J. Steroid Biochem. Molec. Biol. Vol. 39, No. 3, pp. 395–403, 1991
Printed in Great Britain.

0960-0760/91 $3.00 + 0.00
Pergamon Press plc

TESTICULAR FUNCTION IN UREMIC RATS: *IN VIVO* ASSESSMENT OF TESTOSTERONE BIOGENESIS

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(Received 31 January 1991)

Summary—The mechanism of testosterone (T) production defect in uremic rats has not yet been clearly defined and hypothalamo–hypophyseal impairment as well as primary testicular dysfunction have been suggested. In 42 rats followed monthly after subtotal nephrectomy up to 7.1 ± 0.3 months, we observed a progressive significant decline of T and androstenedione (A) compared to control rats. Two months before the terminal phase of chronic renal failure (CRF), T/A ratio abruptly declined. T and its precursors on the 4-ene pathway, A, progesterone (P) and 17-hydroxyprogesterone were evaluated in pampiniform plexus testicular vein (PPTV) and in peripheral blood (PV) in end stage uremic rats (blood urea >30 mmol/l, creatinine clearance <0.5 ml/min). Under basal conditions, all steroids but peripheral P were significantly lower in uremic rats than in controls as well as T/P and A/P ratios. After human chorionic gonadotropin (hCG) stimulation, T concentration in PV and PPTV remained highly significantly lower than in controls whereas T precursor concentrations were partially corrected by hCG administration. T/P ratio remained lower than in controls whereas A/P ratio was not significantly lower than in controls. Those data show a decline in all the steps of T biogenesis in uremic rats in basal conditions. The defect in 17β-hydroxysteroid dehydrogenase evidenced by T/A decrease at the end stage of CRF seems of primary testicular origin as it is not corrected by hCG administration as shown by T/P and A/P ratios in PPTV and in PV.

INTRODUCTION

Chronic renal failure (CRF) is known to be associated with impairment of gonadal function in men and in women. In uremic men, hypogonadism includes disorders of Leydig cell function and spermatogenesis (for review see [1]). The origin of testicular endocrine dysfunction has not yet been clearly defined: in human CRF and in experimental models, mainly in uremic rats, hypothalamo–hypophyseal impairment as well as primary testicular defect have been suggested [1–7]; but up to now, only limited experimental studies have been dedicated to this problem and detailed characterization of the pathogenic mechanism of hypogonadism has not yet been reported.

In rats, experimental chronic uremia secondary to subtotal nephrectomy results in a decrease of peripheral levels of testosterone (T) [2, 3, 5, 8–11] and luteinizing hormone (LH) [2–6]. Testicular response to stimulation with human chorionic gonadotropin (hCG) is controversial [5, 9] as well as the degree of hypothalamo–hypophyseal impairment [4, 7, 11]. Previous data on testicular dysfunction in uremic rats have been collected in short term CRF only, most often <3 months after subtotal nephrectomy [2, 3, 9–11]. It is noteworthy that, after subtotal nephrectomy, a compensatory hypertrophy first develops [12] and that the glomerulosclerosis lesions responsible for the CRF appear only 3 months later and are well organized around 5 months [13]. So, an uremic model used to better understand hypogonadism of human CRF, should be studied for a longer period of time. On the other hand, except one observation of reduced androstenedione (A) in uremic rats [10], the different steps of T biogenesis have not been investigated. The aim of the present study was to follow androgen levels during the development of CRF after subtotal nephrectomy and to study the precursors of T of the biogenetic 4-ene pathway in

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Trivial names and abbreviations: Androstenedione: 4-androstene-3, 17-dione (A); progesterone: 4-pregnene-3, 20-dione (P); 17-hydroxyprogesterone: 17-hydroxy-4-pregnene-3,20-dione (17OHP); and testosterone: 17β-hydroxy-4-androsten-3-one (T).

end stage uremic rats. As steroid concentration in testicular venous blood provides a more accurate reflection of testicular function and steroid secretion [14], we used a previously described pampiniform plexus venous blood (PPTV) sampling technique [15].

MATERIALS AND METHODS

Animals

Mature male Wistar rats were used for all experiments. They were housed under controlled light (12/12) and temperature (20–22°C) and fed with standard rat chow and water *ad libitum*. 42 rats were followed up monthly from the nephrectomy until the end stage CRF was reached. 18 normal rats of matched age were followed up in the same conditions and served as control group, as previous studies show no differences between normal and sham operated rats concerning Leydig cell function [3]. Among those groups, spermatic venous blood was drawn from end stage uremic rats in basal conditions ($n = 14$) or after hCG ($n = 8$) and in control rats ($n = 9$ and $n = 7$, respectively).

