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Growth of the Rat Prostate Gland Is Facilitated by the Autonomic Nervous System[1]

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ABSTRACT

Many factors are implicated in the development of prostatic growth: androgens, growth factors, and stromo-epithelial interaction. This study examines the role of the sympathetic and parasympathetic branches of the autonomic nervous system control of different aspects of rat prostate growth and atrophy. Unilateral sympathectomy leads to decreases in ventral prostate weight, DNA, and protein content in the lesioned side. Unilateral parasympathectomy leads to increases in ventral prostate weight, DNA, and protein content in the intact side. The separate effects of sympathectomy and parasympathectomy are maintained across a diverse combination of neural manipulations. Significant re-innervation does not occur by 60 days after manipulation as assessed by tissue norepinephrine levels. There appears to be a differential effect of the autonomic nervous system on growth and maintenance of the ventral prostate. The mechanism of contralateral hyperplasia and ipsilateral atrophy has potential significance in understanding human abnormal prostate growth.

INTRODUCTION

Several factors are implicated in normal prostate development and growth: androgens, growth factors, and stromo-epithelial cell interactions. These factors are also speculated to play a role in benign prostatic hyperplasia. The rat prostate provides a convenient model for examining the actions of these agents in regulating prostate growth, maturation, and function. Much effort has been devoted to investigating the factors listed above; however, little attention has been paid to characterizing the role of neural innervation of the rat prostate in normal and abnormal growth patterns.

The prostate gland of the rat receives both sympathetic and parasympathetic neural input [1–3]. Sympathetic input is supplied by the hypogastric nerve, while parasympathetic input is furnished by the pelvic nerve. The pelvic ganglion, through which these nerves travel, provides autonomic innervation not only to the prostate but also to most of the pelvic viscera.

Wang et al. [4] demonstrated that denervating the rat prostate results in the loss of functional and structural integrity of the gland. To further characterize the role of autonomic innervation on growth and maintenance of the prostate gland, we lesioned selected components of the prostate's autonomic nervous supply. From the differential effects of sympathectomy, parasympathectomy, and ganglionectomy upon prostate morphology and function we conclude that the sympathetic and parasympathetic branches play differential roles in prostate growth and maintenance of secretory function. Thus autonomic innervation must be considered as an important influence in the interplay of factors regulating prostate growth.

MATERIALS AND METHODS

Animal Care and Surgery

Thirty-day-old Sprague-Dawley rats (Harlan Sprague-Dawley Inc., Cumberland, IN) were housed in an air-conditioned room with lights-on between 0600 and 1800 h. Food and water were provided to the animals ad libitum.

The rats were anesthetized with isoflurane in 100% oxygen. A midline, lower abdominal incision was made to expose the urogenital complex. The pelvic ganglion lies in a parasagittal plane on the lateral surface of the lateral lobes of the prostate. It is located under several fascial layers, caudal to the point where the ureter and vas deferens intersect. The pelvic nerve is found entering the dorsal aspect of the ganglion, usually traveling with 1–2 small arteries that supply the ganglion [2]. The hypogastric nerve travels near the ureter and enters the ganglion's superior border.

A KAPS Industrial Dissecting Microscope, glass nerve hooks, and microscissors were used to cut the pelvic and hypogastric nerves; a small length of nerve fiber (1–2 mm) was removed just proximal to the ganglion, thereby creating a preganglionic parasympathectomy and sympathectomy, respectively. In one group, both nerves were cut. The nerves were cut proximal to the ganglion because sympathetic and parasympathetic fibers are indistinguishable after they exit the ganglion. In the ganglionectomy groups, the pelvic ganglion was dissected free and completely removed without disturbing the adjacent tissues or vascular supply. All procedures were performed on the left side. Selective lesions of the autonomic nerve supply to the prostate of

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Sprague-Dawley rats were surgically created by pre-ganglionic sympathectomy (Sym), preganglionic parasympathectomy (Para), combined preganglionic parasympathectomy and sympathectomy (Sym-Para), and ganglionectomy (PG). The sham (SH) group were age-matched animals that underwent the same exposure of the pelvic ganglion without the neural manipulation or lesioning.

An additional control group consisting of normal nonmanipulated 30-day-old rats were included in this study. These 30-day-old "normal" rats were killed to obtain ventral prostate weights only. These weights were used as baseline values when results from our subsequent neural manipulation studies were examined. Knowing the ventral prostate weight of a 30-day rat is important because of potential questions raised concerning "prostate atrophy" versus "decreased rate of prostate growth" after creation of neural lesions.

The prostate derives its blood supply from the superior vesical artery, which arises from the internal iliac [5, 6]. The superior vesicle artery travels near the base of the seminal vesicle and splits at the junction of the bladder, and ventral and lateral lobes of the prostate before supplying them and the dorsal lobe. Special attention was paid not to disturb these vascular channels.

