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ANDROGEN METABOLISM IN THE HYPERTROPHIC PROSTATE

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SUMMARY

Since dihydrotestosterone rather than testosterone is the principal intracellular androgen in the prostate and since dihydrotestosterone concentration is increased in hypertrophic prostate of dog and man, long term studies were undertaken to test the possibility that unregulated production of dihydrotestosterone is the cause of prostatic hypertrophy. Control and castrated two year-old dogs were given triolein or pharmacological doses of testosterone or dihydrotestosterone (75 mg/week) for 18–24 months. Although two control dogs developed prostatic hypertrophy (15·5 and 19·4 g in weight), none of the castrated animals developed prostatic hypertrophy, despite the fact that prostate dihydrotestosterone content was as high in testosterone and dihydrotestosterone-treated dogs (1·0 and 0·7 μg dihydrotestosterone/100 g tissue) as in the controls with benign prostatic hypertrophy (0·6 μg/100 g tissue). This suggested that mode of delivery of the hormone to the gland was critical or that some testicular hormone other than testosterone or dihydrotestosterone is required for the development of prostatic hypertrophy. Therefore, six aged male dogs with prostatic hypertrophy were subjected to vas duct ligation and followed for six months. No change occurred in prostate weight or the tissue content of testosterone and dihydrotestosterone. Thus, some testicular hormone other than testosterone or dihydrotestosterone is required for the development of prostatic hypertrophy.

INTRODUCTION

Benign prostatic hypertrophy, enlargement of the prostate that results in obstruction of the lower urinary and gastrointestinal tracts in the ageing male, is a disorder that is almost universal in the dog and man but that occurs only rarely if at all in other species. The fact that prostatic development and growth are fundamentally androgen mediated and that prostatic hypertrophy never occurs in the castrate male has led to the general assumption that the unregulated growth that results in the disorder must either reflect some abnormality in circulating hormones or some abnormality in the receptor/recognition machinery of the gland itself. The purpose of the present study was to examine the question whether unregulated dihydrotestosterone formation is the cause of benign prostatic hypertrophy in man and dog.

METHODS

The technique utilized for the tissue analysis of steroid content of tissues is a double isotope derivative assay that has been described in detail [1].

RESULTS

It was recognized in several laboratories in 1968–69 that dihydrotestosterone, the 5α-reduced derivative of testosterone, is the major steroid bound to nuclear chromatin in the prostate and some other androgen target tissues [2, 3]. Since that time a considerable body of evidence has accrued to indicate that dihydrotestosterone formation may well be involved in many androgen actions [4, 5].

The concept that dihydrotestosterone formation might be involved in prostatic hypertrophy originated in a comparative study of dihydrotestosterone formation in the prostates of some eleven different species by Gloyna and Wilson [6]. In this study the rate of dihydrotestosterone formation by tissue slices from the prostates of adult animals varied from high levels in rat, man, baboon, lion and dog to virtually undetectable levels in species such as bull and rabbit. It is well established that there is a wide species variation in the degree of development of the prostate gland, and when these rates were plotted against the weight of the prostate in the mature animal, expressed as g/kg of body weight, it was apparent that there exists a reasonable linear correlation between the rate of dihydrotestosterone formation and the ultimate weight of the gland. Furthermore, it was possible to show that in all species, dihydrotestosterone formation was rapid during the early developmental stages of growth. For example, in the immature dog, cat, and bull there is little difference in the rates of dihydrotestosterone formation. In the dog, dihydrotestosterone formation actually increases with age. There is little change in the rate in the cat, whereas the capacity virtually disappears in the prostate of the mature bull after growth has ceased. A more detailed comparison was made in the prostates of the rabbit and rat. The rate of formation remains fixed in the rat from birth to at least 36 weeks of age, whereas in the rabbit the capacity is lost just prior to 12

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weeks of age as the capacity for growth diminishes. Considered together, these findings of correlations between dihydrotestosterone formation and growth suggested to us that unregulated production of dihydrotestosterone formation over many years' time might result in prostatic hypertrophy.

