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Renal Dopaminergic System Activity in Uninephrectomized Rats up to 26 Weeks after Surgery

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Key Words
Kidney · Dopamine · Renal mass reduction · Blood pressure

Abstract
Background: Dopamine of renal origin exerts natriuretic and diuretic effects by activating D_1-like receptors located at various regions in the nephron. Two weeks after uninephrectomy the renal dopaminergic system was suggested to be involved in the adaptative increase of sodium excretion. ***Aim:*** The aim of the present study was to evaluate the renal adaptations in sodium handling and renal dopaminergic system activity in uninephrectomized (Unx) rats up to 26 weeks after the surgery. ***Results:*** A time-dependent increase in both systolic and diastolic blood pressure was observed in Unx rats up to 26 weeks after uninephrectomy. This was accompanied by a compensatory increase in aromatic L-amino acid decarboxylase at 2 weeks but not 10 and 26 weeks after uninephrectomy. In contrast to what has been found 2 weeks after uninephrectomy, at 10 and 26 weeks after surgery the natriuretic response to volume expansion was reduced in Unx rats and this was accompanied by insensitivity of natriuresis to dopamine D1 receptor selective antagonist (Sch23390). ***Conclusion:*** A time-dependent decrease in dopamine sensitive natriuresis is observed in Unx rats throughout the 26 weeks after uninephectomy. It is suggested that this may contribute to compromise sodium excretion and increase blood pressure.

Introduction

The epithelial cells of proximal tubules, but not of distal segments of the nephron, are endowed with a high aromatic L-amino acid decarboxylase (AADC) activity, the enzyme responsible for the conversion of circulating or filtered L-3,4-dihydroxyphenylalanine (L-Dopa) to dopamine [1–3]. The renal dopaminergic system appears to be highly dynamic and basic mechanisms for the regulation of this system are thought to depend mainly on the availability of L-Dopa, its fast decarboxylation into dopamine and precise cell outward amine transfer mechanisms, dopamine interaction with specific receptors and accurate intracellular signal transduction [3–6]. Dopamine of renal origin, by activating D_1-like receptors located at various regions in the nephron, exerts natriuretic and diuretic effects [7] accounting for up to 50% of sodium excretion, namely during moderate sodium surfeit [8, 9]. At the level of the proximal tubule, the overall increase in sodium excretion produced by dopamine results mainly from the inhibition of several sodium transporters including Na^+, K^+-ATPase and Na^+-H^+ exchanger at the basolateral and apical membranes, respectively [10]. The renal dopaminergic system plays an important role in the regulation of blood pressure, sodium homeostasis and kidney function [8]. Evidence has been gathered suggesting that deficiencies in this system may be involved in sodium retention and may contribute to the

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increase of blood pressure with sodium sensitive characteristics [11, 12].

Animal models of reduced renal mass undergo a series of adaptive mechanisms to maintain sodium homeostasis. Compensatory changes in the tubular handling of sodium include an increased excretion of sodium per nephron [13]. In this way, sodium balance can be maintained despite a diminished glomerular filtration rate. In rats submitted to uninephrectomy an increased renal dopamine synthesis was observed in the remnant kidney at 2 weeks after surgery [14, 15]. This was accompanied by a dopamine sensitive enhanced natriuresis with no changes in blood pressure values, suggesting that early after uninephrectomy renal dopamine may play an important role in keeping uninephrectomized rats within sodium balance [14, 15]. However, the role of the renal dopaminergic system in sodium handling in more advanced phases after renal mass ablation still remains to be established.

The aim of the present study was to evaluate renal adaptations in sodium handling, blood pressure and renal dopaminergic system activity in rats submitted to uninephrectomy up to 26 weeks after surgery.

Materials and Methods

In vivo Studies

All in vivo investigation was performed in accordance with the European Directive number 86/609, transposed to the Portuguese Law by DL 129/92 and by Portaria 1005/92.

Normotensive male Wistar-Han rats (Harlan, Barcelona, Spain), weighing 190–210 g, were selected after a 7-day period of stabilization and adaptation to blood pressure measurements. The animals were kept under controlled environmental conditions (12:12 h light/dark cycle and room temperature 22 ± 2°C); fluid intake and food consumption were monitored daily throughout the study. All animals were fed ad libitum throughout the study with ordinary rat chow (Panlab, Barcelona, Spain) containing 1.9 g · kg^{-1} of sodium. Blood pressure (systolic and diastolic) and heart rate were measured weekly throughout the study in conscious restrained animals, between 7.00 and 10.00 a.m., using a photoelectric tail-cuff pulse detector (LE 5000, Letica, Barcelona, Spain). Four determinations were made each time and the means were used for further calculation.