To eliminate potential stress-related fluctuations of serum testosterone levels, at the time of neural surgery, we performed a bilateral epididymo-orchiectomy and placed a 2-cm piece of medical-grade silastic tubing (Dow Corning Corp., Midland, MI) filled with crystalline testosterone (Sigma, St. Louis, MO) subcutaneously in all groups (Sym, Para, Sym-Para, PG, and SH) [7]. Previous work in our lab has been published demonstrating the physiologic appropriateness of 2-cm testosterone/silastic tubing implants in castrated rats as measured by body weight, serum testosterone, ventral prostate weight, and prostatic secretions (volume, protein content, and acid phosphatase activity [8]. Twenty-eight to 30 days after surgery, the rats were killed with Metofane (Pitman Moore, Mundelein, IL) anesthesia and subsequent decapitation. The ventral, lateral, and dorsal lobes from both sides were each dissected out, weighed, and immediately either placed in liquid nitrogen and stored at −80°C for later determination of DNA and protein levels or placed in formalin for subsequent histological examination. Tissue catecholamine levels found in the ventral prostates were measured at 30 and 60 days postoperatively (at 60 and 90 days of age, respectively) in two groups (SH and Sym-Para). Ventral lobe prostate binding protein (PBP) levels were measured in four groups (SH, Sym, Para, and Sym-Para) 30 days postoperatively. The weights of the seminal vesicles and coagulating glands were measured in the SH, Sym, Para, and Sym-Para groups at 30 days after neural manipulation.

DNA and Protein Determination

For DNA and protein determination, the tissue samples were homogenized in 2–4 ml of ice-cold PBS. For DNA analysis, the homogenate was centrifuged with 20% trichloroacetic acid (TCA) to remove the acid-soluble compounds from the homogenate. Because nucleic acids are readily soluble in hot TCA, the pellet was treated twice at 90°C; the remaining tissue proteins formed an insoluble residue. The combined supernatants were used for DNA determination according to the method of Schneider [9], with calf thymus DNA used as the standard. For assessment of protein, an aliquot of the homogenate was treated with 20% TCA, and the protein content was determined by the method of Lowry et al. [10].

PBP Determination

The PBP level was ascertained by using an enzyme-linked fluorogenic immunoassay. Duplicate wells of polystyrene microfluor-B plates (Dynatech Laboratories, Alexandria, VA) were coated with 100 μl of 1.25 μg/ml of homogenized prostate protein in 0.1 M $NaHCO_3$ (pH 9.0) for 3 h at room temperature. The wells were then back-coated with 360 μl of PBS containing 1% (w/v) BSA (fractionated by heat shock; Sigma Chemical Company) and 0.02% sodium azide for 1.5 h at room temperature. The plates were washed three times with PBS containing BSA (Fraction V, Sigma Chemical Co.), sodium azide, and 0.1% (v/v) Tween 20; appropriate dilutions of an anti-PBP antibody (rabbit anti-rat IgG; the 1° Ab) were added to the wells, and the plates were incubated overnight at 4°C. The plates were again washed. Subsequently, 100 μl of biotinylated goat anti-rabbit IgG (2° Ab; 1:2000 dilution Vector Laboratories, Burlingame, CA) was added to the wells, which were left to stand for 2 h at room temperature. Then, 100 μl of streptavidin-β-galactosidase (1:2000 dilution; GIBCO BRL, Gaithersburg, MD) was added to each well. After 2 h at room temperature and another washing, the assay was developed by addition of 100 μl per well of the substrate, 4-methylumbelliferyl-ß-D-galactoside (Sigma Chemical Company), prepared to 0.1 mg/ml in 10 mM sodium phosphate buffer, pH 7.5, containing 1 mM $MgCl_2$, and 0.1 M NaCl. After 5-min incubation, the plates were read at 450 nm in a fluorescence concentration analyzer (Pandex FCA, Iddex Corp., Portland, ME), and the results were reported as relative fluorescence units (RFU). For the positive control, purified PBP was used to coat the wells [11]. Negative controls included omission of the antigen and of the primary antibody.

In addition to qualitatively detecting PBP in the tissue samples, we also developed a system for quantifying this protein. Quantification was based on a competitive inhibition assay in which the anti-PBP antibody was incubated in solution with increasing concentrations (0–100 μg/ml) of pure PBP. With PBP coated in the wells, the reactivity of the inhibited antibody was then determined. With this used as a standard inhibition curve, it was possible to determine the inhibition capacity of the tissue samples when they replaced PBP as inhibitors. This standard curve allowed us to report the data as nanograms or micrograms of PBP per

TABLE 1. Consequences of procedures on ventral prostate.