Nephrectomy technique

Uremic rats were prepared by one step subtotal nephrectomy performed on 60-day-old animals [13] under ether anesthesia. A 2 cm long dorsal midline incision of the skin was performed and both kidneys were exposed through a flank incision 1 cm right and left of the spinal column. The left kidney was first exposed, carefully dissected in order to leave the adrenal gland and its blood supply intact and then removed after ligation of the renovascular pedicle. The right kidney was then exposed and upper and lower poles were removed after careful dissection of the surrounding tissue. Hemostasis was obtained through a smooth pressure with fingers on the cut surfaces. No severe bleeding occurred during the operation and the mortality for the whole procedure was $< 10\%$.

Post operative assessment

After subtotal nephrectomy, rats were assessed for metabolic and hormonal parameters monthly until end stage chronic renal failure was obtained: body weight was measured, 24 h urines were collected in metabolic cages and blood was drawn by retroorbital puncture under light ether anesthesia. Blood urea and creatinine as well as urinary creatinine and creatinine clearance rate were determined monthly. The same survey procedure was applied to the control rats.

Biochemical and hormonal studies

The follow-up of blood urea, creatinine clearance and plasma T and A was performed monthly in nephrectomized and control rats. When end stage CRF was reached (blood urea > 30 mmol/l; creatinine clearance rate < 0.5 ml/min) spermatic venous blood was drawn from one branch of the PPTV as described previously [15] either under basal conditions or 2 h after intramuscular (i.m.) administration of 80 IU/kg hCG [16]. All the blood samplings were performed between 10 a.m. and 1 p.m. in order to reduce interindividual variations due to the circadian rhythm of testicular steroids [17]. T, A, progesterone (P), 17-hydroxyprogesterone (17OHP) were evaluated in PPTV and peripheral blood (PV) drawn from the abdominal aorta just after PPTV sampling. Peripheral levels of LH and hCG, when administered, were also determined.

Biochemical assays

Blood creatinine and urea nitrogen were determined on a Kodak Ektachem DT; urinary creatinine measurement was made using Jaffe reaction on an Abbott TDX.

Hormone assays

All steroid concentrations were determined by radioimmunoassay after column chromatography on either celite for T and A [18] or sephadex LH 20 for P and 17OHP [19]. All the methods were validated for assay in rat, according to the statistical procedures described by Scholler [20].

LH was determined by a homologous double antibody radioimmunoassay [21]. In brief, highly purified rat LH (NIDDK-rLH-I-6) used as tracer after iodination and reference preparation NIDDK-r-LH-Rp2 used as standard were provided by Dr A. F. Parlow. The first antiserum was an antiβLH antiserum raised in the guinea pig and the second precipitating antibody was an antiguinea pig γglobulin antiserum raised in the rabbit [22].

Plasma hCG levels after i.m. administration were determined using an immunoradiometric assay (Pharmacia β hCG RIACT).

Statistical methods

All results are expressed as the mean ± SEM. Comparisons of two groups were carried out as follows: normality of distributions was assessed using Lilliefors, Kolmogorov–Smirnov modified, or Shapiro–Wilks tests; whenever normality could be assumed, comparisons of samples were made with Student's t-test; Mann–Whitney or Wilcoxon tests were otherwise addressed; correlations were evaluated by Spearman's rank correlation coefficient ρ [23].

One way analysis of variance (ANOVA) was used to compare several groups, then followed by Duncan's test when the null hypothesis of equal means was rejected by ANOVA. In some cases, when distributions could be considered as lognormal or when variances were unequal, data were transformed logarithmically in base 10 before analysis [24]. Comparisons between hormonal profiles in uremic and control groups at various months were achieved by two way analysis of variance [25].

All these statistical analyses were carried out using RS/1 statistical procedures (BBN Software Products Corp., Cambridge, MA, U.S.A.) implemented on a Vax 3500 (Digital Equipment Corp., Maynard, MA, U.S.A.).

RESULTS

Hormonal profiles during the alteration of renal function

42 rats were studied monthly from the first month after subtotal nephrectomy (3 months of age) until end stage CRF which occurred between 4 and 12 months after surgery (7.1 ± 0.3 months). The amount of original renal tissue removed was 74.2 ± 0.4%. The control group of 18 rats was studied under the same conditions from 3 to 14 months of age. Body weight and renal function parameters are represented in Table 1.