Uninephrectomy. In anesthetized rats (pentobarbital sodium, 60 mg · kg^{-1}, i.p.) the surgical ablation of the right kidney was performed, according to what was previously described [14] – uninephrectomized (Unx) rats. Control animals were rats submitted to sham surgery under similar conditions, however their kidneys remained intact – sham-operated (Sham) rats. After total recovery from surgery (4–6 h), the rats were placed in an animal facility, where they had free access to food and water. Survival rate was 100%.

Metabolic Study. 10 and 26 weeks after surgery, the rats were placed in metabolic cages (Tecniplast, Buguggiate-VA, Italy) for the collection of 24-hours urine for quantification of sodium, potassium, creatinine, urea and catecholamines. The vials collecting urine for quantification of catecholamines contained 0.5 ml hydrochloric acid (6 M), to avoid the spontaneous oxidation of the amines and its derivatives. All animals received tap water ad libitum. The daily sodium intake was similar between Unx and Sham rats throughout the study (table 1). 10 and 26 weeks after surgery the animals were anaesthetized with pentobarbital sodium (60 mg · kg^{-1}, i.p.) and blood was collected from the heart in tubes containing lithium/heparin for later determination of biochemical parameters. The kidneys were rapidly removed and weighed. The outer cortex was isolated and fragments were used for latter determination of AADC activity. Other fragments from renal cortex weighing around 100 mg were placed in vials containing 0.5 ml of perchloric acid 0.2 M and stored at –80°C until quantification of catecholamines and metabolites, by HPLC with electrochemical detection.

Volume Expansion. In another set of experiments, 2, 10 and 26 weeks after surgery, the animals were anesthetized with pentobarbital sodium (60 mg · kg^{-1} followed by 20 mg · kg^{-1} · h^{-1}, i.p.) and placed on a thermostatically controlled heating table to maintain a rectal temperature of 37°C. The rats were tracheotomized and the left jugular vein was catheterized by a PE50 tube (Becton Dickson, Lisboa, Portugal) for volume expansion (VE) and infusion of Sch-23390 (30 μg · kg^{-1} bolus followed by 30 μg · kg^{-1} · min^{-1}) or the vehicle (0.9% NaCl, bolus of equal volume per kg). After an abdominal incision, the urinary bladder was catheterized through a suprapubic incision for urine sampling. After the completion of surgical procedures, the infusion of Sch-23390 or vehicle started at a rate of 5 ml · kg^{-1} · h^{-1} for 120 min; during this period two consecutive 60-min urine samples were collected (t = 0–120 min, basal). After this stabilization period, the VE was started by infusion of isotonic saline (0.9%) at a rate of 100 ml · kg^{-1} · h^{-1} during 30 min (5% body weight); during this phase, three consecutive urine samples were collected lasting 10 min each (t = 120–150 min, VE). Thereafter, the infusion was again reduced to 5 ml · kg^{-1} · h^{-1} for 90 min; during this recovery period, urine sampling was performed every 10 min until the end of the experiment (t = 150–240 min, R-VE).

In vitro Studies

AADC Activity. The AADC activity was determined at 2, 10 and 26 weeks after surgery in fragments of renal cortex as previously described by Soares-da-Silva [16] using L-Dopa as substrate (100–10,000 μM). The assay of dopamine was performed by HPLC with electrochemical detection. The protein content in cell suspension (1.5 mg · ml^{-1}) was determined by the method of Bradford [17].

Assay of Catecholamines. The assay of catecholamines and its metabolites in urine, renal tissues and in samples from AADC studies was performed by HPLC with electrochemical detection, as previously described [18, 19]. In our laboratory, the lower limit of detection of dopamine and dopamine metabolites (DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-metoxytyramine and HVA, homovanillic acid) and noradrenaline ranged from 350 to 1,000 fmol.