	Side	Symp (n = 19)	Para (n = 17)	Symp-Para (n = 37)	PG (n = 17)	SH (n = 31)
Weight, g/lobe (% of sham)	Denervated	0.116 ± 0.005 (77.3)*	0.137 ± 0.011 (91.7)	0.125 ± 0.007 (83.4)*	0.126 ± 0.010 (84.2)*	0.150 ± 0.005 (100.0)
	Intact	0.159 ± 0.011 (102.4)	0.201 ± 0.011 (129.5)*	0.181 ± 0.005 (114.2)*	0.191 ± 0.013 (123.7)*	0.161 ± 0.005 (100.0)
DNA, μg/lobe (% of sham)	Denervated	247.72 ± 98.15 (77.9)	324.10 ± 66.24 (101.9)	206.40 ± 73.17 (64.9)*	259.29 ± 65.67 (81.6)	317.87 ± 66.83 (100.0)
	Intact	355.02 ± 108.72 (97.9)	471.24 ± 140.12 (129.9)*	396.59 ± 104.01 (109.3)	531.85 ± 103.34 (146.6)*	362.67 ± 82.02 (100.0)
Protein, mg/lobe (% of sham)	Denervated	9.78 ± 1.82 (76.1)	14.27 ± 4.17 (111.1)	10.57 ± 2.56 (82.3)	11.01 ± 3.43 (85.8)	12.84 ± 2.80 (100.0)
	Intact	14.76 ± 6.50 (117.8)	18.18 ± 4.52 (145.1)*	15.75 ± 3.89 (125.7)	22.24 ± 6.94 (177.5)*	12.53 ± 3.84 (100.0)

*$p < 0.05$ compared to same-side sham using ANOVA followed by t tests.

milliliter of solution. The percentage of inhibition was calculated as follows: % inhibition = [1 − (RFU with Inhibitor/RFU without inhibitor] × 100.

Catecholamine Determination

Norepinephrine (NE) levels were determined by adding each frozen tissue sample to plastic tubes containing 400 μl of 0.1 N perchloric acid and 0.1 M sodium metabisulfite (1000:1 solution). After 2 ng of dihydroxybenzylamine was added as an internal standard, the samples were homogenized by sonication and frozen at −80°C until assayed. The catecholamine was separated by reverse-phase chromatography and measured by use of an ESA Coulchem Electrochemical Detector as described elsewhere [12].

Statistical Analysis

A one-way ANOVA, followed by a two-tailed pairwise t-test if the ANOVA p-value was 0.06 or less, was used to compare the results of the experimental groups with those of the sham. A p value of 0.05 or less was considered statistically significant for the t-tests. All statistical analysis was performed on a Macintosh IIx computer.

RESULTS

Ventral Lobe

The consequences of these procedures on ventral prostate weight, DNA, and protein content were examined 30 days after the autonomic manipulations (Table 1). After sympathectomy, the mean weight (g) of the ventral lobe on the denervated side decreased by 22.7% with respect to the SH group ($p < 0.05$), whereas the intact side showed almost no difference compared to the sham. To ascertain whether this decrease in weight represented a change in cell size or cell number, we measured DNA and protein content. The mean DNA content (μg/lobe) of the denervated side decreased by 22.1% with respect to the sham (p = nonsignificant (NS), while the intact side had almost no change. The mean protein content of the denervated side decreased 23.9% with respect to the SH group (p = NS). The intact side had a 17.8% increase as compared to sham (p = NS). These findings indicate that the weight decreases in the denervated prostate after sympathectomy were the result of atrophy. The changes in DNA and protein paralleled those changes seen with weight even though they did not reach statistical significance.

After parasympathectomy, the weight of the denervated side decreased 8.3% (p = NS) with respect to the sham while the intact side increased significantly by 24.8% ($p < 0.05$ with respect to the sham). DNA and protein content had parallel increases (29.9% and 45.1%, respectively) on the intact side and insignificant decreases (1.9% and 11.1%, respectively) on the denervated side. These increases in the protein content and DNA of the intact side reached statistical significance ($p < 0.05$) paralleling the changes in the weight. These increases in the weight, protein content, and DNA content on the intact side represent prostatic hyperplasia. In contrast to the sympathectomy, under this neural manipulation, there is no effect on the denervated side.

Combined preganglionic parasympathectomy and sympathectomy approximated the linear sum of the individual manipulations. The denervated side had a decrease in weight (16.6%), DNA (35.1%), and protein (17.7%) although only the weight and DNA content were found to be statistically significant ($p < 0.05$) and consistent with atrophy. Similarly, the intact side had increases in weight (12.4%), DNA (9.3%), and protein (25.7%). Only the weight change was statistically significant ($p < 0.05$), but the overall trend is one consistent with hyperplasia. These findings suggest that the combined preganglionic parasympathectomy and sympathectomy equal the effect of the denervation done separately.

Removing the pelvic ganglion also approximates the effect of combined parasympathectomy and sympathectomy, and its effect is similar to the linear sum of the individual neural manipulation. After pelvic ganglionectomy, the denervated side had decreases in the weight (15.8%), DNA (18.4%), and protein (14.2%) as compared to sham. Only the weight was statistically significant ($p < 0.05$). The intact

