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VENTRAL PROSTATE STRUCTURE AND SERUM TESTOSTERONE LEVELS IN RATS WITH DIFFERENT ANDROGEN STATUS AFTER CHRONIC TREATMENT WITH PROPRANOLOL

ALEKSANDRA GLAVAŠKI*, T. SOLAROVIĆ**, MIRJANA HRISTIĆ*, V. SAVIĆ*** and BOSILJKA PLEĆAŠ*

*Department of Physiology, Faculty of Pharmacy**; Institute of Pharmacy of Serbia; Department of ***Organic Chemistry, Faculty of Pharmacy; Belgrade, Yugoslavia

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The effects of chronic, 15-day, administration of the β-adrenergic antagonist propranolol (4 mg/kg/d; subcutaneously) on the ventral prostate structure and serum testosterone concentrations were examined in rats with different androgen status, that is immature, adult testosterone-injected (1mg/rat) and chemically castrated animals. Chemical castration was evoked by an intraperitoneal injection of ethane dimethanesulfonate (EDS) (75 mg/kg). A ventral prostate response was observed in immature and in adult chemically castrated animals. Stereological analysis, performed on paraffin sections of the gland, suggested that in immature rats a discharge of glandular secretion occurred. In addition, in these animals alterations were found in the morphometric parameters of the ventral prostete blood vesels, their total volume being decreased. In chemically castrated rats, administration of propranolol from the day of EDS application partially prevented the postcastrational atrophy of the ventral prostate. The changes in the ventral prostate both in immature and adult chemically castrated rats were not accompanied by alterations in blood testosterone level. These results show that chronic treatment with propranolol may affect both contractile and secretory elements of the rat ventral prostate depending on the androgen status of the animals and, accordingly, on the site of propranolol-action.

Key words: Propranolol, immature and adult rats, ethane dimethanesulfonate, ventral prostate, testosterone, stereology.

INTRODUCTION

A growing body of evidence indicates that the autonomic innervation plays a substantial role in the maintenance of the structure and function of the prostate gland. The rat ventral prostate is innervated by both the sympathetic and

parasympathetic divisions of the autonomic nervous system (Langworthy, 1965; Purinton et al., 1972; Vaalasti and Hervonen, 1979). α_1-Adrenergic receptors are present in the prostatic stroma, on the smooth muscle cells surrounding the acini and ducts, and they are responsible for the contraction ofprostatic tissue elicited by the catecholamines or α_1-adrenergic agonists (James et al., 1989; Wang et al., 1991a; Testa et al., 1993; Ruffolo and Hieble, 1994; Killam et al., 1995). On the other hand, specific and high affinity β-adrenergic receptors of the β_2 subtype are localised in the epithelium of the prostate (Dubée et al., 1986; Poyet et al., 1986; Marchetti et al., 1988; Gousse et al., 1991) and their distribution suggests a role in epithelial cell activity. However, the physiological significance of these receptors is virtually unknown. Isoproterenol, a β-adrenergic agonist, has been reported to stimulate production of prostatic bindingprotein (Thompson et al., 1987). It is also believed that the glandular atrophy observed following long-term prostatic denervation (Wang et al., 1991b) or experimentally induced diabetes (Gousse et al., 1991) is due to the lack of stimulation by β-adrenergic receptors. Recently, we have reported that chronic treatment with propranolol, a β-adrenergic receptor antagonist, influenced the adult rat ventral prostate vasculature without affecting the glandular component (Plećaš et al., 1997a).

Since it is clearly established that a close correlation exists between the β-adrenergic receptor concentration in the ventral prostate and serum androgen levels (Poyet et al., 1986; Collins et al., 1988; Marchetti et al., 1988; Guillerma Juarranz et al., 1994; Chen et al., 1995), the aim of this work was to investigate, by a morphometric technique, whether the ventral prostate response *in vivo* depends on the androgen status of the animals. Therefore, the effects of propranolol were examined in sexually immature rats and in adult animals injected with testosterone or chemically castrated. Chemical castration was performed with ethane dimethanesulfonate (EDS), a specific cytotoxic agent for adult rat Leydig cells (Jackson and Jackson, 1984). As propranolol may influence blood testosterone level (Plećaš et al.,1997), which has a primary role in controlling glandular structure and function (Cunha et al., 1987), serum concentrations of this hormone were also determined.