Plasma and Urine Ionogram and Biochemistry. The quantification of sodium, potassium, urea and creatinine, in plasma and

Table 1. Body weight, increase in renal mass, metabolic balance and renal function in sham-operated (Sham) and uninephrectomized (Unx) rats at 10 and 26 weeks after surgery

	10 weeks		26 weeks	
	Sham	Unx	Sham	Unx
Body weight, g	417 ± 6	421 ± 9	480 ± 14**	474 ± 10**
Plasma urea, mg · dl^{-1}	37.4 ± 1.1	44.9 ± 1.1*	36.6 ± 1.4	44.2 ± 1.7*
Plasma creatinine, mg · dl^{-1}	0.47 ± 0.07	0.79 ± 0.10*	0.55 ± 0.02	0.63 ± 0.02*
Plasma Na^+, mmol · l^{-1}	138.9 ± 0.7	136.9 ± 1.0	136.1 ± 1.6	137.6 ± 1.7
Plasma K^+, mmol · l^{-1}	5.1 ± 0.2	5.4 ± 0.3	6.5 ± 0.5	6.2 ± 0.6
Fluid intake, ml · day^{-1}	20.9 ± 0.7	24.2 ± 1.4*	15.2 ± 1.1**	18.8 ± 1.2*, **
Na^+ intake, mmol · day^{-1}	1.6 ± 0.1	1.8 ± 0.1	1.2 ± 0.1**	1.1 ± 0.1**
Urine volume, ml · day^{-1}	11.1 ± 0.4	14.7 ± 1.1*	8.9 ± 1.4	11.1 ± 0.9*
Urine Na^+, mmol · day^{-1}	1.7 ± 0.1	1.8 ± 0.1	1.2 ± 0.1**	1.1 ± 0.1**
Urine K^+, mmol · day^{-1}	1.6 ± 0.1	1.8 ± 0.1	1.2 ± 0.1**	1.3 ± 0.1**
C_{creat}, ml · min^{-1}	2.6 ± 0.4	1.9 ± 0.3*	2.2 ± 0.1	1.6 ± 0.1*
FE_{Na+}, %	0.36 ± 0.07	0.71 ± 0.11*	0.30 ± 0.04	0.47 ± 0.08*
FE_{K+}, %	6.0 ± 0.3	8.4 ± 1.2*	6.9 ± 1.0	9.9 ± 0.9*

Values are means ± SE; n = 9–12 experiments per group. C_{creat} = Creatinine clearance; FE = fractional excretion.

* Significantly different from values in sham-operated rats ($p < 0.05$).

** Significantly different from values at ten weeks after surgery ($p < 0.05$).

urine samples, was performed by Cobas Mira Plus analyser (ABX Diagnostics, Switzerland) as previously described [14]. Creatinine clearance and fractional excretion of sodium and potassium were calculated as previously described [14].

Drugs. The compounds DOPAC; dopamine hydrochloride; HVA; L-Dopa; 3-MT; noradrenaline bitartrate and Sch-23390 were obtained from Sigma (St. Louis, Mo., USA).

Statistics. Results are means ± SE of values for the indicated number of determinations. Maximal velocity (V_{max}) and Michaelis-Menten coefficient (K_m) values were calculated from nonlinear regression analysis using GraphPad Prism statistics software package [20]. Statistical analysis was performed by one-way ANOVA followed by Student's t test for unpaired comparisons. $p < 0.05$ was assumed to denote a significant difference.

Results

Ablation of renal mass in uninephrectomized rats had no significant effects on body growth, 10 and 26 weeks after uninephrectomy (table 1). Kidney growth, however, was significantly altered in Unx rats. 10 and 26 weeks after surgery, the Unx rats presented a hypertrophied remnant renal mass with a weight increase of 84 ± 11% and 86 ± 5%, respectively. Plasma levels of sodium and potassium were similar in Sham and Unx rats both at 10 and 26 weeks after surgery (table 1). In addition, no significant differences were observed between Unx and Sham rats in either daily intake or urinary excretion of sodium (table 1). Fluid intake and urine volume were greater in Unx rats than in Sham animals both at 10 and 26 weeks after surgery (table 1). In addition, the Unx rats presented increased plasma creatinine and urea values as well as a decreased creatinine clearance both at 10 and 26 weeks after surgery (table 1). The fractional excretion of both sodium and potassium were greater in Unx animals, throughout the study. Systolic and diastolic blood pressures were higher in Unx rats then in Sham at 10 weeks after surgery and progressively increased overtime (fig. 1).

