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ORIGINALS

Effect of Prolactin and the Anti-Prolactin Bromocriptin* on the Testosterone Uptake and Metabolism in Androgen-Sensitive and Insensitive Canine Organs**

D. Helmerich and J. E. Altwein

Department of Urology, University of Mainz Medical School, Mainz, F.R.G.

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Summary. Prolactin promotes the growth and function of the prostate in low doses, whereas high doses or previous castration reduce this effect. The antiprolactin bromocriptin should reverse the prolactin action. In the castrated dog the highest accumulation of H^3-testosterone given i.v. occured in the prostate as compared with muscle, urethra, penis, liver and kidney. Prolactin pretreatment increased the radiosteroid uptake only in the liver. Conversely, bromocriptin suppressed the tracer incorporation into the liver, but increased prostatic accumulation. The highest testosterone reduction occured in the prostate of the untreated castrated dogs as compared with other organs. Prolactin suppressed 5α -dihydrotestosterone formation but otherwise did not significantly influence testosterone turnover. Bromocriptin, however, stimulated dihydrotestosterone formation in the prostate and caused complete inhibition of hepatic testosterone reduction.

Key words: Prostate - Prolactin - Anti-Prolactin.

Laboratory studies in animals have shown that pituitary hormones are involved in the development and maintenance of the prostate. Chase et al (7), Grayhack et al (12), and Bern et al (4) noticed a synergistic action of prolactin and testosterone on the growth and function of the rat prostate. This effect was confirmed by the finding that ovine anti-prolactin serum led to prostatic atrophy in rabbits (3). In pursuing the prolactin-prostate interrelationship, Golder et al (11) found that there was stimulation of cAMP-formation in the prostate in vitro with low prolactin concentrations. Lasnitzki (14) observed that low doses of prolactin increased the size and proliferation of the epithelial cells of rat prostates grown in vitro. However, using high prolactin concentrations this effect was reversed.

Employing short term incubation of rat prostate, the inhibition of adenyl cyclase with high doses of prolactin was noticed (20).

Recently, Aragona et al (2) reported on the presence of prolactin binding sites in the rat prostate.

Because of these observations and potential clinical implications, we decided to investigate the mode of action of prolactin and its inhibitor bromocriptin on testosterone (T) uptake and metabolism in the canine prostate in an vivo experiment.

MATERIAL AND METHODS

15 male dogs (mongrels, 1-2 years, average weight 11.8 kg) were castrated and divided into 3 groups:

1. controls (n=5);
2. pretreatment with 500 IU prolactin i.m. over 3 days (n=5);
3. pretreatment with 5 mg bromocriptin orally over 3 days (n=5).

24 hrs after discontinuation of the pretreatment, i.e., 96 hours post castration, each dog received 35 μ Ci 7α -H^3-testosterone/kg body weight in a 20% ethanol solution i.v.

* Parlodel^R from Sandoz AG, CH-4000 Basel

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under nembutal anaesthesia (25 mg/kg body weight) Blood was drawn 2, 5, 7.5, 10, 15, 20, 30 and 60 min after injection. At 60 min following injection the dogs were sacrificed, the prostates completely excised, and tissue specimens taken from the penis, urinary bladder, liver, kidney and rectus abdominis muscle. The tissues were washed in a 0.9% NaCl-solution, blotted and weighed. The extraction and identification of H^3-testosterone and its metabolites was carried out according to the method of Orestano et al (18). Disintegrations per minute (Dpm) was calculated from counts per minute (cpm) as reported by Stern et al (19).

The protein determination in the various tissues was performed according to the method of Lowry et al (16). DNA was measured as reported by Burton (6). Ovine prolactin was purchased from Ferring Arzeimittel, Düsseldorf. Bromocriptin was provided by Sandoz AG, Basel (Switzerland). The other chemicals used have been listed previously (18). The plasma kinetics of H^3-testosterone will be reported separately.