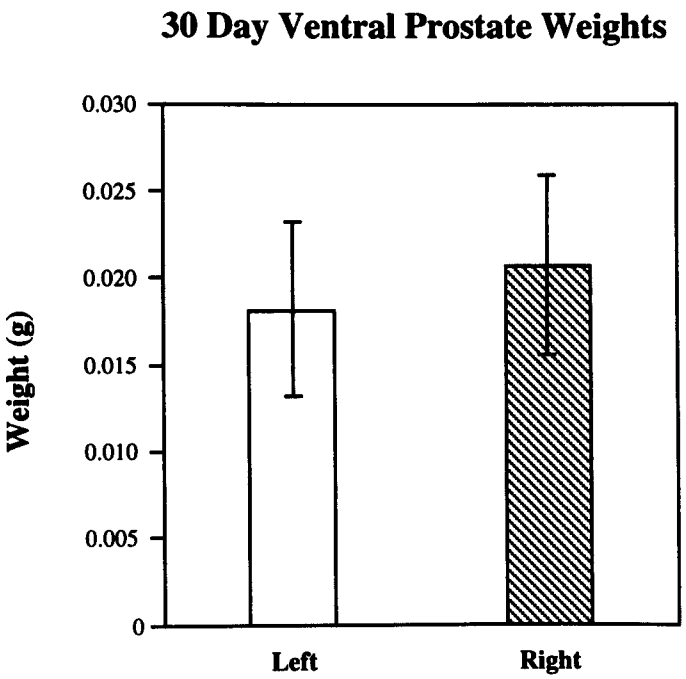

FIG. 1. Mean wet weight (± SEM) of the ventral prostates in 30-day-old rats.

side had significant ($p < 0.05$) increases in weight (18.6%), DNA (46.6%), and protein (77.5%) compared to those of the SH group. Again, sympathectomy leads to atrophy in the lesioned side while parasympathectomy causes hyperplasia in the intact side.

Comparing all surgical groups, a sympathectomy led to ipsilateral ventral lobe atrophy whereas parasympathectomy led to contralateral hyperplasia, suggesting that sympathetic and parasympathetic innervations offer differential control over the growth of the prostate gland. The simultaneous parasympathectomy and sympathectomy results in the linear sum of the procedures done separately. Similarly, removing the ganglion equals the same physiologic effect as combined simultaneous parasympathectomy and sympathectomy. The consistency of the effects of sympathectomy and parasympathectomy regardless of the simultaneous manipulations supports the conclusion that the dichotomy of function in ventral prostate autonomic innervation is real and has a fundamental regulatory purpose. The weights of the normal nonmanipulated 30-day-old ventral prostates are shown on Figure 1. These prostates are smaller than those of the sham-operated and lesioned groups, which were 60 days old at the time they were killed. This indicates that the prostates, even though lesioned, continued to grow at reduced rates (i.e., they showed a reduced rate of growth rather than atrophy). This suggests that neurally manipulated groups (Sym, Para, Sym-Para, PG) had an inhibition of cell division and growth, since the 30-day-old rat prostates had not reached adult size.

In the lateral and dorsal lobes of the prostate, the outcomes of the surgical manipulations had little effect on

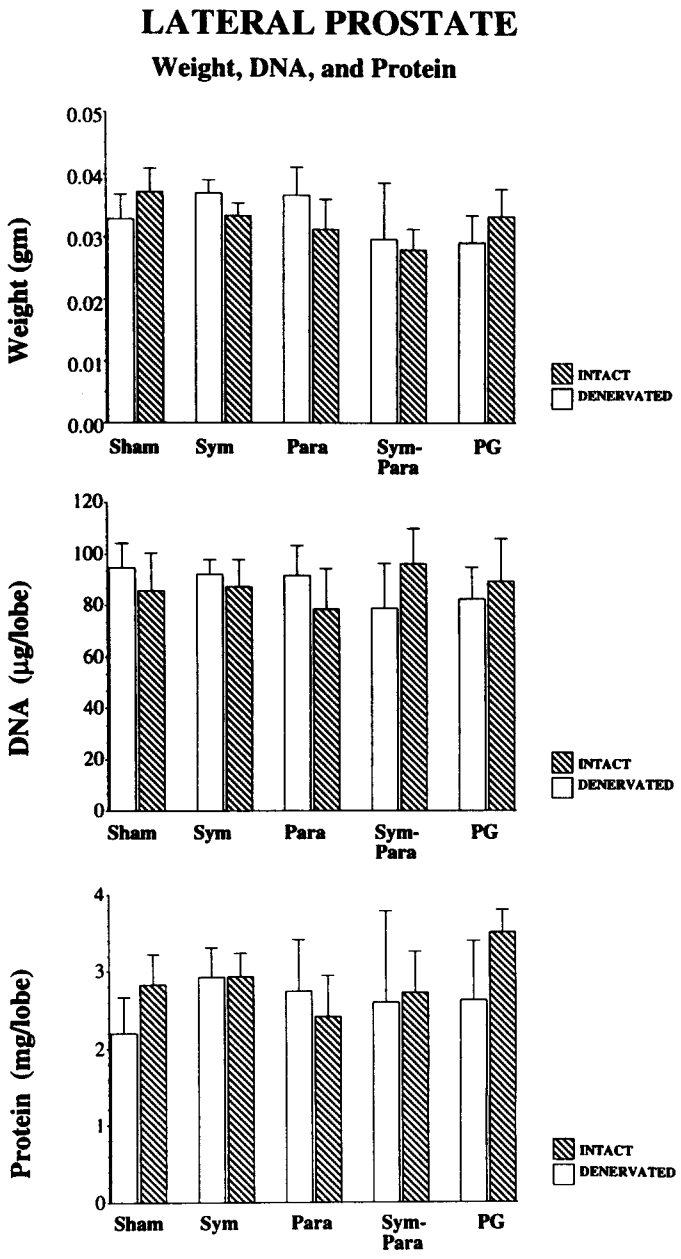

FIG. 2. Mean (± SEM) weight, DNA, and protein from intact and denervated lobes of rat lateral prostates. Numbers in each treatment group are identical to those found in Table 1.