To explore this relation further, a double isotope derivative technique was adapted for the measurement of tissue androgen content in normal and hypertrophic human prostates [1]. There was no significant difference between the two types of gland in the content of testosterone. However, the content of dihydrotestosterone was significantly greater in the hypertrophic tissue (0·60 μg/100 g) than in the normal glands (0·13 μg/g), and when these data were plotted in relation to the age of the subject it is apparent that the content rises strikingly with age in the hypertrophic but not in the normal glands [1].

Prostatic hypertrophy in man begins in the periurethral area of the gland. When the regional androgen concentrations within the gland were assessed, it was shown that the content of dihydrotestosterone was higher in the periurethral region of the normal gland than in the outer lobes, and in three prostates with early concentric hypertrophy involving the periurethral regions only dihydrotestosterone content in the involved portion of the gland was higher still whereas in the uninvolved portion of the gland, dihydrotestosterone content was unchanged [1]. Finally, dihydrotestosterone formation from radioactive testosterone was measured and shown to remain as high in the hypertrophic as in the normal gland. Thus, although the mechanism by which dihydrotestosterone accumulation occurs remained unexplained, these findings were compatible with the thesis that dihydrotestosterone might be involved in the pathogenesis of prostatic hypertrophy in man.

However, from all these types of evidence it was not possible to exclude an alternate possibility, namely that the changes observed are the result rather than the cause of prostatic hypertrophy. To examine the cause and effect relations of this phenomenon, it was necessary to turn to an experimental model. Although there are histological differences between the processes in the two species, prostatic hypertrophy in the dog bears a striking resemblance to that in man in its almost universal occurrence in the ageing male, its natural history, its functional manifestations, and its endocrine dependence [7, 8]. It was logical, therefore, to choose the dog to examine critically the dihydrotestosterone thesis. First, the concentrations of testosterone and dihydrotestosterone were measured in immature, mature, and hypertrophic prostates [9]. The findings were similar to those in man. There was little change in testosterone content with age, whereas the content of dihydrotestosterone, the major androgen recovered at all ages, increased strikingly in the hypertrophic gland.

The critical question, however, is whether dihydrotestosterone can cause prostatic hypertrophy in the castrate animal. To examine this possibility in detail, a long series of studies have been undertaken over the past four years. Young male dogs (averaging $1\frac{1}{2}$ to 2 years of age) and with an average prostate weight of approximately 2·8 g were either treated with triolein alone, or they were castrated and given either triolein or testosterone or dihydrotestosterone, 75 mg/week dissolved in triolein. In the first study the animals were killed after nine months [9]. In castrate animals treated only with triolein, prostate weight had regressed to 1·8 g. In the testosterone-treated group, however, the weight was 3·6 g, not significantly different from control group, and in the dihydrotestosterone group the weight was nearly doubled, averaging 6·6 g. Furthermore, when sections of these glands were examined histologically, the findings were of interest. In the control gland, the acini were lined with columnar epithelium and surrounded by thin fibrous septae. After castration virtually all glandular elements had disappeared, leaving only undifferentiated stroma. The testosterone-treated tissue appeared normal, whereas the prostate from the dihydrotestosterone-treated animal contained large, irregular-shaped alveoli, a finding characteristic of canine prostatic hypertrophy [7]. At this point in the studies, the production by dihydrotestosterone of accelerated growth and microcyst formation in prostate were considered compatible with a possible etiological role for this hormone in the production of prostatic hypertrophy in the dog.

However, we had not succeeded in producing true prostatic hypertrophy in the castrated animal. According to the criteria of Berg [7], the hypertrophic prostate in the dog always weighs more than 15 g in weight. The animals treated for nine months did not fulfil the weight criteria, and they did not develop

Table 1. Effect of testosterone and dihydrotestosterone treatment for two years on the dog prostate

Group	Number	Treatment	Prostate Weight	Hormone Content μg/100 g or 100 ml			
				Testosterone		Dihydrotestosterone	
			g	Prostate	Plasma	Prostate	Plasma
I Control	4	Triolein	14	0.09	0.10	0.55	0.01
II Castrate	4	Triolein	1.8	0.07	0.01	0.10	0.01
III Castrate	4	Dihydrotestosterone	6.6	0.02	0.01	0.58	0.12
IV Castrate	4	Testosterone	3.6	0.15	0.68	0.99	0.08

