Dr. Knoell Consult GmbH[1], Mannheim, Germany; Japan Clinical Research[2], Lilly Research Laboratories, Eli Lilly Japan K.K., Kobe, Japan; Institute of Organic Chemistry[3], University of Regensburg, Germany; Experimental Oncology[4], Schering AG, Berlin, Germany

The prostate growth stimulation by progesterone is due to androgenic products and progesterone receptor-mediated mechanisms

T. Nishino[1], K. Ishibashi[2], C. Hirtreiter[3], Y. Nishino[4]

Received March 23, 2009, accepted April 24, 2009

Dr. Tsuyuki Nishino, Dr. Knoell Consult GmbH, Dynamostraße 19, D-68165 Mannheim, Germany
tnishino@dr-knoell-consult.com

Pharmazie 64: 587–589 (2009) *doi: 10.1691/ph.2009.9583*

The antiprogestin mifepristone has been demonstrated to inhibit the growth of R3327HI rat prostatic carcinoma. A comparable antitumor effect of onapristone (ON) on rat Dunning tumors was found in our laboratories. We found the localization of progesterone (P4) receptors (PR) in prostate and prostatic tumors. These findings suggest the involvement of P_4 in the mechanism of hormone-dependent growth of prostate and tumors. To study the influence of P4 on the growth of ventral (VP) and dorsolateral prostate (DLP), orchiectomized rats were treated (s.c.) daily with P_4 (0.3, 1.0, 3.0 or 10.0 mg), dihydrotestosterone (DHT, 0.05 mg), estradiol (E_2, 3.0 μg), ON (3.0 mg), ICI 182780 (1.0 mg) or flutamide (FL, 3.0 mg) for 12 days. One day after the last treatment, animals were sacrificed, and the organ weight of VP and DLP was determined. P_4 increased the organ weight of VP and DLP in a dose-dependent manner. In contrast to DHT, which preferentially stimulated the growth of VP, P_4 led rather to an increase in the weight of DLP. The effect of P_4 on the DLP was enhanced by a simultaneous application of DHT or E_2. The antiprogestin ON and the pure antiestrogen ICI 182780 had no appreciable effect on the P_4-induced growth of VP and DLP. ON inhibited, however, the E_2/P_4-induced growth of DLP without affecting the growth of the VP. In contrast the antiandrogen FL suppressed the stimulatory effect of P_4 on both the VP and DLP. These findings suggest that the stimulatory effect of P_4 on the rat DLP may be partly due to androgenic products derived from P_4 and may be also mediated by PR.

1. Introduction

Progesterone receptors have been localized in male genital tracts of different species (Belis et al. 1984; Ganjam and Amann 1976; Jones and Connell 1982). While Price and co-workers (1955) have found the stimulatory effect of progesterone (P_4) on rat lateral prostate, no effect of P_4 on the wet weight and DNA content in the rat prostate was observed in the study of Belis et al. (1984). Although the patho-physiological significance of P_4 is still obscure, increasing evidence has demonstrated the presence of PR's in most cases of BPH and prostatic carcinoma (Kumar et al. 1990), and the antiprogestin mifepristone has been demonstrated to inhibit the growth of R3327HI rat prostatic carcinoma (Mobbs and Johnson 1991). A similar antitumor effect with the antiprogestin onapristone on rat Dunning tumors was found in the laboratory of Schering AG. These findings indicate that P_4 or PR-mediated effect may be involved in the mechanism of hormone-dependent growth of BPH and prostatic carcinoma.

The present study was undertaken to investigate the influence of P_4 on the growth of ventral (VP) and dorso-lateral prostate (DLP) of the rat.

2. Investigations and results

Figure 1 shows the influence of DHT, E_2 and P_4 on the wet weight of VP and DLP in orchiectomized rats. P_4 increased the organ weights of VP and DLP in a dose-dependent manner (Fig. 2a and b). In contrast to DHT which preferentially stimulates the growth of VP, P_4 led rather to an increase in the weight of DLP than VP. The antiprogestin ON and the pure antiestrogen ZM had no appreciable effect on the P_4-induced growth of VP and DLP (Table 1). In contrast, the antiandrogen FL was able to suppress the stimulatory effect of P_4 on VP and DLP. ON at that dose tested had no influence on the DHT- and E_2-induced growth of prostate (Table 2). ON inhibited, however, the E_2/P_4-induced growth of DLP without affecting the growth of VP (Table 3). In animals treated with P_4, serum testosterone level was significantly higher than that of the control (Table 4). Immunohistochemical study indicated the localization of PR in the rat prostate and the Dunning R3327HI rat prostatic tumor.