Plasma T and A profiles observed in uremic and control rats are represented in Figs 1 and 2. T/A ratios are shown in Fig. 3. Steroid levels decline progressively from 3 months of age both in control and nephrectomized rats. T and A levels are significantly lower in uremic rats than in the control group from the first till the twelfth month after nephrectomy. T/A remains stable and comparable in uremic and control rats until 10 months after surgery and then dramatically drops in uremic rats on M11 and M12. Results of two way ANOVA show that nephrectomy significantly affects T levels ($F = 157.7$; $P \simeq 0$) and A ($F = 156.1$; $P \simeq 0$) as does the period of time ($F = 10$; $P \simeq 0$ for T; $F = 9$; $P \simeq 0$ for A). There is a significant interaction between renal status and months for T ($F = 1.6$; $P = 0.01$) but not for A ($F = 0.9$; $P = 0.5$).

According to the interindividual variations of survival, the last groups of the uremic rats included only a few points. So, to confirm those results, we studied the same data from M-11 to the date of sacrifice at end stage CRF (M0). Mean values then obtained are given in Table 2. As above, the same significant differences concerning T and A are observed in this other presentation of the results and T/A is significantly lower in uremic rats than in controls at M0 and M-1 ($P < 0.05$).

In nephrectomized rats, T and A levels are strongly negatively correlated with blood urea: $\rho = -0.478$ and $\rho = -0.434$, respectively ($P < 0.001$) and they are positively correlated with creatinine clearance rate: $\rho = 0.467$ and $\rho = 0.412$, respectively ($P < 0.001$). T and A levels are significantly correlated in uremic as well as control rats: $\rho = 0.812$ and $\rho = 0.773$, respectively ($P < 0.001$).

LH levels were determined in 24 end stage uremic rats and 18 matched control rats. In uremic rats, plasma LH was under the detection limit of the method (0.05 ng/ml) in 19 animals and low (between 0.1 and 0.2 ng/ml) in the other 5. The mean LH concentration observed in 18 control rats was 0.47 ± 0.08 ng/ml.

Steroid levels in PV and PPTV in uremic and control rats are represented in Figs 4, 5, 6 and 7. Under basal conditions, T, A and 17OHP levels were significantly lower in uremic rats than in controls in PV blood as well as in PPTV blood. P decrease in uremic vs control rats was significant only in PPTV blood. T/P and A/P ratios were significantly lower in uremic rats than in controls (Table 3). T/A in PPTV was found to be significantly lower ($P < 0.05$) by Mann–Whitney test, in uremic rats than in controls (28.2 ± 16.3 vs 43.4 ± 17.3).

Two hours after hCG administration, T levels remained highly significantly lower in uremic rats in PV and PPTV, whereas the difference between uremic and normal rats was less significant than under basal conditions for A and 17OHP and not statistically different for P.

After hCG administration only T/P ratio remained significantly lower in uremic rats, whereas A/P ratio was not significantly affected by renal status (Table 3); T/A ratio in PPTV

Table 1. Mean body weight (BW), blood urea (U) and creatinine clearance (CC) in nephrectomized rats (N) from M1 to M12 after nephrectomy and in controls (C)

	BW (g)		U (mmol/l)		CC (ml/min)	
Months	N	C	N	C	N	C
M1	377 ± 8 (38)	371 ± 7 (14)	12.7 ± 0.5	6.6 ± 0.3	1.6 ± 0.1	2.0 ± 0.1
M2	434 ± 9 (31)	429 ± 10 (15)	11.8 ± 0.6	6.3 ± 0.3	1.6 ± 0.1	2.5 ± 0.2
M3	477 ± 8 (39)	461 ± 15 (14)	12.0 ± 0.5	6.1 ± 0.4	1.6 ± 1	2.4 ± 0.1
M4	5.00 ± 9 (38)	515 ± 15 (13)	14.7 ± 1.1	6.0 ± 0.4	1.3 ± 0.1	2.6 ± 0.2
M5	516 ± 11 (36)	548 ± 14 (14)	24.4 ± 5.1	5.7 ± 0.3	1.2 ± 0.1	2.8 ± 0.2
M6	533 ± 9 (29)	565 ± 15 (14)	27.2 ± 4.8	5.4 ± 0.3	1.0 ± 0.2	2.5 ± 0.2
M7	541 ± 12 (20)	574 ± 14 (12)	27.6 ± 4.0	5.2 ± 0.3	0.8 ± 0.1	2.6 ± 0.2
M8	533 ± 20 (13)	580 ± 22 (7)	52.6 ± 17.5	5.0 ± 0.3	0.9 ± 0.2	2.8 ± 0.3
M9	517 ± 31 (8)	641 ± 19 (4)	47.7 ± 14.1	4.7 ± 0.3	0.7 ± 0.3	3.4 ± 0.2
M10	552 ± 38 (5)	616 ± 30 (6)	28.3 ± 8.9	5.4 ± 0.3	0.9 ± 0.3	3.2 ± 0.4
M11	575 ± 31 (4)	606 ± 24 (4)	37.7 ± 14.7	5.6 ± 0.5	0.8 ± 0.3	3.8 ± 0.4
M12	530 ± 70 (2)	628 ± 22 (4)	44.2 ± 10.8	4.8 ± 0.3	0.2 ± 0.1	3.7 ± 0.2

Values are the mean ± SEM. The number of animals is in parentheses.

was significantly lower in uremic rats than in controls (14.9 ± 12.4 vs 26.1 ± 8.1) as under basal conditions ($P < 0.02$).

