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Title: PROSTATE GROWTH RESTRAINT OF aADRENERGIC AGONISTS AND ANTAGONISTS TO DHT-INDUCED PROSTATE GROWTH

Aims of Study: -

Adrenergic antagonists, used alone or together with antiandrogens are frequently employed in the treatment of the symptoms associated with increased prostate growth. Furthermore in experimental studies, DHT was found to stimulate prostate growth without affecting □1 adrenoceptors, while castration or 5□reductase inhibitors to decrease it[1, 2] In the present study we examined whether the □1 adrenergic antagonist prazosin [PRZ] or agonist phentolamine [PNN] modulates DHT-induced prostate growth, by evaluating its effect of on the growth of, ventral and dorsal prostate as well as the weight the bladder. In addition we evaluated the functional effects of this treatment on the micturition characteristics of conscious rats. Protocol was designed to characterize the short term, 4 week and long term 15 week, outcome of a 2 week DHT-treatment given together.

Methods:

Studies were carried on 72 male seven-week-old rats having a mean weight 261±9.9 gm range. Animals were selected at random, divided into 4 equal groups, and treated for 2 weeks as follows: [1]: Vehicle CONTROL: 0.1ml sesame oil [SO/sc.], [2]: DHT [1.25mg/kg/sc], [3], DHT [1.25mg/kg/sc]+PRZ[30□/kg/sc] in SO; [4]: DHT[1.25mg/kg]+PNN[30□/kg/sc] in SO. At the end of the 4th week time the micturition characteristics of 36 rats were evaluated over a 6 hour time period by placing rats in a metabolic cage to monitor the frequency F and volume V associated with each micturition. Subsequently rats were killed and by careful dissection the weight of the bladder [b], ventral [v], dorsal [d] total prostate [t] determined. Statistical comparisons were made with respect to controls and given values are mean±se

Results:

Table shows micturition and weight parameters measured on the 4th & 15th–week.

Effect on micturition: In the short term DHT treatment produces a significant increase in the frequency and a decrease in the volume voided per micturition. In the long-term the influence of DHT on micturition is not significantly different from controls in all of the defined groups suggesting that this treatment protocol did not have a persistent functional effect on micturition.

	4 WEEKS				15 WEEKS			
	CONTROL	DHT	D+PRZ	D+PNN	CONTROL	DHT	D+PRZ	D+PNN
F[/hr]	0.93±0.06	1.25±0.05*	1.18±0.07*	1.23±0.06*	0.83±0.09	0.80±0.04	0.85±0.07	0.79±0.07
V[g]	0.74±0.05	0.55±0.03*	0.57±0.04*	0.55±0.04*	0.57±0.14	0.48±0.07	0.49±0.09	0.64±0.06
t[mg]	393.3±39.8	474.3±11.8	457.2±12.3	466.5±27.1	483.3±45.6	576.3±25.7	530.0±36.4	703.2±42.2
v[mg]	337.7±33.9	361.7±13.1	388.3±14.7	370.0±23.9	416.0±40.6	428.0±25.4	419.8±28.9	521.5±22.3
d[mg]	55.7±6.9	112.7±7.8*	68.8±5.4*	96.5±18.9*	67.3±6.0	148.3±8.7*	111.2±10.4*	181.7±25.4*
b[mg]	122.5±14.0	119.7±3.7	112.0±9.6	132.8±8.2	123.3±11.3	125.8±6.1	119.3±10.4	147.2±7.9*

Effect on prostate weight. Consideration of the effects of DHT alone on prostate weight shows that DHT and particularly DHT+PNN produce a significant increase on the weight of the whole prostate which is maintained for

the duration of the 15 weeks. This treatment appears to be targeted on the dorsal segment of the prostate, which accounts for the most significant change both during the 4th and 15th week. Conversely DHT+PNN significantly enhanced dorsal prostate growth which was sustained up to the 15th week of observation. Consideration of the effect of treatment on the bladder the data suggest that the combination of DHT+PNN produces the most significant increase in bladder weight.