Daily urinary dopamine excretion, as well as, dopamine precursor (L-Dopa) and metabolites (DOPAC, HVA and 3-MT) were similar between Unx and Sham rats at 10 and 26 weeks after surgery (table 2). In addition, the urinary excretion of noradrenaline was also found to be similar between Unx and Sham rats at 10 and 26 weeks after surgery (table 2). Renal tissue levels of L-Dopa and dopamine did not differ between the Unx and Sham rats throughout the study (table 3).

The activity of AADC was determined in homogenates of renal cortex with L-Dopa as substrate, which resulted in a concentration-dependent formation of dopamine. At 2 weeks after surgery, the V_{max} values for renal AADC activity were higher in Unx rats than in Sham

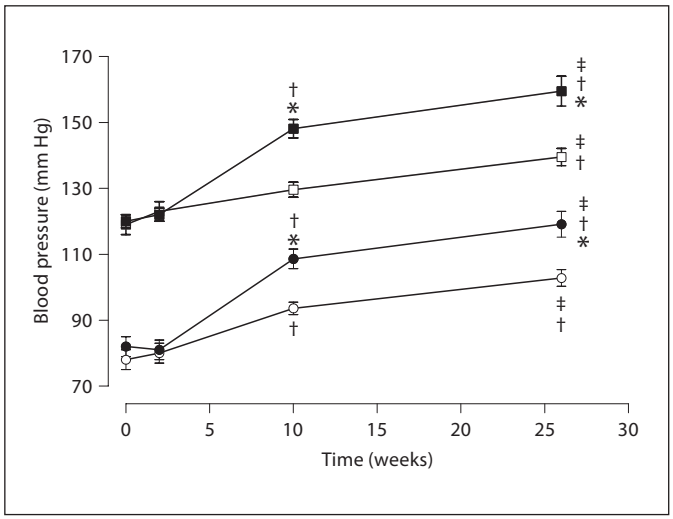

Fig. 1. Systolic (■, □) and diastolic (●, ○) blood pressure in uninephrectomized (Unx, ■, ●) and sham-operated (Sham, □, ○) rats at 2, 10 and 26 weeks after surgery. Symbols represent means of 9–12 experiments per group, and error bars represent SE. * Significantly different from values in sham-operated rats ($p < 0.05$). † Significantly different from values before and at 2 weeks after surgery ($p < 0.05$). ‡ Significantly different from values at 10 weeks after surgery ($p < 0.05$).

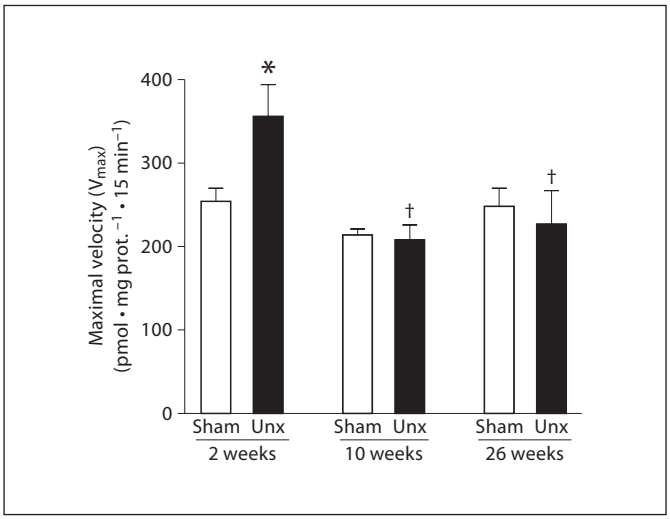

Fig. 2. Maximal velocity (V_{max}) of aromatic L-amino acid decarboxylase (AADC) activities in homogenates of renal cortex from sham-operated (Sham) and uninephrectomized (Unx) rats at 2, 10 and 26 weeks after surgery. Values are means ± SE; n = 9–12 experiments per group. * Significantly different from values in sham-operated rats ($p < 0.05$). † Significantly different from values at 2 weeks after surgery ($p < 0.05$).