In order to evidence a relative accumulation of T precursors on the 4-ene pathway, mean ratios of PPTV concentrations of 4-ene steroids to their sum were calculated for each uremic and control rat under basal conditions and after hCG. Mean values are displayed in Fig. 8. All the differences between corresponding compounds of uremic and control groups, before and after hCG, were highly significant ($P < 0.01$), except for A before hCG. Moreover, the bargraphs show the relative accumulation of T precursors and the modified distribution of their concentrations after hCG.

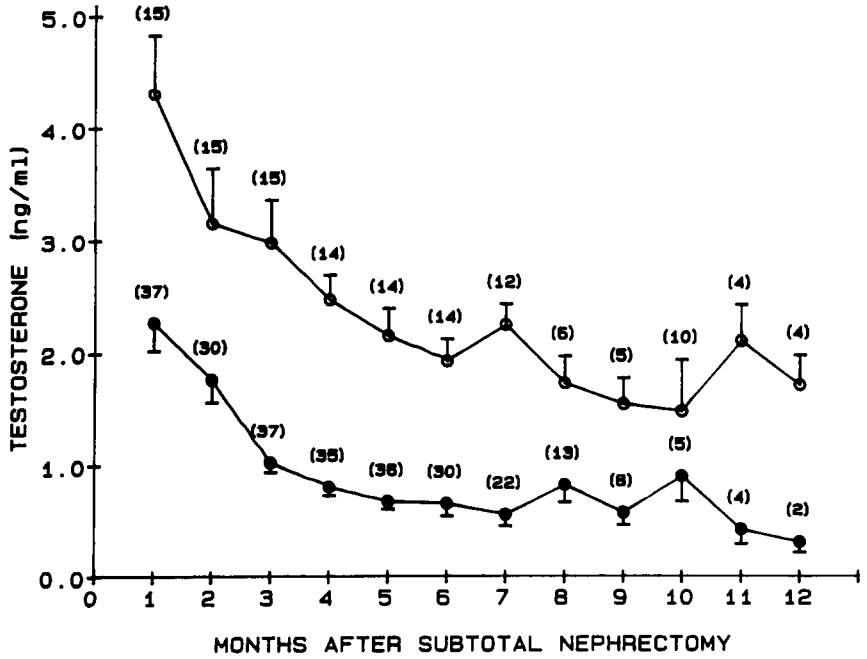

Fig. 1. T profiles (mean ± SEM) in nephrectomized rats (●) from 1 to 12 months after subtotal nephrectomy and in matched control rats (○). The number of animals is in parentheses.

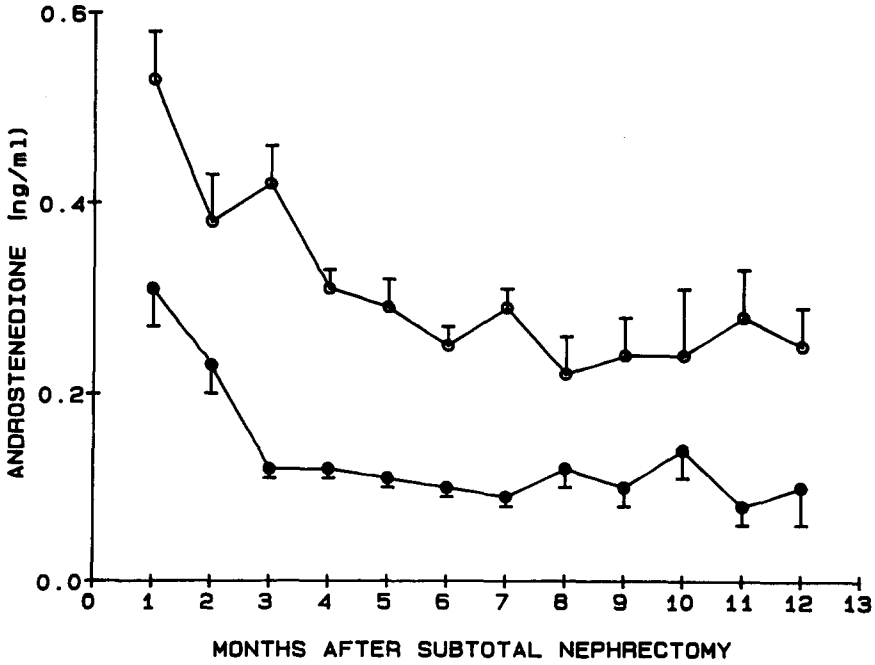

Fig. 2. A profiles (mean ± SEM) in nephrectomized rats (●) from 1 to 12 months after subtotal nephrectomy and in matched control rats (○).