Conclusion:

The results of this study show that a 2 week DHT-treatment produced sustained prostate growth, which is restricted to the dorsal lobe of the rat's prostate. After induction, dorsal lobe growth is sustained for a considerable period of time. □1 adrenergic blockade appears to restrains the effect of DHT-induced growth of the dorsal prostate but does not effect the ventral lobe. This study has also demonstrated that, while during short term follow-up the anatomical changes produced by DHT treatment on prostate weight are correlated with corresponding functional changes in micturition parameters, this correlation does not persist in the long-term follow-up of 15 weeks. Thus while DHT appears to produce an increased frequency and lower volume of micturition in the short term, its functional effect on micturition is not sustained; be it alone or in combination with PRZ or PNN. It is speculated that this absence of long-term-correlation between the frequency/volume micturition parameters may be partly accounted by plastic changes in bladder function given bladder weight increase is sustained over the 15 weeks of the study. By implication the present study suggests PRZ affects both dynamic and static component of the prostate. While the smooth muscle density of the rat prostate is low compared to other species, a similar density of □1 adrenoceptors was found in dog and human.[3] Indeed it has been reported that, DHT administration to rats provokes a prazosin-sensitive simulation of the micturition characteristics of BPH patients[4, 5.] Finally the observed antigrowth effect of PRZ, provides support to emerging in vitro evidence from human prostate cells suggesting that □1 antagonists suppress growth by inducing apoptosis[6]. In view of these observations, the it is appropriate to consider the biological effectiveness of other clinically used □1 antagonists in restraining growth in addition to producing smooth muscle relaxation to facilitate micturition.

[1] Eur. J Pharmacol. [341] 119-126 1998, [2] B J Pharmacol. [131] 1454-60 2000, [3] J Pharm. Exp. Ther. [270] 722-727 1994. [4] Gen. Pharmacol. [20] 869-874 1989, [5]The Prostate [35]102-108 1998. [6]Cancer Res. [60] 4550-5 2000

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Title: COMPARATIVE INFLUENCE OF TADENAN (TAD) AND ALPHA1 ANTAGONISTS (PRZ) TO DHT-INDUCED PROSTATE GROWTH. FOCUS ON THE VENTRAL LOBE

Aims of Study:

Prostate lobes are known to possess heterogeneous sensitivity to androgen modulation. For this reason the ventral lobe of the rat's prostate is often used as an experimental model to identify the cellular and molecular processes that are involved in the onset of prostate cell apoptosis subsequent to DHT withdrawal. In previous observations we found that TAD significantly reduces the weight of the ventral prostate and counteracts DHT-induced growth (Urology 55:292, 2000). In the present study we examined whether PRZ can also counteract DHT-induced prostate growth. Specifically we considered the effect of PRZ, together with the known effects of TAD, in modulating the growth produced by DHT on dorsal and ventral lobes of the prostate.

Methods:

In the present study we used data from 81 male SD rats having a mean weight 261±9.9gm, treated with DHT at a dose of 1.25mg/kg/sc dissolved in 0.1 ml of sesame oil (SO) as vehicle, TAD at a dose of 100mg/Kg/p.o. dissolved in peanut oil (PO), and PRZ (30μg/kg/sc) using the following protocol: 1:CONTROL, Vehicle, 6 weeks;n=18. 2:DHT, weeks 1-2 + vehicle, week 2-6; n=18. 3:Pre-TAD+DHT, TAD week 1-2, DHT week 3-4 vehicle, week 5-6;n=9. 4:TAD, week 1-6; n=9. 5:DHT+PRZ week 1-2 + vehicle, week 2-6;n=9. 6:DHT+TAD week 1-2+ vehicle, week 2-6;n=9, 7:DHT+Post-TAD DHT week 1-2, TAD for week 3-6;n=9. Rats were killed and by careful dissection the weight of the ventral and dorsal prostate determined. Statistical comparisons of the pooled wet weights were made and indicated in the legend of figure 1. Numerical values are given as mean±se.

Results:

Figure 1 illustrates the effect of treatment on prostate weight of the ventral lobe for the 7 groups considered. As indicated, compared to controls, the effect of DHT treatment, group 2, is to produce a significant increase # ($p<0.05$) in the weight of the ventral lobe while in the presence of TAD, groups 5,7, and PRZ, group 6, growth is restrained. Pre-administration with TAD, group 3, appears to suppress DHT-stimulated growth. Indeed TAD alone significantly reduces the weight of the ventral lobe to values lower than controls.

