SHR show increased responsiveness to α-adrenergic stimuli (Uchino et al, 1991). If such hyperresponsiveness also takes place in prostatic tissue, it might contribute to the development of hyperplasia: subchronic α-adrenergic stimulation leads to prostatic hyperplasia in rats (Golomb et al, 1998), and inhibition is associated with programmed cell death in the human prostate (Kyprianou et al, 1998). 4) SHR were found to show important alterations in the neuroendocrine function of the hypothalamic-pituitary axis, which affect their sex-hormones homeostasis. They show higher affinity of androgen receptors in the adrenal medulla than normoten-

sive controls (Kumai et al, 1997), and higher circulating levels of follicle-stimulating hormone (FSH) and testosterone (Aguilar et al, 1992). In the latter study, Aguilar et al found that the efficiency of testosterone to stimulate ventral prostate growth and the ability of estradiol to reduce FSH plasma levels were decreased in SHR. However, they assessed prostate growth state mainly by determining prostatic weight, but not on histologic criteria. Because adrenergic stimulation depletes the prostate of its secretion (Golomb et al, 1998), prostatic weight may not necessarily reflect the hyperplastic or the atrophic status of the prostate in this model. 5) SHR were found to produce increased amounts of nerve growth factor (NGF) by smooth muscle cells (Clemow et al, 1998, 1999). NGF overproduction can contribute to hyperinnervation of the different organs increasing further neurally mediated growth of the gland, or directly affect its growth. 6) High blood pressure in SHR alters organ blood supply and vascular structure and may affect the production of different autocrine and paracrine factors by the vasculature. Such indirect vascular and metabolic alterations may account for in vivo changes in the hypertensive animals.

The relative contribution of these factors to prostatic growth should be studied in order to comprehend how a strain of rats that was bred on the basis of high blood pressure turned out also to suffer from spontaneous BPH and LUTS. The availability of a rodent model of spontaneous BPH and LUTS may also provide an adequate tool to assess the mode of action and efficacy of drugs that are designed to alleviate these conditions.

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