DISCUSSION

In this study, we presented for the first time the profiles of androgens measured monthly up to 12 months after subtotal nephrectomy as well as the T biogenetic precursor concentrations in PPTV of uremic rats before and after hCG.

Our uremic model derived from Stoykova's technique where about 70% of renal tissue was removed provides a progressive CRF resulting in end stage uremia in 7.1 ± 0.3 months which can be compared to CRF occurring in human nephropathies.

Rat uremic models are mainly obtained by 5/6 nephrectomy derived from the technique

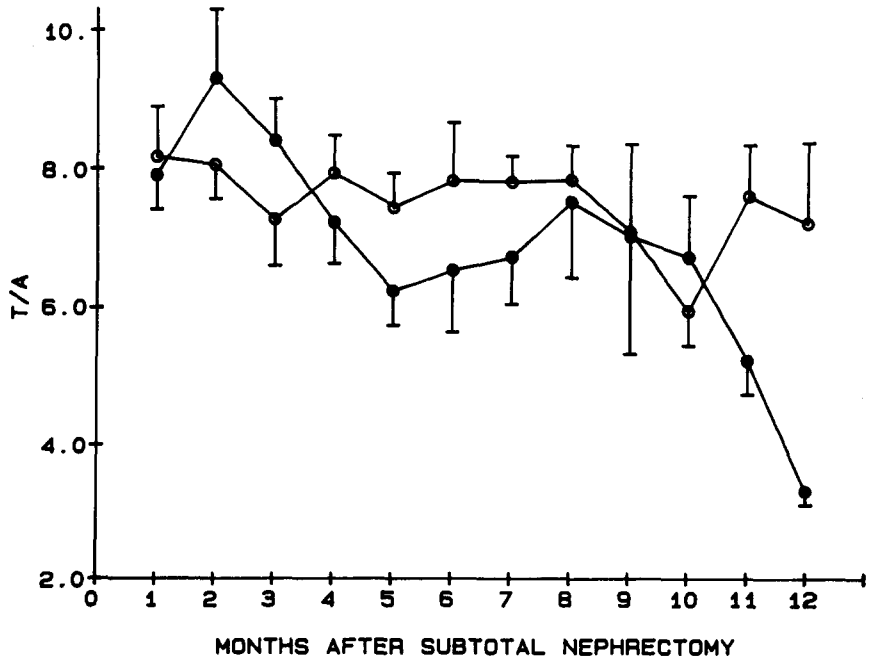

Fig. 3. T/A ratio (mean ± SEM) in nephrectomized rats (●) from 1 to 12 months after subtotal nephrectomy and in matched control rats (○).

Table 2. Mean plasma T, A and T/A ratio from M-11 to M0 (sacrifice) in nephrectomized (N) and control (C) rats

	T(ng/ml)		A (ng/ml)		T/A	
Months	N	C	N	C	N	C
M-11	1.04 ± 0.47 (2)	3.93 ± 0.65 (3)	0.18 ± 0.05	0.44 ± 0.05	5.5 ± 1.1	9.2 ± 1.4
M-10	2.63 ± 0.39 (4)	2.86 ± 0.78 (3)	0.27 ± 0.03	0.33 ± 0.04	10.0 ± 1.8	8.4 ± 1.4
M-9	2.71 ± 0.92 (4)	4.97 ± 0.62 (5)	0.27 ± 0.08	0.55 ± 0.10	10.3 ± 2.5	9.5 ± 1.0
M-8	2.38 ± 0.60 (6)	2.66 ± 0.39 (6)	0.23 ± 0.04	0.30 ± 0.04	11.0 ± 1.5	9.0 ± 0.5
M-7	2.25 ± 0.50 (13)	2.96 ± 0.80 (7)	0.30 ± 0.06	0.33 ± 0.07	8.4 ± 1.4	8.6 ± 0.6
M-6	1.83 ± 0.21 (22)	2.96 ± 0.62 (12)	0.23 ± 0.04	0.41 ± 0.06	9.5 ± 0.9	7.5 ± 0.8
M-5	1.45 ± 0.17 (29)	3.05 ± 0.47 (15)	0.21 ± 0.03	0.40 ± 0.05	8.10 ± 0.8	7.4 ± 0.5
M-4	1.26 ± 0.15 (34)	2.26 ± 0.33 (11)	0.18 ± 0.03	0.32 ± 0.03	7.6 ± 0.6	7.0 ± 0.6
M-3	0.95 ± 0.11 (33)	2.47 ± 0.27 (10)	0.13 ± 0.01	0.33 ± 0.02	8.2 ± 0.8	7.6 ± 0.7
M-2	0.68 ± 0.07 (33)	2.38 ± 0.23 (15)	0.11 ± 0.01	0.37 ± 0.04	7.0 ± 0.7	6.7 ± 0.4
M-1	0.59 ± 0.05 (37)	1.78 ± 0.16 (18)	0.10 ± 0.01	0.25 ± 0.02	6.00 ± 0.04	7.3 ± 0.4
M0	0.28 ± 0.02 (42)	1.93 ± 0.28 (18)	0.06 ± 0.01	0.25 ± 0.2	5.1 ± 0.4	7.7 ± 0.7