Table 2. Urinary levels of dopamine, L-Dopa, DOPAC, 3-MT, HVA and noradrenaline in sham-operated (Sham) and uninephrectomized (Unx) rats at 10 and 26 weeks after surgery

	10 weeks		26 weeks	
	Sham	Unx	Sham	Unx
Dopamine	11.2 ± 1.0	11.4 ± 1.0	9.7 ± 1.4	8.3 ± 0.4
L-Dopa	0.16 ± 0.02	0.20 ± 0.04	0.18 ± 0.03	0.35 ± 0.15
DOPAC	22.7 ± 3.3	25.0 ± 2.7	22.9 ± 3.1	24.0 ± 2.6
3-MT	20.8 ± 1.7	15.7 ± 2.3	21.3 ± 2.9	27.3 ± 2.1
HVA	194.8 ± 14.1	214.9 ± 13.5	199.5 ± 10.8	228.3 ± 16.2
Noradrenaline	6.5 ± 0.6	6.0 ± 0.5	7.0 ± 0.9	5.1 ± 0.5

Values are means ± SE; n = 9–12 experiments per group. Values are expressed in nanomoles per day. L-Dopa = L-3,4-Dihydroxyphenylalanine; DOPAC = 3,4-dihydroxyphenylacetic acid; 3-MT = 3-methoxytyramine; HVA = homovanilic acid.

Table 3. Levels of dopamine and L-Dopa in renal cortex from sham-operated (Sham) and uninephrectomized (Unx) rats at 10 and 26 weeks after surgery

	10 weeks		26 weeks	
	Sham	Unx	Sham	Unx
Dopamine	92.9 ± 6.9	103.0 ± 3.1	97.9 ± 3.3	91.4 ± 1.7
L-Dopa	159.1 ± 16.7	178.8 ± 10.3	182.2 ± 38.3	165.9 ± 42.8

Values are means ± SE; n = 5–8 experiments per group. Values are expressed in picomoles per gram. L-Dopa = L-3,4-Dihydroxyphenylalanine.