MATERIAL AND METHODS

Animals and treatments. Wistar rats were housed in a temperature-controlled (21 ± 2^{0}C) room with a 12 h light-dark cycle (light on from 08,00 h). Pelleted food and tap water were available *ad libitum.* The animals were dividen into 3 groups on the basis of their adrogen status:

I. Sexually immature rats, 21-days old;

II. Adult rats (250-300 g) which received one subcutaneous injection of testosterone oenanthate (Testosteron Depo, ICN Galenika, Yugoslavia) in a dose of 1 mg *per* animal in 0.1 ml of neutral olive oil;

III. Chemically castrated rats; their Leydig cells were destroyed with an intraperitoneal injection of EDS in a dose of 75 mg/kg in 2 ml of dimethylsulfoxide in water(1:3). Since this substance is not commercially available it was synthesized according to Jackson and Jackson (1984).

Experimental animals from all three groups were subjected to 15-day propranolol treatment. The drug (Propranolol HCl; ICN Galenika, Yugoslavia) was dissolved immediately before use in saline to a daily dose of 4 mg/kg and administered subcutaneously. The treatment started on the 21st day of lifeye of immature rats and on the day of testosterone injection or chemical castration in adult rats. Control animals received saline in the same protocol. An additional group of immature rats was treated with urapidil (Ebrantil, Byk Gulden, Germany; 2 mg/kg diluted in saline) for 15 days, because we reported earlier that this α_1-adrenergic receptor antagonist may influence the ventral prostate structure (Plećaš et al., 1996).

One hour after the final injection the rats were anaesthetised with ether and blood samples were taken by cardiac puncture after opening the chest wall. They were then killed by decapitation and the ventral prostates and the testes were dissected out and individually weighed.

Morphometry. The ventral prostetes were fixed in Bouin's solution, dehydrated in a graded series of ethyl alcohol and embedded in paraffin. Serially cut sections 6 mm thick were stained with hematoxylin and eosin.

Stereological measurments were done on 10 sections (50 randomly chosen test areas) per animal taken from the three representative regions of the gland, distal, intermediate and proximal. Analysis was performed by the point and intersection counting method (Weibel, 1979), using the multipurpose test system with 42 points and 21 lines, at a magnification of 100x, as described previously (Plećaš at al., 1994; Plećaš et al., 1996; Plećaš at al., 1997a).

Morphometric analysis of the ventral prostate blood vessels was performed on 50 test areas of the gland containing mainly stromal tissue at a magnification of 400x, by counting the number of test points falling on the blood vessels and the number of intersections of test lines with the inner surface of the endothelium. The results are expressed per whole gland.

Serum testosterone measurement. After separation the serum was frozen and stored at -20^{0}C until the time of hormone assay. Testosterone concentrations were determined using a commercial RIA kit (Testosterone, INEP - Zemun). All samples were analyzed in duplicate.

Statistics. Data are presented as means ± SEM. The difference between two means was tested by the Wilcoxon nonparametric test and between three means by one-way analysis of variance (ANOVA) followed by Duncan's multiple comparisons.

RESULTS

Serum testosterone levels. Propranolol-treatment influenced serum testosterone concentration in adult testosterone-injected rats, causing a significant decrease only when comparing with the value determined in control, non-adrogenized rats (Table 1).

Body and reproductive organ weights. Administration of propranolol significantly reduced the final body weight in immature rats (Table 1). In these animals both propranolol- and urapidil-treatment decreased the testis weight (Table 1).

Table 1. Serum testosterone concentrations and the body, testis and ventral prostate weights in rats with different androgen status subjected to 15-day treatment with propranolol or urapidiyel.

Group	Serum testosterone (ng/ml)	Body weight (g)	Testis weight+ (mg)	Ventral prostate weight (mg)
Immature rats				
21-day-old-rats[x]	0.56 ± 0.09	59 ± 4	310 ± 15	44 ± 2
Saline	0.52 ± 0.05	168 ± 8	1246 ± 41	69 ± 4
Propranonol	0.64 ± 0.21	128 ± 4**	951 ± 35**	57 ± 3
Urapidil	0.70 ± 0.13	140 ± 8	988 ± 41**	55 ± 2
Adult rats				
Oll+saline	2.57 ± 0.37	354 ± 7	1336 ± 36	332 ± 38
T+saline	1.57 ± 0.36	372 ± 12	1237 ± 58	441 ± 25*
T+propranolol	0.83 ± 0.03*	338 ± 6	1178 ± 84	375 ± 18
EDS+saline	0.49 ± 0.04	356 ± 5	717 ± 50	54 ± 3
EDS+propranolol	0.50 ± 0.07	354 ± 5	760 ± 41	72 ± 4**

T, testosterone oenanthate; EDS, ethane dimethanesulfonate.
+, in immature rats testis weight refers to both testes and in adult animals to the left one.
x, these untreated animals were killed on the 21st day of life.
Results are expressed as means ± SEM; body and organ weights are for 5 animals, whereas serum testosterone concentrations are for 6-8 animals in each group.
*P<0.05 and **<0.01 compared to appropriate age-matched saline-injected control.