prostate growth. Although each lobe on the lesioned side in many surgical groups was slightly lower in weight, DNA, and protein content than in the intact lobe, neither side was statistically different when compared to the SH group (Figs. 2 and 3).

The levels of ventral lobe PBP were recorded as a measure of epithelial cell secretory function and differentiation of the prostate and compared between SH, Sym, Para, and Sym-Para groups. As shown in Figure 4, the levels on the lesioned side in the experimental groups did not differ from the sham levels. However, there was an increase on the

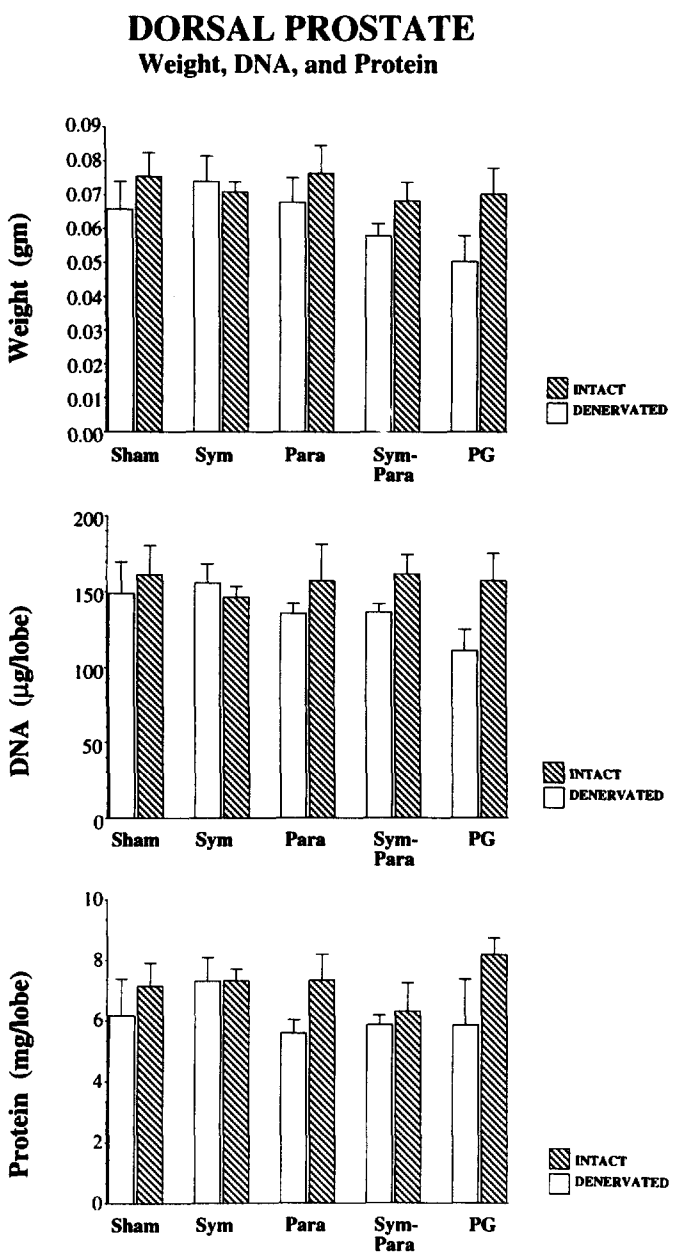

FIG. 3. Mean (± SEM) weight, DNA, and protein from the intact and denervated lobes of the rat dorsal prostates. Numbers in each treatment group are identical to those found in Table 1.

intact side in the Sym ($p < 0.05$), Para ($p < 0.05$), and Sym-Para (p = NS) groups when compared to the SH. This increase is consistent with the increase in protein, DNA, and wet weight seen on the intact side, and supports the concept of hyperplasia.