RESULTS

The uptake of the total androgen associated radioactivity (TAAR) into target and non-target organs is depicted in Figures 1 and 2. TAAR within the prostate exceeded the concentration measured in the penis by 53%, in rectus abdominis muscle by 73%, in kidney by 52%, in liver by 43% and in urethra by 57%. The prolactin pretreatment (group 2) resulted in insignificant changes regarding the TAAR-incorporation into each organ studied except the liver (Fig. 2), where TAAR rose to 304% of the control value. Conversely, bromocriptin reduced the TAAR-uptake into the liver as compared to the control group ($p < 0.005$). However, in the prostate, bromocriptin was accompanied by an increase of the TAAR-incorporation to 151% of the control value ($p < 0.005$).

In Table 1 this relation was recalculated regarding the protein and DNA content of the castrated-dog prostate. Bromocriptin resulted in an augmented TAAR-uptake reaching 298% of the control value when expressed per 15 mg protein or 241% of the control value when expressed per mg DNA (Table 1). The metabolites of H^3-testosterone found within the organs studied are depicted in Figures 3 and 4. Testosterone itself and a number of T-degradation products, 5α-dihydrotestosterone (DHT) and 5α, 3α-androstanediol (Adiol), accounted for 65% of the intraprostatic TAAR in the control. The corresponding value for the penis is 56%. This figure, however, is mis-

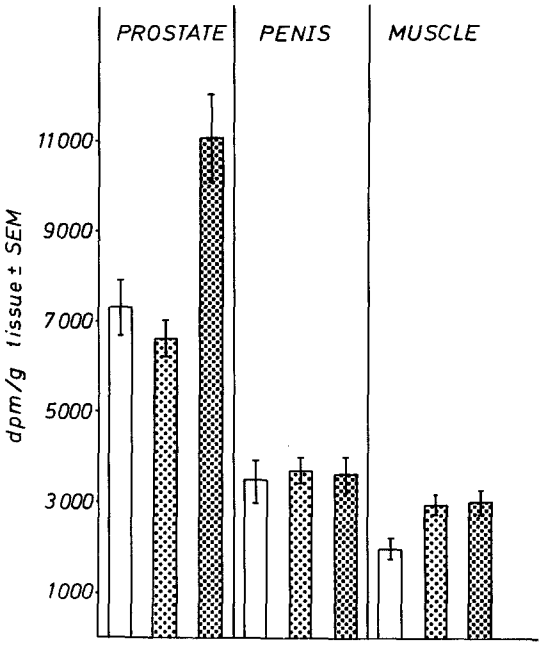

Fig. 1. Uptake of TAAR into the prostate, penis and rectus abdominis muscle according to pretreatment. The left column in each panel represents the control group (1), the middle column shows the prolactin, and the right column the bromocriptin pretreatment groups

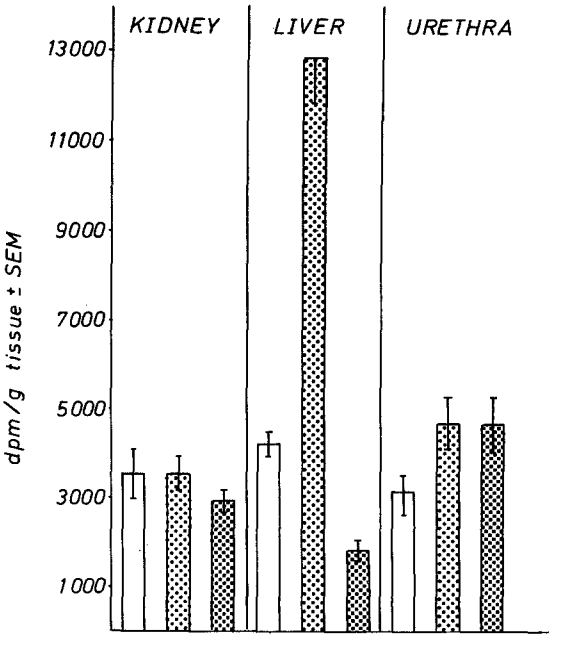

Fig. 2. Uptake of TAAR into the kidney, liver and urethra according to pretreatment. Columns as in Fig. 1