Significant changes in the ventral prostate weight were found in immature rats treated with propranolol or urapidil as well as in chemically castrated adult rats treated with propranolol (Table 1). Ventral prostates of experimental immature rats were smaller than in age-matched controls, whereas in chemically castrated propranolol-treated animals they were heavier than in EDS-injected controls.

Morphometric parameters of the ventral prostate. Stereologic analysis of the ventral prostate of immature rats revealed that both propranolol and urapidil affected glandular structure (Table 2). Administration of propranolol significantly reduced the total volume of acinar lumen and the total luminal surface of epithelium, but increased the mean epithelial height. In these animals the total volume of the ventral prostate blood vessels was also decreased (Table 4).

In immature rats treated with urapidil several morphometric parameters of the ventral prostate were reduced, including the total volume of acinar lumen, surface density and total luminal surface of epithelium as well as the total length of acini (Table 2).

In adult rats, propranolol treatment was only effective in chemically castrated animals increasing the relative volumes of luminal and stromal compartments, total volumes of epithelium and lumenof acini, total luminal surface of epithelium and the mean diameter of the acinar lumen(Table 3).

Alyemost the same changes in the ventral prostate, compared with non-adrogenized controls, were found in the testosterone-injected control group and testosterone-injected propranolol-treated rats (Table 3).

Table 2. Morphometric parameters of the ventral prostate of immature rats subjected to 15-day propranololol- or urapidil-treatment from the 21st day of age.

	21-Day-old-rats+	Saline	Propranolol	Urapidil
Relative volume (mm^3/mm^3)				
Epithelium	0.326 ± 0.015	0.261 ± 0.013	0.312 ± 0.028	0.257 ± 0.015
Lumen	0.357 ± 0.018	0.437 ± 0.021	0.389 ± 0.020	0.405 ± 0.008
Stroma	0.318 ± 0.016	0.302 ± 0.021	0.299 ± 0.016	0.337 ± 0.018
Svep (mm^2/mm^3)	16.70 ± 0.46	16.45 ± 0.83	14.62 ± 0.42	14.17 ± 0.66**
Lvac (mm/mm^3)	69.71 ± 7.41	47.52 ± 4.42	50.65 ± 3.73	42.13 ± 3.07
Total volume (mm^3)				
Epithelium	14 ± 1	18 ± 2	17 ± 2	15 ± 1
Lumen	16 ± 1	30 ± 2	22 ± 1**	24 ± 1*
Stroma	14 ± 1	21 ± 2	17 ± 1	20 ± 2
Sep (mm^2)	728 ± 29	1121 ± 599	809 ± 37**	815 ± 56**
Lac (mm)	3001 ± 227	3214 ± 209	2810 ± 262	2422 ± 202*
h (μm)	19.4 ± 1.2	16.0 ± 1.2	21.4 ± 0.7*	18.2 ± 0.7
Dlu (μm)	86 ± 6	106 ± 4	107 ± 5	115 ± 5
λ (μm)	116 ± 5	106 ± 9	125 ± 7	133 ± 10

+, these untreated animals were killed on the 21st day of life.
Svep, surface density of epithelium; Lvac, length density of acini; Sep, total luminal surface of epithelium; Lac, total length of acini; λ, mean epithelial heigh; Dlu, mean diameter of acinar lumen; h, mean distance between acini.
Results are expressed as means for 5 animals in each group ± SEM.
*P<0.05 and **P<0.01 compared to appropriate age-matched saline-injected control.

Table 3. The effect of 15-day propranolol treatment on the morphometric parameters of the ventral prostate of testosterone oenanthate- or ethane dimethanesulfonate (EDS)-injected adult rats.