Values are the mean ± SEM. The number of animals is in parentheses.

of Platt *et al.* [26]. After a first compensatory hypertrophic stage related to the enlargement of existing nephrons in adults [12, 27], glomerulosclerosis resulting in a CRF develops progressively from the third month following subtotal nephrectomy [13, 28]. The duration of the follow-up of such models varies from 2 weeks to 12 months. But among the few studies previously dedicated to the impairment of the pituitary–testicular axis in uremic rats, gonadal function was investigated in early stages of CRF, most often around 4 weeks [2, 3, 6, 9, 10] and rarely over 3 months [8, 11].

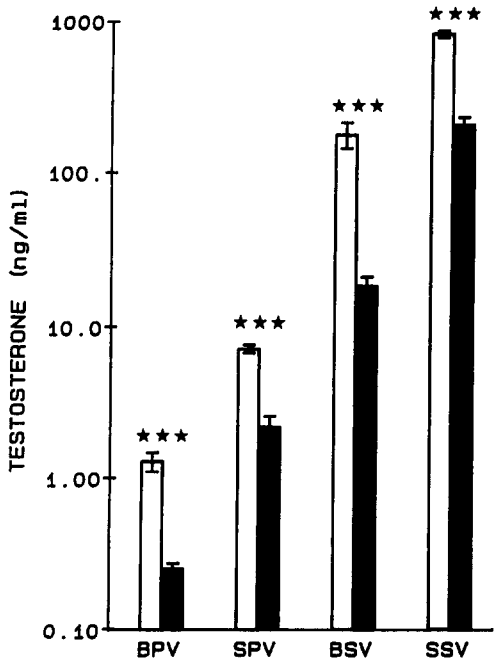

Fig. 4. T concentrations (mean ± SEM) in peripheral vein under basal conditions (BPV) and after hCG stimulation (SPV) and in spermatic vein under basal conditions (BSV) and after hCG stimulation (SSV) in uremic rats (■) and in controls (□). ★★★$P < 0.002$.

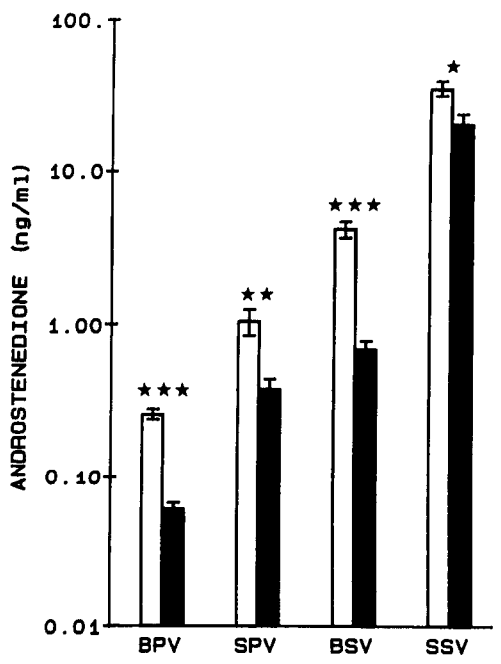

Fig. 5. A concentrations (mean ± SEM) in peripheral vein under basal conditions (BPV) and after hCG stimulation (SPV) and in spermatic vein under basal conditions (BSV) and after hCG stimulation (SSV) in uremic rats (■) and in controls (□). ★$P < 0.05$; ★★$P < 0.01$; ★★★$P < 0.002$.