Table 1. The uptake of the total androgen associated radioactivity (TAAR) into the prostate and formation of testosterone (T), 5α-dihydro-testosterone (DHT), and 3α-, 5α-androstanediol (Adiol) 60 min. after i.v.-injection of 35μ Ci H^3-testosterone /mg body weight into castrated dogs. The dpm are indicated per 15 mg protein and 1 mg DNA, respectively. SEM = Standard error of the mean

Units	TAAR	T	DHT	ADIOL	Pretreatment
DPM/15 MG Protein ± SEM	1190 ± 102	82 ± 9	528 ± 44	160 ± 36	Control
	916 ± 58	394 ± 32	245 ± 30	168 ± 28	Prolactin
	3554 ± 316	183 ± 50	2117 ± 272	281 ± 27	Bromocriptin
DPM/MG DNA ± SEM	8122 ± 693	563 ± 59	3606 ± 302	1094 ± 242	Control
	4654 ± 292	2005 ± 162	1243 ± 150	855 ± 145	Prolactin
	19582 ± 1744	1006 ± 274	11667 ± 1499	1550 ± 149	Bromocriptin

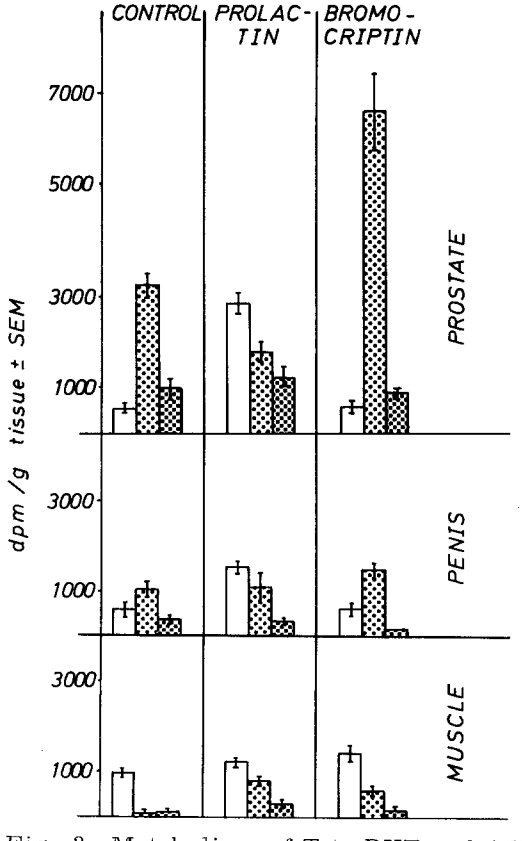

Fig. 3. Metabolism of T to DHT and Adiol according to pretreatment in prostate, penis and muscle. The left column in each panel represents H^3-testosterone, the middle column H^3-5α-dihydrotestosterone, and the right column H^3-5α, 3α-androstanediol

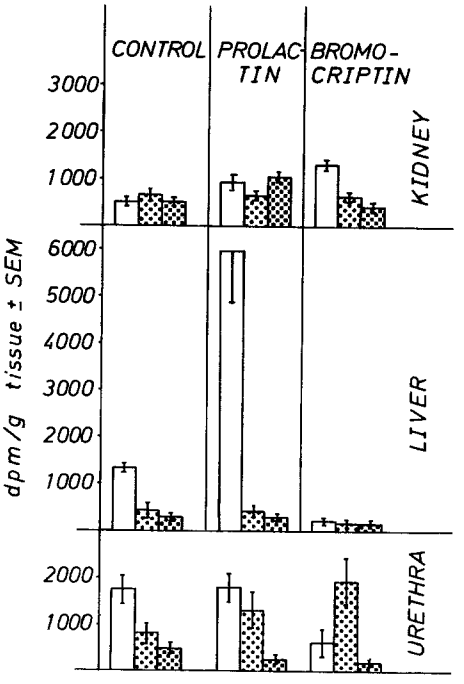

Fig. 4. Metabolism of T to DHT and Adiol according to pretreatment in kidney, liver and urethra. Columns as in Fig. 3

leading, since the penile TAAR is less than 50% of the intraprostatic TAAR. In muscle, kidney, liver and urethra this effect is even more pronounced.