	Oil + saline	Testosterone oenanthate + saline	Testosterone oenanthate + propranolol	EDS + saline	EDS + propranolol
Relative volume (mm^3/mm^3)					
Epithelium	0.229±0.013	0.186±0.013	0.181±0.019	0.207±0.019	0.207±0.014
Lumen	0.571±0.022	0.595±0.027	0.595±0.020	0.366±0.022	0.484±0.042*
Stroma	0.200±0.021	0.218±0.017	0.224±0.018	0.426±0.037	0.283±0.011*
Svep (mm^2/mm^3)	11.75±0.018	10.92±0.039*	10.71±0.16*	16.89±0.73	17.47±0.62
Lvac (mm/mm^3)	18.81±0.63	15.37± 0.63**	14.15±0.60**	68.35±3.74	58.84±5.59
Total volume (mm^3)					
Epithelium	77±11	82±9	67±7	11±1	15±1*
Lumen	188±20	262±15*	224±18	20±2	35±4 **
Stroma	67±10	97±11	83±5	23±2	23±3
Sep (mm^2)	3899±439	4809±288	4018±209	914±65	1261±59**
Lac (mm)	6286±823	6743±291	5298±302	3673±195	4210±336
h (μm)	19.6±1.3	17.3±1.9	16.9±1.9	12.2±0.8	11.9±0.9
Dlu (μm)	195±9	218±2*	222±8*	86±2	111±9*
λ (μm)	107±7	116±13	117±6	128±12	95±11

Svep,surface density of epithelium; Lvac, length density of acini; Sep, total luminal surface of epithelium; Lac, total length of acini; h, mean epithelial height; Dlu, mean diameter of acinar lumen; λ, mean distance between acini.
Results are expressed as means for 5 animals in each group ± SEM.
*P<0.05 and **P<0.01 compared to appropriate saline-injected control.

Table 4. Morphometric parameters of the ventral prostate blood vessels of rats with different androgen status treated for 15 days with isoproterenol or urapidil.

Group	Relative volume x10^{-3} (mm^3/mm^3)	Total volume (mm3)	Length density (mm/mm^3)	Total length (mm)
Immature rats				
21-day-old rats+	5.6 ± 0.6	0.25 ± 0.04	56.2 ± 7.1	783 ± 100
Saline	6.8 ± 1.2	0.47 ± 0.09	66.6 ± 4.9	1366 ± 121
Propranolol	4.9 ± 0.5	0.27 ± 0.03*	60.3 ± 5.7	1008 ± 128
Urapidil	5.2 ± 0.5	0.30 ± 0.03	60.1 ± 3.3	1176 ± 49
Adult rats				
Oil +saline	9.4 ± 2.2	3.2 ± 0.9	70.5 ± 3.0	4747 ± 8.7
T + saline	8.3 ± 0.9	3.8 ± 0.6	58.8 ± 6.9	5620 ± 716
T + propranolol	8.1 ± 1.0	3.1 ± 0.4	61.9 ± 7.3	5031 ± 316
EDS +saline	20.2 ± 3.4	1.1 ± 0.2	105.7 ± 7.7	2489 ± 405
EDS + propranolol	15.4 ± 3.1	1.1 ± 0.2	111.1 ± 9.6	2468 ± 291

+, these untreated animals were killed on the 21st day of life.
T, testosterone oenanthate; EDS, ethane dimethanesulfonate.
Results are expressed as means for 5 animals in each group ± SEM.
*P<0.05 compared to appropriate age-matched saline-injected control.

DISCUSSION

The results of this work show that prolonged, 15-day, β-adrenergic receptor blockade, evoked by propranolol, affects both the glandular and stromal component of the rat ventral prostate without changing serum testosterone levels. The effects of propranolol depend on the gonadal status of the animals. Thus, the prostate response to tha drug was observed in immature and in adult chemically castrated rats, but not in adult testosterone-injected animals.

In immature rats given propranolol from the 21st day of age,the total volume of acinar lumen and total luminal surface of the epithelium were decreased and the mean height of the epithelium was increased. The character of the morphological changes suggests that a contractile response of periacinar smooth muscl cells was evoked. Consequently, due to evacuation of the glandular secretion, epithelial cells were released from the pressure of the acinar lumen content(Lamano Carvalho et al., 1990). Although it was assumed that β-adrenergic receptors were not involved in the prostate contractions (Wang et al., 1991a), stimulation of these receptors with isoproterenol resulted in stromal muscle cell relaxation (Wang et al., 1991a; Tsuji et al., 1992;Plećaš et al., 1997b).

In immature rats, propranolol significantly reduced the total volume of the ventral prostate blood vessels, indicating a vasocontrictor response. This effect might be the consequence of compensatory sympathetic reflexes (Hoffman and Lefkowitz,1992), since data concerning the presence and number of β-adrenergic receptors in the prostate blood vessels are lacking. Anyhow, a vasoconstriction following the propranolol treatment was also expressed in the ventral prostate of adult rats (Plećaš et al., 1997a), whereas the opposite response, i. e. vasodilation, was found when isoproterenol was administered (Plećaš eta l., 1997b). The reactivity of the ventral prostate blood vessels to propranolol clearly depends on the adrogen status of the animals, since it was suppressed in adult testosterone-injected or in chemically castrated rats.