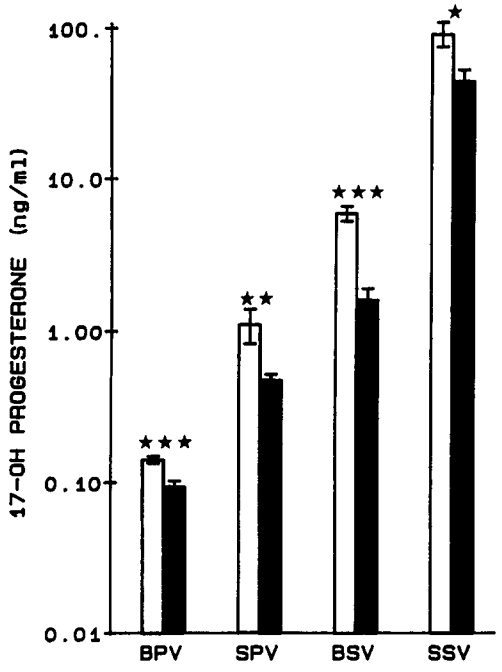

Fig. 6. 17OHP concentrations (mean ± SEM) in peripheral vein under basal conditions (BPV) and after hCG stimulation (SPV) and in spermatic vein under basal conditions (BSV) and after hCG stimulation (SSV) in uremic rats (■) and in controls (□). $^{\star}P < 0.05$; $^{\star\star}P < 0.01$; $^{\star\star\star}P < 0.002$.

In most of those studies the degree of renal function impairment is milder than the one observed in our end stage uremic rats except for

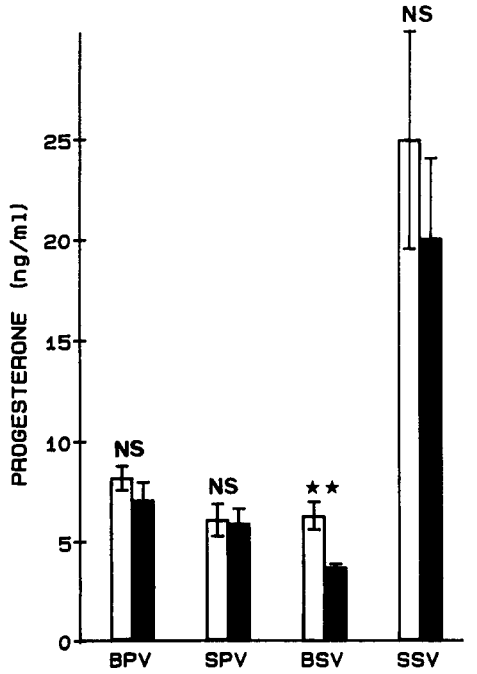

Fig. 7. P concentrations (mean ± SEM) in peripheral vein under basal conditions (BPV) and after hCG stimulation (SPV) and in spermatic vein under basal conditions (BSV) and after hCG stimulation (SSV) in uremic rats (■) and in controls (□). $^{\star\star}P < 0.01$; NS, not significant.

Table 3. T/P and A/P ratios in uremic (U) and control (C) rats under basal conditions and after hCG administration (mean ± SEM)

Basal	U ($n = 14$)	C ($n = 9$)
T/P PV	$0.04 \pm 0.01^{***}$	0.16 ± 0.06
T/P PPTV	$5.0 \pm 3.4^{***}$	31.3 ± 22.7
A/P PV	$0.01 \pm 0.005^{***}$	0.03 ± 0.01
A/P PPTV	$0.19 \pm 0.10^{***}$	0.71 ± 0.37
hCG	U ($n = 8$)	C ($n = 7$)
T/P PV	$0.44 \pm 0.37^{**}$	1.36 ± 0.61
T/P PPTV	$13.4 \pm 7.0^{***}$	43.0 ± 18.5
A/P PV	0.07 ± 0.03 NS	0.14 ± 0.09
A/P PPTV	1.17 ± 0.82 NS	1.85 ± 1.15

$^{**}P < 0.01$; $^{***}P < 0.002$; NS, not significant.

Handelsman *et al.* [9] who removed 90% of renal tissue and da Costa e Silva *et al.* [8] who evaluated gonadal function 3–5 months after subtotal nephrectomy.