3. Discussion

P_4 preferably stimulates the growth of DLP in orchiectomized rats. The P_4-induced increase in the prostatic

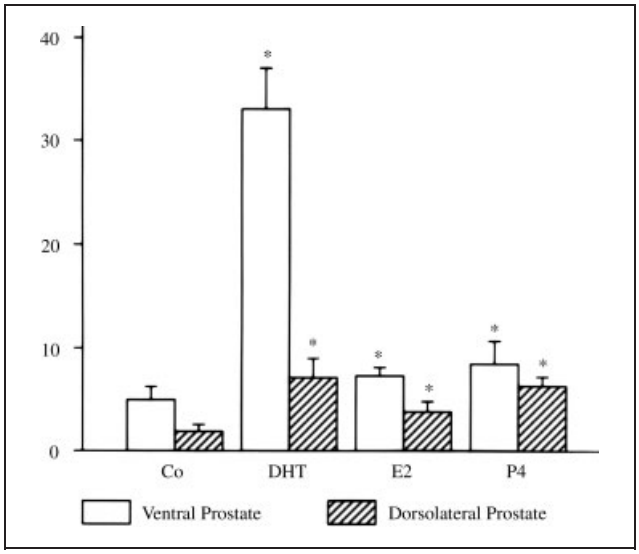

Fig. 1: Organ weight in mg/100 g body weight; Co = control (orchidectomy), DHT = 5α-dihydrotestosterone 0.05 mg, E2 = estradiol 3 μg, P4 = progesterone 3 mg, * = significant difference in comparison with the control group ($p < 0.05$) (Dunnett-test)

weights (VP and DLP) is not influenced by a concomitant administration of the antiprogestin ON or the antiestrogen ZM, but inhibited by the antiandrogen FL. DHT and E_2 potentiate the stimulatory effect of P_4 on the prostatic growth. ON inhibits the E_2/P_4-induced growth of DLP. A high level of testosterone is found in the serum obtained from rats treated with P_4. PR in the prostate and the Dunning tumor were localized immunohistochemically.

These findings suggest that the stimulatory effect of P_4 on the rat DLP may be partly due to androgenic products derived from P_4 and may be also mediated by PR.

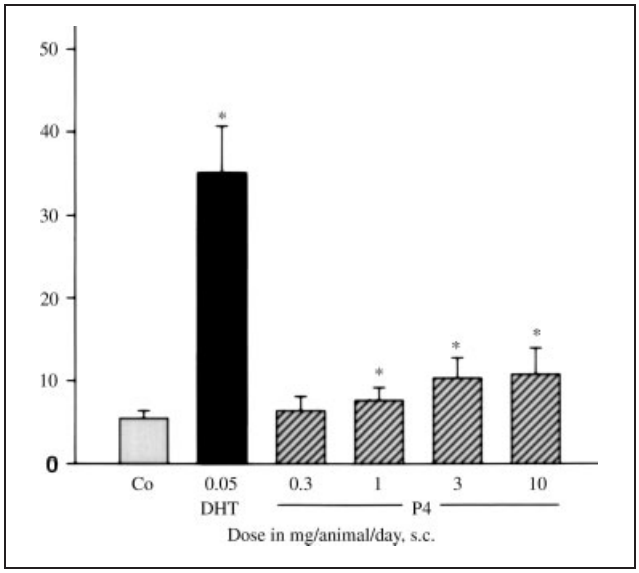

Fig. 2a: Ventral prostate. Organ weight in mg/100 g body weight; Co = control (orchidectomy), DHT = 5α-dihydrotestosterone P4 = progesterone, * = significant difference in comparison with the control group ($p < 0.05$) (Dunnett-test)