Recently, we have reported that 15-day administration of urapidil, an α_1-adrenergic receptor antagonist, may evoke a contractile response in the adult rat ventral prostate (Plećaš et al., 1996). Here, the same urapidil-treatment of immature rats resulted in decreases in the ventral prostate weight, volume of acinar lumen and the total length of acini. These results indicate that α-adrenergic receptor blockade in the period of intensive prostate growth (Smith et al., 1977) may preclude normal glandular develpment. This is in agreement with the findings that chemical (Lamano Carvalho et al., 1990) or surgical (McVary et al., 1994) sympathectomy leads to structural atrophy and functional disturbance of the prostate.

In adult chemically castrated rats a completely different response of the ventral prostate to propranolol was observed from that seen in immature animals. Administration of the drug from the day of EDS application partially prevented involution of the ventral prostate. These animals had heavier glands, greater volumes of epithelial and luminal compartments and larger diameter of aciar lumen. Since the increase in epithelial lumen was not associated with increased

epithelial cell height, the number of these cells was probably also greater than in EDS-injected controls.

The question arises why the ventral prostates of immature and adult chemically castrated rats responded differently to propranolol. The β-adrenergic receptor in the prostate is a case of positive regulation by testosterone (Poyet et al., 1986; Marchetti et al., 1988; Guillerma-Juarranz et al., 1994; Chen et al., 1995; Collins et al., 1995). However, serum testosterone concentrations of immature and adult chemically castrated rats were actually very similar. On the other hand, in immature propranolol-treated rats the body and the testis weight gains were significantly suppressed suggesting an effect of propranolol on the secretion of other hormone(s), some of which could directly influence the prostate gland (McKeehan et al.,1984). In addition, in adult rats propranolol might influence local factors, which were not expressed in the gland of immature animals. Anyhow, it appears that the different target cells were affected by propranolol treatment in immature and adult rats.

In our previous study (Plećaš et al., 1997b) it was reported that isoproterenol partially prevented regression of the ventral prostate in adult chemically castrated rats. Almost the same effect was observed with propranolol in the present work. A possible explanation could be the up-regulation of β-adrenergic receptors in the target tissue, a phenomenon described for the brain (Takita et al., 1995) and heart (Conlon et al., 1995). If so, the tissue sensitivity to endogenous catecholamines would be enhanced.

In summary, chronic treatment with propranolol may evoke a contractile response of the rat ventral prostate, changes in the blood flow to the gland or even hinder atrophic changes. The effect of propranolol greatly depends on the androgen status of the animals, being expressed under conditions of low blood testosterone levels. Most likely, different levels of propranolol actions are involved.

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STRUKTURA VENTRALNE PROSTATE I NIVO TESTOSTERONA U SERUMU PACOVA SA RAZLIČITIM STATUSOM ANDROGENIH HORMONA POSLE HRONIČNOG TRETMANA PROPRANOLOLOM

ALEKSANDRA GLAVAŠKI, T. SOLAROVIĆ, MIRJANA HRISTIĆ, V.SAVIĆ i BOSILJKA PLEĆAŠ

SADRŽAJ

U radu je ispitivan uticaj hroničnog, petnaestodnevnog tretmana propranololom (4 mg/kg/d; subkutano), antagonista β-adrenergičnih receptora, na strukturu ventralne prostate i koncentraciju testosterona u serumu pacova sa različitim nivoom androgena: polno nezrelih, odraslih koji su primili jednu injekciju testosteron enantata (1 mg/pacov) i odraslih hemijski kastriranih. Hemijska kastracija je izvršena davanjem jedne intraperitonealne injekcije etandimetansulfonata(EDS; 75 mg/kg). Odgovor ventralne prostate uočen je kod polno nezrelih i odraslih hemijski kastriranih pacova. Rezultati stereološke analize ukazuju da je kod polno nezrelih životinja verovatno došlo do kontraktilnog odgovora glatke muskulature strome i vazokonstrikcije u žlezdi. Kod hemijski kastriranih odraslih pacova tretman propranololom primenjen od dana davanja EDS delimično sprečava postkastracionu involuciju žlezde. Promene u ventralnoj prostati obe grupe životinja tretiranih propranololom nisu praćene promenama nivoa testosterona u krvi. Rezultati ovog rada pokazuju da hroničan tretman propranololom, zavisno od androgenog statusa životinja i time i nivoa delovanja propranolola, može da utiče na kontraktilnost ventralne prostate ili broj njenih sekretnih ćelija.