Testosterone persists as the major hormone in muscle, liver and urethra, whereas DHT is the leading degradation product in the prostate and penis, two androgen-sensitive organs (Figs. 3 and 4).

Prolactin pretreatment (group 2) reversed the relation between T and DHT in the prostate and penis, whereas the Adiol-formation in these two androgen-sensitive organs remained unchanged as compared to the control group. In the kidney and urethra of the castrated dog, prolactin did not significantly influence the T-turnover.

In the liver, prolactin enhanced the TAAR-incorporation. In studying the fractionated androgen-content in the liver, it was found that unmetabolized T accounted for 5975 dpm/g tissue, which is by far the largest T-value registered. Its degradation products remained in the range of the control group.

Bromocriptin pretreatment (group 3) suppressed the TAAR-uptake and T-degradation within the liver, thus reversing the prolactin effect. Kidney and muscle showed a rather indifferent pattern of T-metabolites as compared to groups 1 and 2. Bromocriptin pretreatment caused an increase in the TAAR-uptake into the prostate (Fig. 1), and a striking augmentation of DHT-formation, reaching 6592 dpm/g prostatic tissue. This effect is even more pronounced when relating it to the prostatic DNA-content (Table 1).

DISCUSSION

In the untreated, castrated dog, the in vivo uptake of radioactivity into the prostate exceeded the other androgen-sensitive and insensitive organs. This was reflected in an increased T-reduction, leading to the formation of DHT and Adiol, the major T-reduction products within the prostate. In the penis, a moderate, non-significant augmentation in the DHT-appearance was noted. The remaining organs, however, did not show this reduction capacity. Bruchovsky et al (5) and Gloyna et al (10), have described a similar pattern of DHT-formation in vivo and in vitro in the comparable organs of male rats.

Ovine prolactin did not enhance the H^3-radioactivity uptake into the castrated-dog prostate. Lloyd et al (15) also noted this effect, when measuring the accumulation of radiosteroids in the dorsal lobe of the rat prostate in vitro in the presence of high ovine prolactin concentrations. In contrast, low doses of prolactin caused a soaring uptake of radiosteroids.

The same prolactin dose-related effect was noted by Golder et al (11), who assayed the rat prostate adenylate cyclase and discovered an enhancement at low concentrations but no effect at high concentrations. Whether the castration-induced reduction of prolactin binding to the prostate accounts for the low T-uptake is still a moot question (13).

Prolactin inhibited the T-metabolism to its reduction products DHT and Adiol in the penis and prostate of the castrated dog confirming the in vitro findings of Mawhinney et al (17). The liver augmented its T-uptake but not its metabolism in the prolactin-treated group. This is due to the castration-induced augmentation of prolactin receptors in the liver (2).

Bromocriptin specifically inhibits prolactin-release from the anterior pituitary (9). The striking effect of bromocriptin upon the prostate consisted of significantly increased radioactivity uptake and DHT-formation. The penis displayed unchanged radioactivity uptake and insignificantly raised DHT-formation.

Performing in vivo studies in rats, Danutra et al (8) found only little effect of bromocriptin on the uptake and turnover of H^3-testosterone in the prostate. Alger et al (1) studied bromocriptin in rats, but did not see a significant alteration in the weight of accessory sex organs.

In our study the urethra showed a T-degradation pattern imitating the H^3-testosterone uptake and metabolism of the prostate but at a lower level.

In essence, this study indicates that prolactin increases the uptake of H^3-testosterone into the liver, but not into the prostate of the castrated dog. Other androgen-sensitive organs behaved similarly.

The anti-prolactin bromocriptin, however, increased the accumulation of radiosteroids in the prostate, but reduced their uptake into the liver.

The intraprostatic T-reduction was decreased after prolactin, but augmented significantly after bromocriptin.

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Prof. Dr. J.E. Altwein
Urologische Univ.-Klinik
Langenbeckstr. 1
D-6500 Mainz
Federal Republic of Germany