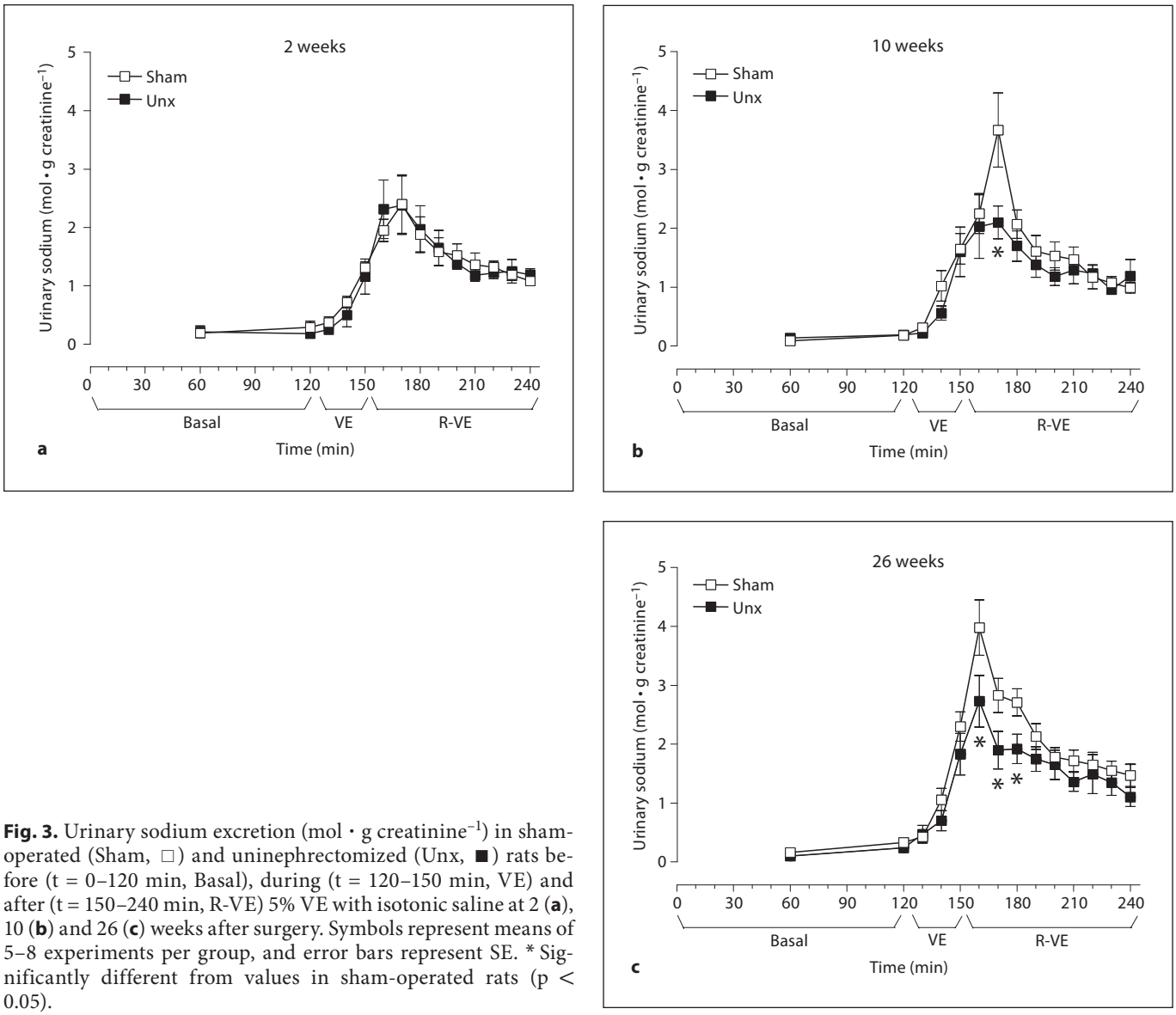

Fig. 3. Urinary sodium excretion (mol · g creatinine^{-1}) in sham-operated (Sham, □) and uninephrectomized (Unx, ■) rats before (t = 0–120 min, Basal), during (t = 120–150 min, VE) and after (t = 150–240 min, R-VE) 5% VE with isotonic saline at 2 (**a**), 10 (**b**) and 26 (**c**) weeks after surgery. Symbols represent means of 5–8 experiments per group, and error bars represent SE. * Significantly different from values in sham-operated rats ($p < 0.05$).

animals whereas at 10 and 26 weeks after surgery the renal AADC activity was similar between the two groups (fig. 2). The decarboxylation reaction was a saturable process, with K_m values of the same magnitude in all groups (2 weeks, 2.4 ± 0.2 vs. 2.2 ± 0.1; 10 weeks, 2.2 ± 0.3 vs. 2.6 ± 0.4; 26 weeks, 2.1 ± 0.5 vs. 2.6 ± 0.3; mM).

The urinary sodium excretion before (t = 0–120 min), during (t = 120–150 min) and after (t = 150–240 min) VE in Unx and Sham rats at 2, 10 and 26 weeks after surgery is depicted in figure 3. Two weeks after surgery (fig. 3a) the natriuretic response to VE was similar between Unx and Sham rats whereas at 10 and 26 weeks after surgery (fig. 3b, c) the natriuretic response to VE was lower in Unx rats than in Sham animals.

The effect of Sch-23390 on the accumulated urinary sodium excretion before, during and after VE in Sham and Unx rats is depicted in figure 4. As can be observed, 2 weeks after uninephrectomy, Sch-23390 decreased the accumulated urinary sodium excretion during the recovery period (fig. 4a) whereas at 10 and 26 weeks after surgery the infusion of Sch-23390 did not significantly change the urinary sodium excretion before, during or after VE (fig. 4b, c).