The tissue levels of NE were contrasted between the following groups: 30-day SH, 30-day Sym-Para, 60-day SH, and 60-day Sym-Para (Fig. 5). These were measured as an assessment of denervation. The NE levels in the ventral prostate 30 and 60 days after a combined sympathectomy-parasympathectomy remained low on the left and right sides compared to those of their respective shams ($p < 0.05$ at

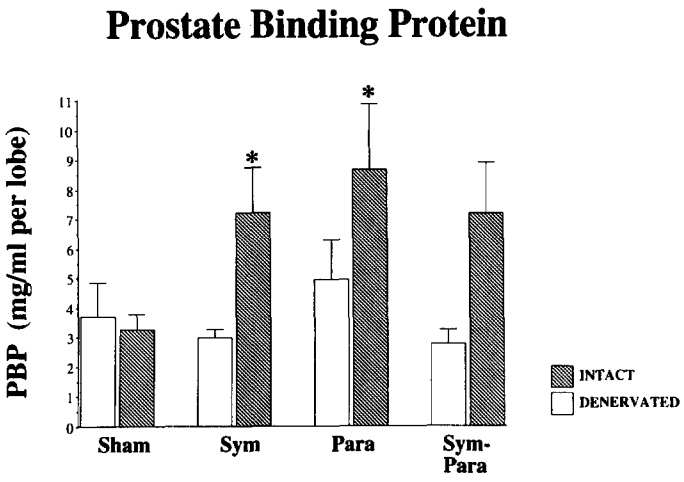

FIG. 4. Mean (± SEM) of rat PBP from ventral lobes. * = < 0.05, one-way ANOVA.

60 days, p = NS at 30 days). This implies that there was no reinnervation of the prostate.

In a separate set of studies, the weights of the coagulating gland and seminal vesicle were measured in sham, sympathectomy, parasympathectomy, and sympathectomy-parasympathectomy rats. The weight of the seminal vesical remained constant after the denervations. Although the weight of the coagulating gland appears decreased after the ablations, these changes were not statistically significant (Fig. 6, a and b). These findings suggest that denervation affects the ventral lobe of the prostate differently from other accessory sex glands.

Histology

Qualitative histologic review of the ventral prostate specimens submitted for hematoxylin and eosin staining failed to reveal morphologic changes when the various groups were compared (SH vs. Sym vs. Para vs. Sym-Para).

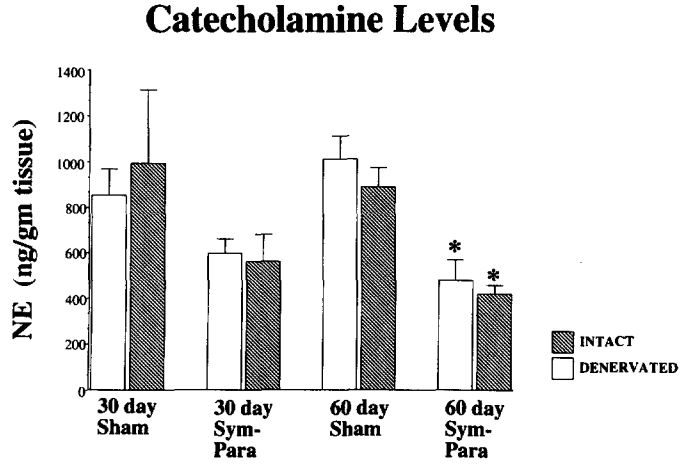

FIG. 5. Mean (± SEM) of ventral lobe tissue NE tissue levels (ng/gm tissue). *$p < 0.05$, one way ANOVA with respect to the 60-day sham.

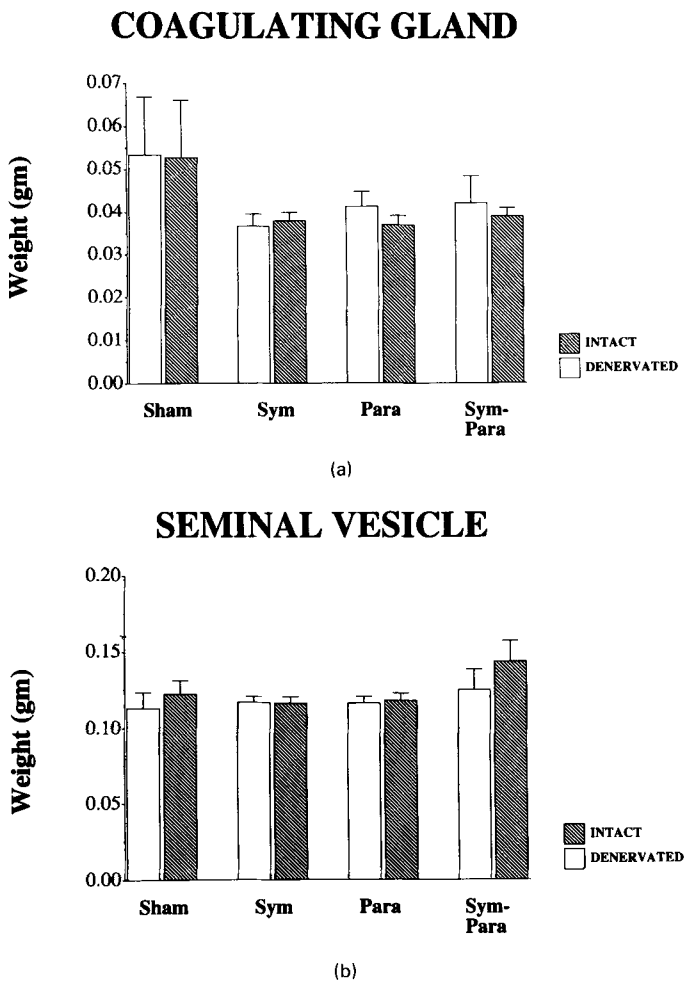

FIG. 6. a) Mean wet weight (± SEM) of rat coagulating gland. b) Mean wet weight (± SEM) of rat seminal vesicle.