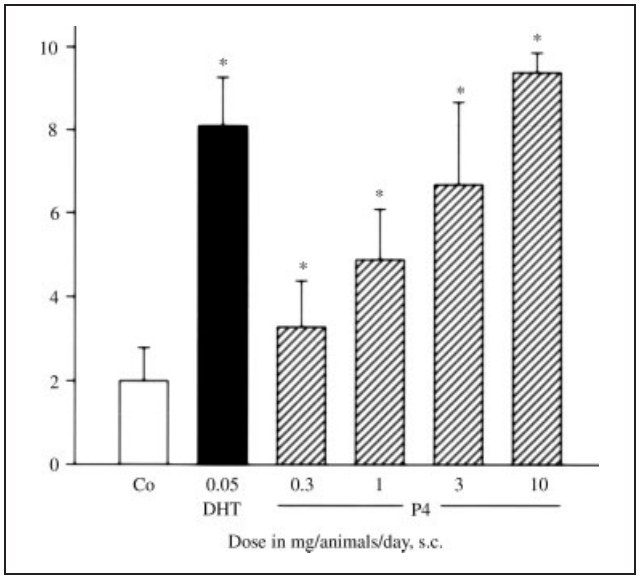

Fig. 2b: Dorsolateral prostate. Organ weight in mg/100 g body weight; Co = control (orchidectomy), DHT = 5α-dihydrotestosterone P4 = progesterone, * = significant difference in comparison with the control group ($p < 0.05$) (Dunnett-test)

Table 1: Influence of antihormones on the progesterone-induced growth of ventral and dorsolateral prostate in orchidectomized rats

	Dose in mg/animal (s.c.)	Prostatic weight mg/100g bodyweigth ventral	Prostatic weight mg/100 g body weight dorsolateral
Control	(vehicle)	5.0 ± 1.2	1.8 ± 0.5
DHT	0.05	33.1 ± 3.9*	7.1 ± 1.8*
P4	3	8.4 ± 2.2*	6.2 ± 1.0*
P4 + ON	3 + 3	7.2 ± 1.8*	5.9 ± 2.0*
Control	(vehicle)	3.9 ± 0.7	1.6 ± 0.3
DHT	0.05	41.2 ± 7.9*	9.7 ± 3.2*
P4	3	9.1 ± 1.8*	7.3 ± 3.5*
P4 + ZM	3 + 3	8.3 ± 2.1*	6.7 ± 1.7*
Control	(vehicle)	3.3 ± 1.5	1.7 ± 0.6
DHT	0.05	34.4 ± 8.5*	7.2 ± 1.8*
P4	3	8.7 ± 2.4*	6.9 ± 2.0*
P4 + FL	3 + 3	5.0 ± 1.1*	2.1 ± 0.5**

DHT = 5α Dihydrotestosterone, P4 = progesterone, ZM = ZM 182780 and FL = flutamide. No. of animals used = 8/group. Animals were treated once daily for 12 days. * and ** = significant difference in comparison with the control group and in comparison with the P4-group, respectively ($p < 0.05$) (Dunnett-test)

Table 2: Influence of onapristone on the 5α-dihydrotestosterone- or estradiol-induced growth of ventral and dorsolateral prostate in orchidectomized rats

	Dose in mg/animal (s.c.)	Prostatic weight mg/100g bodyweigth ventral	Prostatic weight mg/100 g body weight dorsolateral
Control	(vehicle)	3.3 ± 1.5	1.7 ± 0.6
DHT	0.05	34.4 ± 8.5*	7.2 ± 1.8*
ON	3	5.3 ± 0.9	2.0 ± 0.6
DHT + ON	0.05 + 3	43.9 ± 6.0*	8.2 ± 3.0*
Control	(vehicle)	4.8 ± 0.6	1.5 ± 0.8
DHT	0.05	33.6 ± 7.7*	6.0 ± 1.7*
E2	3×10^{-3}	5.9 ± 1.3	3.8 ± 1.8*
ON	3	5.3 ± 1.3	1.7 ± 0.9
E2 + ON	$3 \times 10^{-3} + 3$	7.4 ± 1.4*	4.1 ± 2.0*

DHT = 5α Dihydrotestosterone, E2 = estradiol, and ON = onapristone. No. of animals used = 8/group. Animals were treated once daily for 12 days. * = significant difference in comparison with the control group ($p < 0.05$) (Dunnett-test)