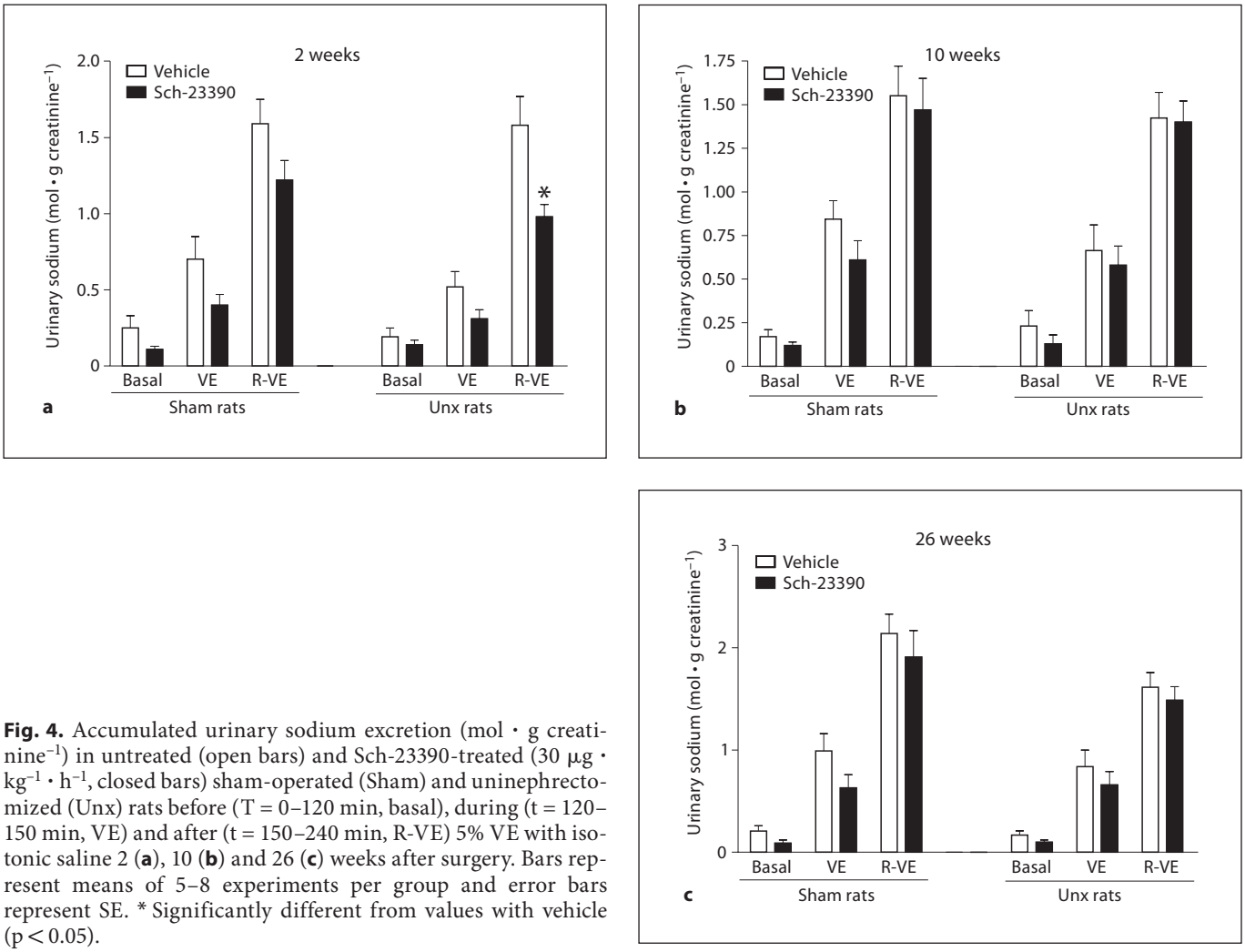

Fig. 4. Accumulated urinary sodium excretion (mol · g creatinine^{-1}) in untreated (open bars) and Sch-23390-treated (30 μg · kg^{-1} · h^{-1}, closed bars) sham-operated (Sham) and uninephrectomized (Unx) rats before (T = 0–120 min, basal), during (t = 120–150 min, VE) and after (t = 150–240 min, R-VE) 5% VE with isotonic saline 2 (**a**), 10 (**b**) and 26 (**c**) weeks after surgery. Bars represent means of 5–8 experiments per group and error bars represent SE. * Significantly different from values with vehicle ($p < 0.05$).

Discussion

In the present study, uninephrectomy was associated with the known consequences of partial renal ablation, namely (1) progressive increase in compensatory renal growth, (2) significant azotemia, and (3) significant increase in fractional excretion of sodium. Two weeks after uninephrectomy, blood pressure was found to be similar to that in corresponding controls and this was accompanied in Unx rats by well preserved natriuretic response to VE. By contrast, 10 and 26 weeks after renal mass ablation, the Unx rats presented a progressive increase in both systolic and diastolic blood pressure going along with blunted natriuretic response to VE. These findings, when viewed collectively with the compensatory increase in renal AADC activity and the accompanied dopamine-sensitive enhanced natriuresis 2 weeks after uninephrectomy, but not 10 or 26 weeks after renal mass ablation, suggests that the role of the renal dopaminergic system in the control of sodium homeostasis is decreased in a time-dependent manner following uninephrectomy.