DISCUSSION

Although it is widely accepted that androgen ablation causes involution of the rat prostate [13, 14], only recently has the trophic role of innervation of the gland been realized. Thompson et al. [15] illustrated that autonomic neural innervation plays an important role in the growth and differentiation of prostate tissue. We lesioned the components of the autonomic nervous system that supplied the prostate on one side. Our study demonstrates that denervation leads to ipsilateral atrophy and contralateral hyperplasia of the ventral lobe. Wang et al. [4] showed that complete bilateral denervation of the prostate leads to a drop in the DNA and protein content of the ventral lobe. The atrophy in Wang's study represents a fall in cell number from a prior steady-state, adult level. In our study, this atrophy represents an inhibition of cell division and growth since 30-day-old rat prostates have not reached adult size (Fig. 6). This concept is supported by our own data as well as by the literature [16].

Fibers of sympathetic preganglionic nerves, whose cell bodies lie in the upper lumbar spinal cord, travel in the hypogastric nerve [17]. Parasympathetic preganglionic fibers, which originate in the sacral spinal cord, travel in the pelvic nerve [18]. Because other potential sources of neural innervation exist, cutting the hypogastric or pelvic nerve on one side may not result in a complete unilateral sympathectomy or parasympathectomy. Blood vessels provide one possible route: they carry sympathetic fibers that may advance into the prostate once it is relatively denervated. Langworthy [2] demonstrated anatomically that a few fine nerve fibers arising from the pelvic ganglion cross the midline over the urethra. Another source of innervation may therefore be fibers coming from the contralateral pelvic ganglion. Lastly, the urethra and prostatic ducts also contain an intrinsic serotonergic system comprised of small paracrine cells [19–24]. How these cells influence prostate growth and function is not known.

In our study, the following surgical manipulations were performed on the left side in the pelvis of male rats: sympathectomy, parasympathectomy, combined sympathectomy-parasympathectomy, and pelvic ganglionectomy. Perhaps not surprising is that sympathectomy leads to atrophy of the lesioned side. This is supported not only by a decrease in ventral prostate weight, but also a decrease in DNA and protein content, implying a decrease in cell number. By contrast, parasympathectomy leads to hyperplasia of the intact side as demonstrated by increases in weight, DNA, and protein. The accompanying increase in DNA and protein imply an increase in cell number, not hypertrophy. Combined parasympathectomy and sympathectomy results in a near linear sum of the effect of each manipulation alone, namely an atrophy of the lesioned side and hyperplasia of the intact side. Pelvic ganglionectomy has the same effect as combining preganglionic parasympathectomy and sympathectomy, suggesting that decentralization of the ganglion is equivalent to simple removal of the ganglion. There is consistency of effect, with atrophy on the lesioned side and hyperplasia on the intact side regardless of what combination of sympathectomy and parasympathectomy is performed. The predictability of this effect across the various combinations of nerve ablations illustrates the strength of the dichotomy of autonomic regulation of the ventral prostate. As can be observed in the ventral lobe from Table 1, both the Sym-Para and PG groups exhibit a decrease in the denervated side and an increase in the intact side in weight, DNA, and protein content as compared to those in the shams. However, the pelvic ganglionectomy group expresses statistical significance in all three categories, whereas the sympathectomy-parasympathectomy group expresses significance only in two categories: DNA, and weight. The sympathectomy group displays a similar trend, namely the denervated side decrease and the intact side increase in each category except for DNA on the nonlesioned side. The parasympathectomy group shows an increase, instead of a decrease, in DNA and protein on the lesioned side. Otherwise, this group also shows comparable results. These

observations demonstrate that selectively denervating the prostate on one side leads to ipsilateral atrophy and contralateral hyperplasia of the ventral lobe. These data suggest that sympathetic and parasympathetic innervations offer differential control over growth of the prostate gland. The lateral and dorsal lobes, and the coagulating gland and seminal vesicles displayed no significant changes after any surgical manipulation.

Previous anatomic studies support the concept of a dichotomy of autonomic innervation in the prostate. Gosling [25] has shown histochemically that cholinergic fibers supply some epithelial cells and several smooth muscle cells of the capsule and stroma, but adrenergic fibers principally supply smooth muscle cells of the stroma and capsule. Prior studies from our lab and others concur that a differential physiologic effect of the autonomic system exists in the prostate. Wang et al. [8] and Bruschini et al. [26] have demonstrated that sympathomimetic drugs bring about prostatic secretion through the contraction of smooth muscle. However, parasympathomimetic agents cause secretion of prostatic fluid via a different mechanism, presumably through the stimulation of the secretory mechanisms of epithelial cells. Thus, sympathetic fibers functionally innervate the stroma, and parasympathetic ones innervate the epithelium. Observations made in this paper support the above-mentioned anatomic and physiologic separation between the parasympathetic and sympathetic innervation. Our study expands the anatomic and physiologic dichotomy to one invoking fundamental regulation of prostate growth and development as sympathectomy and parasympathectomy have differential effects on the prostate. This effect is found regardless of the combination in prostate neural manipulations.