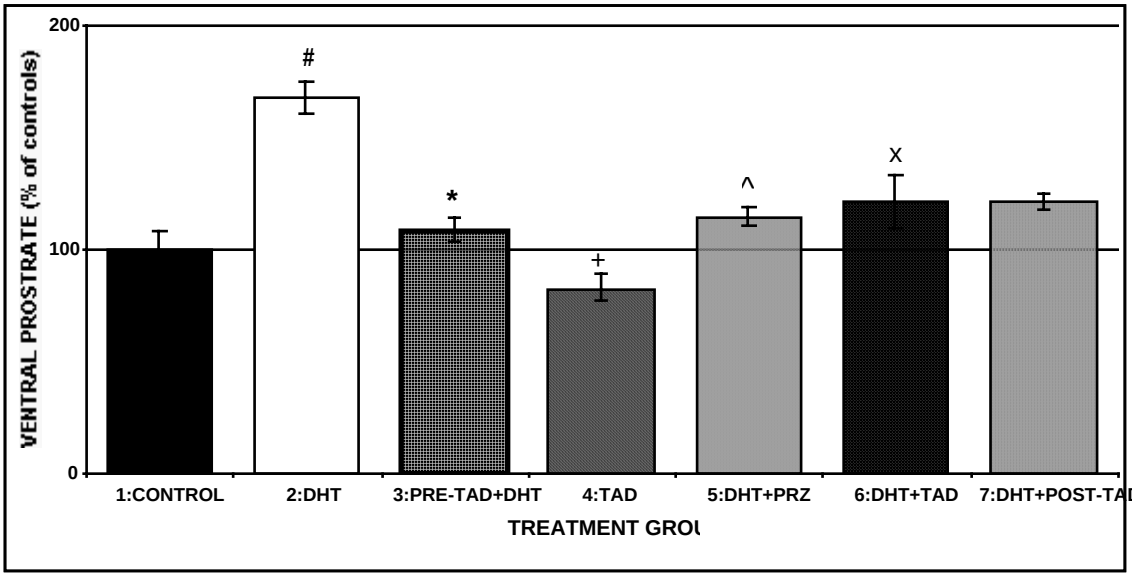

Figure 1: Distribution of the comparative wet weights of ventral prostate of the seven treatment groups. #p<0.01 in a comparison between 1&3; p<0.001 between 2&3; +p<0.05 between 1&4; X,. p<0.01 between 2 and 5,6,7

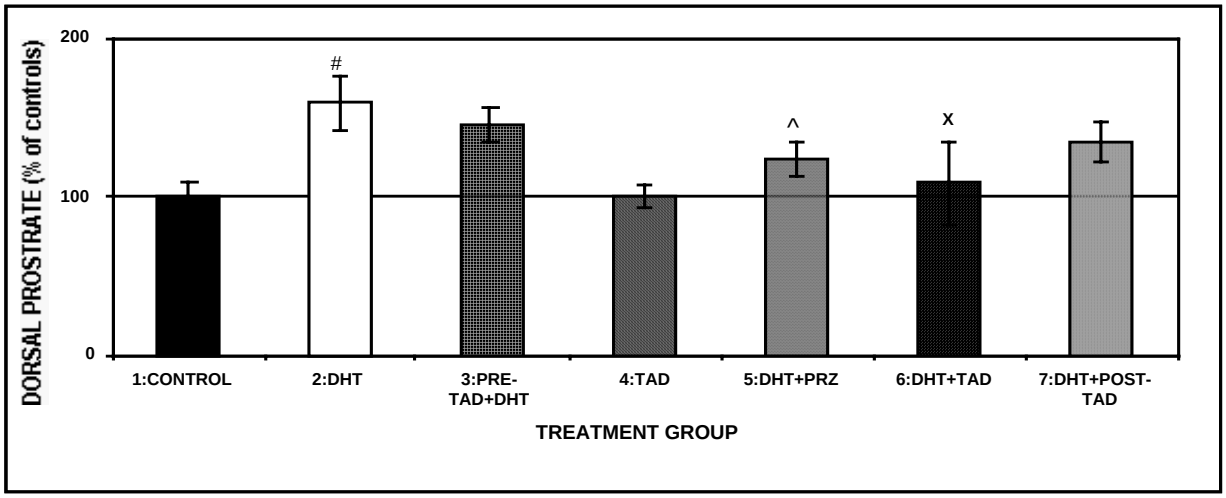

Figure 2: Distribution of the comparative wet weights of the dorsal prostate in the 7 treatment groups. Notation of comparisons indicated is identical to those given by Figure 1.

Conclusion:

Evidence is provided to suggest that, TAD treatment suppresses DHT-induced prostate growth of the ventral prostate. This suppression for growth is most effective, but not exclusively, on the ventral lobe of the prostate and appears to be invariant as to whether it is given before, together or after DHT treatment. Furthermore the results indicate that PRZ also suppresses DHT-induced prostate growth of the prostate. This observation provides evidence that TAD and 1 adrenergic blockade can potentially decrease not only the dynamic component of the prostate, but also its static component, which may be significant in the treatment of BPH. It remains to be established whether the similarity of response between TAD and PRZ is due to it's blocking

activity of the 1 adrenergic receptor.