Kidney transplantation from living donors now accounts for approximately half of all kidney transplants performed in the USA [21]. Unilateral nephrectomy in human subjects is associated with rapid functional adaptation of the remaining kidney with the glomerular filtration rate reaching 65–70% of the prenephrectomy value within a few weeks, and stabilizing for periods up to 15–20 years. An increased incidence of hypertension and decreased natriuretic response to VE [22] has been reported following kidney donation on most, but not all studies [22–24]. However, the factors contributing to the increase

in blood pressure and to the decreased natriuretic response to VE following uninephrectomy have not been systematically evaluated thus emphasizing the importance of long term study of natriuretic systems in this condition.

The results presented here clearly show that 2 weeks after uninephrectomy the Unx rats have an increased renal dopaminergic activity and respond to isotonic saline VE with increased urinary sodium excretion similar to that in corresponding controls, this being sensitive to D1 receptor blockade. The increased renal dopaminergic activity and enhanced natriuresis in the presence of unaltered blood pressure values observed 2 weeks after uninephrectomy agree well with the previous reports indicating that early after renal mass ablation, the remnant kidney exhibits increased renal dopamine output per nephron and augmented dopamine-sensitive phosphaturic and natriuretic responses to parathyroid hormone and VE, respectively [14, 15, 25].

Unlike the findings observed 2 weeks after uninephrectomy, 10 and 26 weeks after renal mass ablation a time-dependent increase in both systolic and diastolic blood pressure was observed and this was accompanied by less-pronounced increase in urinary excretion of sodium during isotonic saline VE. Interestingly, 10 and 26 weeks after uninephrectomy renal AADC activity was not different between Unx rats and corresponding controls and the natriuretic response to VE failed to decrease in response to D1 receptor blockade. Thus, it is likely that the contribution of the renal dopaminergic system to the adaptations of renal function after uninephrectomy, namely enhanced diuresis and natriuresis, may be diminished overtime. Because high blood pressure and sodium retention may be linked to abnormalities in the function of the renal dopaminergic system one can hypothesize that the blunted natriuretic response as well as the progressive increase of blood pressure at 10 and 26 weeks after uninephrectomy may be associated with inability of the remnant kidney to increase dopamine synthesis or with deficient coupling of dopamine receptors to effector mechanisms [12, 26, 27].

In the present study the effect of Sch-23390 in Unx rats was a 38 $\pm$ 5% reduction in urinary excretion of sodium at 2 weeks after surgery whereas in Sham rats the effect of Sch-23390 was a 23 $\pm$ 8% reduction which did not attain statistical significance. These results agree well with previous reports [14, 15], highlighting the importance of the renal dopaminergic system in uninephrectomy. Curiously, the first observation on the tonic role of endogenous renal dopamine as a local natriuretic hormone was observed in Unx dogs, but not Sham dogs [28]. The present study further suggests that the role of natriuretic dopamine in uninephrectomized rats assumes a particular importance in an early phase (2 weeks) but not in later phases (10 and 26 weeks) after uninephrectomy.

The increase of blood pressure in Unx rats was not accompanied by sodium retention during chronic stable sodium intake suggesting that other factors may also contribute to this phenomenon. The relationship between arterial pressure and the rate of sodium excretion is regulated by a number of factors and the increase of blood pressure in the setting of reduced renal mass most probably represents the combined interactions of multiple independent mechanisms that influence cardiac output and total peripheral resistance [29, 30]. These mechanisms affect either the amount of sodium filtered at the glomerulus or its rate of reabsorption from the proximal or distal tubules. Other than physical factors and glomerular ultrafiltration properties, the known homeostatic mechanisms are both intrinsic to the kidney (angiotensin II, nitric oxide) and extrinsic regulatory systems, including renal sympathetic nerves and aldosterone. Other factors may also be important, namely endothelin, prostaglandins and kallikrein, and several lines of investigation have implicated perturbations of these systems in the pathophysiology of renal parenchymal hypertension.

It is concluded that in Unx rats, the role of the renal dopaminergic system in the control of sodium balance may differ overtime. Unlike the findings of compensatory increase of renal dopaminergic system at 2 weeks after uninephrectomy, at 10 and 26 weeks after uninephrectomy a blunted renal dopaminergic system is observed. We suggest that this may be one explanation for the derangement of sodium homeostasis and increase of blood pressure observed in Unx rats at 10 and 26 weeks after renal mass ablation.

Acknowledgments

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