PBP is a major, androgen-sensitive secretory product of the rat ventral prostate, and its measurement provides a good assay for the study of prostate secretion [27, 28]. The level of this glycoprotein was ascertained to determine the effects of these nerve ablations on a parameter of epithelial cell function. The intact side revealed an increase of PBP in the Sym, Para, and Sym-Para groups. This result is consistent with the hyperplasia seen on that side in these groups, as noted by the increase in both DNA and protein levels. Presumably, the denervated side shows no change in PBP levels because androgens provide greater control over PBP production than does innervation [29]. Additionally, the serum half-life is thought to be long, since newly synthesized PBP is stopped within 24 h after castration, yet high levels of PBP remain detectable by 7 days [30, 31].

The tissue NE levels, per gram of tissue, 60 days after a combined sympathectomy-parasympathectomy, remain significantly lower than the levels of the 60-day sham group and, more importantly, comparatively lower than those of the 30-day Sym-Para group. Thus, NE levels continue to decline with time. This evidence suggests that significant reinnervation did not occur.

The weights of the seminal vesicle, coagulating gland, and dorsal and lateral lobes of the prostate were not affected by any of the nerve ablations; this implies that innervation is not as important to growth and maintenance of these glands as to the ventral prostate.

Qualitative histologic assessment of the treatment groups did not reveal gross changes in the histologic appearance. The lack of distinct changes in the stromal or epithelial appearances suggests a "balanced" change with regard to these two major components of prostate growth. Further analysis of histologic features is the subject of additional work using computer-assisted morphometric analysis systems.

Lesioned-side atrophy, evidenced by a decrease in weight and in DNA and protein content, can be rationalized by the fact that the gland was denervated on that side. There is partial or complete loss of neural stimulus. Many organ systems, including glandular tissue, respond to denervation in this manner [32]. The reasons for the intact-side hyperplasia, a novel finding in the prostate to our knowledge, can only be theorized at this time. Much attention in current prostatic research is being paid to the role of growth factors [33–36]. Because several growth factors have been identified in the prostate of the rat, it is plausible that the denervated gland releases one or more of these factors, which travel to the opposite lobe and effect an increase in mitotic activity. These factors would most likely travel in the bloodstream since the sides of the lobes are separated by a septum. The ventral prostate seems to be more sensitive to these putative factors, since we did not see such changes in the dorsal prostate, lateral prostate, coagulating gland, or seminal vesicals. Although unlikely, the growth factor could passively diffuse from one ventral lobe to the adjacent one, thereby acting in a paracrine-like manner. This is anatomically unlikely because of fascial divisions between the two sides. The observed prostatic hyperplasia in the contralateral side of parasympathectomy may involve a compensatory mechanism based on the drop in prostatic secretions, volume, and content on the ipsilateral side.

In addition, it has been shown that cells produce certain proteins in increasing quantities as they are dying [13, 37]. It is possible that as the epithelial or stromal cells are dying due to lack of innervation, they release these proteins into the vasculature or surrounding area. These products may thus communicate with the opposite side, telling it to increase cell number until levels of these proteins return to normal, thereby compensating for the loss of glandular function.

Spinal pattern generators have been identified for the control of sexual reflexes in the male rat [38–40]. An alternative theory to explain the hyperplasia assumes that a similar generator exists and that prostatic secretory activity is under reflex control through the lumbosacral spinal cord. The act of denervation would cause a decrease in reflex activity. The central nervous system may respond by send-

ing an increased rate of signals to the remaining, innervated tissue to bring about the observed hyperplasia.

Regardless of the mechanism, it is clear from this work that the autonomic nervous system has a fundamental regulatory role in the growth and development of the prostate. Furthermore, there appears to be a dichotomy in regulation of the prostate with regard to the parasympathetic and sympathetic systems. This dichotomy is seen regardless of the combination of or means in achieving a parasympathectomy or sympathectomy. This differential regulation of growth is supported by a parallel dichotomy in anatomy and physiology. Finding the mechanism of contralateral hyperplasia and ipsilateral atrophy has potential significance in investigation and understanding of human abnormal prostatic growth.

Summary

1) Unilateral sympathectomy leads to lesioned-side decreases in ventral prostate weight, and DNA and protein content. 2) Unilateral parasympathectomy leads to intact-side increases in ventral prostatic weight, and DNA and protein content. 3) Significant reinnervation does not occur by 60 days post manipulation. 4) Sympathectomy or parasympathectomy has no effect on the dorsal prostate, lateral prostate, seminal vesicals, or coagulating gland. 5) There appears to be a differential effect of the autonomic nervous system on the growth and maintenance of the ventral prostate. 6) The separate effects of sympathectomy and parasympathectomy are maintained across a diverse combination of neural manipulations.

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