In our study, T and A progressively declined in parallel in uremic and control rats under the well known effect of age [29] but T and A concentrations were significantly lower in uremic rats than in matched controls from the first month after surgery till the end stage CRF. All over this period, androgen levels were significantly correlated negatively with blood urea and creatinine and positively with creatinine clearance. These longitudinal findings are in accord with prior transversal observations between peripheral T and blood urea [2, 8] and between T testicular content and blood creatinine [9]. Interestingly peripheral T/A ratio, which was quite constant and comparable in controls and nephrectomized rats in the first months after surgery declined abruptly in the two last months

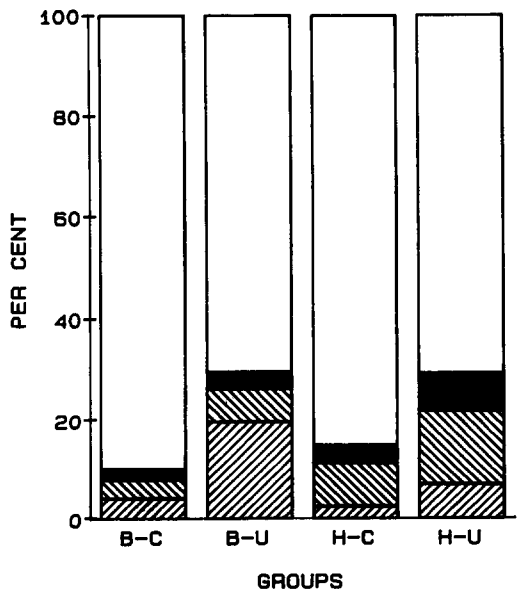

Fig. 8. Mean relative concentrations of 4-ene steroids of control (C) and uremic (U) rats in PPTV before (B) and 2 h after hCG (H): P (□), 17OHP (□), A (■) and T (□).

of the CRF evolution, suggesting a major impairment of the last step of T biogenesis.

Peripheral T levels in end stage uremic rats were reduced by 85% compared to controls; this is comparable to values observed by Holmes *et al.* [11] 3 months after subtotal nephrectomy, but lower than the results from other studies [2, 3, 5, 8–10]. At the same time, peripheral A levels were 4 times lower in uremic rats than in controls as previously reported in the early stages of CRF [10]. Plasma LH was undetectable in most of our uremic rats, as in all previous studies [2–6] but one [8].

The concentration of T in spermatic venous blood from uremic rats has been previously evaluated in only one study [9]: in 6 animals T levels were found to be reduced by 47%, as was the testicular content of T [9, 11] and the *in vitro* release of T by testicular tissue at 2 h, but not at 4 h [9].

In the present study, there was a highly significant decrease in all the steroids in testicular venous blood, T in PPTV being 10 times lower in uremic rats than in controls. 17OHP was also decreased in PV, whereas P was not significantly lower in uremic rats. This is probably due to the fact that anesthesia increases P production by adrenals (data not shown). T/P, A/P and T/A ratios in PPTV were also lower in uremic rats than in controls. All these data are in favor of an impairment of all the steps of T biogenesis.

T response to hCG in uremic rats has been previously investigated *in vitro* and *in vivo* in peripheral blood. After hCG stimulation, T production by isolated Leydig cells was found reduced [3] but T production by testicular tissue after 4 h incubation *in vitro* with hCG was paradoxically higher than in controls [9].

Our data confirm the important decrease of T response, evaluated in PV and in PPTV, 2 h after acute hCG administration. P concentration in PPTV was similar in uremic and control rats, but 17OHP and A were significantly reduced in uremic rats in both PV and PPTV, though less than under basal conditions. T/P and T/A ratios remained lower than in controls whereas A/P ratio was corrected by hCG administration. So it appears that hCG administration partially corrects T biogenesis impairment acting mainly in the first biogenetic steps and this could be in favor of the role of LH deficiency in uremic hypogonadism: 3β-hydroxysteroid dehydrogenase and *P*450 system of 17α-hydroxylase/C_{17-20} lyase are known to be LH dependent, even though the former is a controversial fact [30–33]. But, despite hCG administration, a deficiency in the last biogenetic step, 17β-hydroxysteroid dehydrogenase, persists. This enzyme is generally considered as LH independent [30] but its maintenance is still unclear: hypophysectomy [30] or testosterone–17β-estradiol implants [31] decrease its level or activity but the decrease of this enzymatic activity cannot be corrected by sustained hCG treatment over 4–8 days [30] whereas hCG is capable of restoring *in vitro* T production within a short time [34]. Nonetheless, in our study the response of this enzymatic activity to hCG is weaker than those of the other enzymes of the 4-ene pathway as evidenced by the T/P, A/P and T/A ratios and by the relative accumulation of precursors above this last step of the 4-ene pathway. Therefore, we conclude that in uremic rats T biogenesis impairment includes a defect in 3β-hydroxysteroid dehydrogenase and *P*450 enzymes which could be related to LH deficiency, and an alteration of the 17β-hydroxysteroid dehydrogenase probably of primary testicular origin. This could be further investigated by studying the factors capable of modifying the 17β-hydroxysteroid dehydrogenase activity, as changes of the reversibility of T/A reaction under cofactor imbalance or inhibition by toxic molecules.

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