Table 2. Effect of vas duct ligation on the hypertrophic dog prostate

Group	Number	Prostate Weight g	Hormone Content µg/100 g or 100 ml			
			Testosterone		Dihydrotestosterone	
			Prostate	Plasma	Prostate	Plasma
Control	11	24.4	0.14	0.20	0.40	0.02
Vas duct ligation	6	28.4	0.16	0.23	0.40	0.00

obstructive symptoms. Therefore, two long-term studies were undertaken in which control and castrated two year-old dogs were given either triolein or pharmacological doses of testosterone or dihydrotestosterone (75 mg/week) for eighteen to twenty-four months (Table 1). During this study two of the control dogs developed true prostatic hypertrophy (15·5 and 19·4 g), and the average prostate weight in the control group was 14 g. In the castrate controls, the weight was identical to that in the 9 month study (1·8 g), and the prostate weights of the dihydrotestosterone and testosterone-treated animals were not significantly different after 18–24 months than after 9 months of treatment (6·6 and 3·6 g). This failure to produce hypertrophic growth was very striking because both treatment regimens produced as high a content of dihydrotestosterone in the gland as in the control, hypertrophic group (1 and 0·6 µg vs 0·6 µg per 100 g), and testosterone treatment caused as high a content of prostate testosterone (0·2 µg) as in the normal gland (0·09 µg). Thus, despite an almost exact duplication of the hormonal content of these two androgens in the treated castrate as in the hypertrophic glands, no true hypertrophy resulted. It was clear, furthermore, that the time period chosen for the study was adequate since half the control dogs developed true hypertrophy.

We considered two possible explanations for the failure of long term exogenous androgens to induce prostatic hypertrophy in the dog. Either the mode of delivery of the hormone to the gland was critical, or some testicular hormone other than testosterone is required for the development of prostatic hypertrophy. Since the process in man begins in the periurethral region just distal to the entry of the ejaculatory ducts into the urethra, the possibility was next considered that the androgen delivered directly to the gland via the seminal fluid might play some critical role in the process. Therefore, to be certain that all testicular hormones reached the gland via the blood stream, six male dogs with prostatic hypertrophy were subjected to vas duct ligation and followed for six months (Table 2). There was no difference in the average weight of the gland between treated and control groups (28 and 24 g), and no significant difference was found in the content of testosterone and dihydrotestosterone in plasma and prostate. Clearly, vas duct ligation over this period of time has no significant effect on the hypertrophic prostate.

DISCUSSION

Several tentative conclusions have been drawn from these studies: first, in the normal animal, evidence of several types suggests that dihydrotestosterone formation correlates with growth, and the fact that dihydrotestosterone is a potent androgen suggests that normal growth is mediated by this metabolite. However, the factors that limit prostatic growth in most species have not been defined. Second, whatever its role in the growth of the normal prostate, dihydrotestosterone accumulation alone cannot explain the development of prostatic hypertrophy. However, the data do not exclude the possibility that dihydrotestosterone may be required as a participant rather than the sole cause of the process. Considered together, the evidence seems clear that some testicular hormone(s) other than testosterone or dihydrotestosterone must be critical to the development of benign prostatic hypertrophy. Until this testicular product is defined, it will not be possible to determine whether the species differences in the occurrence of prostatic hypertrophy occur at the level of testis or in the recognition/receptor mechanism of the prostate itself.

REFERENCES

1. Siiteri P. K. and Wilson J. D.: *J. clin. Invest.* **49** (1970) 1737–1745.
2. Bruchovsky N. and Wilson J. D.: *J. biol. Chem.* **243** (1968) 2012–2021.
3. Anderson K. M. and Liao S.: *Nature, Lond.* **219** (1968) 277–279.
4. Wilson J. D.: *New Engl. J. Med.* **287** (1972) 1284–1291.
5. Wilson J. D.: Handbook of Physiol. (In Press).
6. Gloyna R. E. and Wilson J. D.: *J. clin. Endocr. Metab.* **29** (1969) 970–977.
7. Berg O. A.: *Acta endocr., Copenh.* **27** (1958) 140–154.
8. Schlotthauer C. F.: *J. Am. Vet. Med. Ass.* **81** (1932) 645–650.
9. Gloyna R. E., Siiteri P. K. and Wilson J. D.: *J. clin. Invest.* **49** (1970) 1746–1753.