Table 3: Influence of onapristone on the 5α-dihydrotestosterone/progesterone-induced growth of ventral and dorsolateral prostate in orchidectomized rats

	Dose in mg/animal (s.c.)	Prostatic weight mg/100g bodyweigth ventral	Prostatic weight mg/100 g body weight dorsolateral
Control	(vehicle)	5.0 ± 1.2	1.8 ± 0.5
DHT	0.05	33.1 ± 3.9*	7.1 ± 1.8*
E2	3×10^{-3}	7.2 ± 0.8*	3.7 ± 1.0*
P4	3	8.4 ± 2.2*	6.2 ± 1.0*
DHT + P4	3 + 3	35.2 ± 11.2*	14.2 ± 2.1*, **
E2 + P4	$3 \times 10^{-3} + 3$	10.1 ± 3.4*, ##	11.0 ± 3.9*, ##
DHT + P4 + ON	0.05 + 3 + 3	29.3 ± 5.2*	12.8 ± 4.1*, **
E2 + P4 + ON	$3 \times 10^{-3} + 3 + 3$	9.1 ± 3.9*	5.7 ± 1.2*, ##, ###

DHT = 5α-Dihydrotestosterone, E2 = estradiol, P4 = progesterone and ON = onapristone. No. of animals used = 8/group. Animals were treated once daily for 12 days. *, **, ## and ### = significant difference in comparison with the control group, the DHT-group, with the E2-group and with the E2/P4-group, respectively ($p < 0,05$) (Dunnett-test)

Table 4: Serum testosterone concentrations in rats treated with progesterone

	Dose (s.c.) in mg/animal	Serum testosterone nmol/l
Intact	(vehicle)	3.0 ± 0.7*
Control (castrated)	(vehicle)	< 0.35
P4 (castrated)	0.3	0.7 ± 0.1
P4 (castrated)	1.0	4.4 ± 1.0*
P4 (castrated)	3.0	5.9 ± 2.0*

P4 = progesterone, No. of animals used = 8/group. Animals were treated once daily for 12 days. * = significant difference in comparison with the control group ($p < 0.05$) (Dunnett-test)

4. Experimental

Immature male rats (Wistar) weighing about 100 g were orchiectomized prior to start the hormone treatments. Two weeks after castration, daily treatments of animals with hormones and antihormones were initiated and continued for 12 days. The daily dose of 5α-dihydrotestosterone (DHT, 0.05 mg), estradiol (E_2, 3.0 μg), P_4 (3.0 mg), onapristone (ON, 3.0 mg), ZM 182780 (ZM, 1.0 mg) and flutamide (FL, 3.0 mg) was dissolved in 0.2 ml castor oil containing a small amount of benzyl benzoate (20.0%). One day after the last treatment, animals were sacrificed, and organ weights of VP and DLP were determined. Serum testosterone was measured by means of radioimmunological methods. PR-expression in the rat prostate and the Dunning R3327HI rat prostatic tumor was identified using immunohistochemical methods. The Dunnett-test was used for statistical analysis.

Acknowledgement: The authors would like to thank the former Research Laboratories of Schering AG, Berlin, Germany for the possibility to conduct the experiments.

References

Belis JA, Lizza EF, Tarry WF (1984) Progesterone receptors in the prostate. Prog Clin Biol Res 145: 345–361.

Ganjam VK, Amann RP (1976) Steroids in fluids and sperm entering and leaving the bovine epididymis, epididymal tissue, and accessory sex gland secretions. Endocrinology 99: 1618–1630.

Jones LA, Connell CJ (1982) Evidence for progesterone receptors in the epididymis of the prepubertal dog. J Androl 3: 16–17 (1982)

Kumar VL, Wadhwa SN, Kumar V, Farooq A (1990) Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. J Surg Oncol 44: 122–128.

Mobbs BG, Johnson IE (1991) Suppression of the growth of the androgen-insensitive R3327 HI rat prostatic carcinoma by combined estrogen and antiprogestin treatment. J Steroid Biochem Molec Biol 39: 713–722.

Price D, Mann T, Lutwak-Mann C (1955) The stimulating effect of female hormones on the metabolic activity and histological structure of male rat accessory reproductive glands. Anat Rec 122: 363–379.