Seventh Symposium on Salt, Vol. II 323–328 (1993)
Elsevier Science Publishers B.V., Amsterdam

Is the Increase in Sodium Excretion Following Unilateral Nephrectomy Dependent on a Dopaminergic Activation?

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ABSTRACT

Unilateral nephrectomy (UNX) is followed by a prompt increase in sodium excretion from the remaining kidney, a response putatively mediated through a neuroendocrine pathway involving renal nerves, opioïd related peptides and atrial natriuretic peptide. In the present studies the contribution of the dopaminergic system to this natriuretic response was assessed in euvolemic anesthetized Sprague–Dawley rats that were either untreated, or infused with the dopamine antagonist haloperidol at the time of UNX. Within 20–120 min following UNX, increases in $U_{Na}V$ and $U_{K}V$ (from 0.82±0.24 to 2.02±0.44 and from 1.40±0.12 to 2.57±0.26 μEq/min respectively, both $p<0.005$) were observed in untreated rats, whereas glomerular filtration rate, renal plasma flow or mean arterial pressure did not change significantly. Fractional excretion of lithium, an index of proximal tubular handling of sodium, increased from 31.0±3.8 to 41.7±6.7%, $p<0.05$. Haloperidol infusion did not affect the natriuretic/kaliuretic response of the remaining kidney (from 0.98±0.23 to 2.18±0.63 and from 1.62±0.25 to 2.44±0.24 μEq/min, both $p<0.05$), whereas the rise in fractional excretion of lithium was blunted (from 30.8±2.8 to 32.8±3.1%, p = NS). These results indicate that the magnitude of post-UNX natriuresis is not significantly affected by blockade of dopamine receptors. However, haloperidol significantly attenuated the rise in fractional excretion of both lithium, and potassium. In conclusion, the present studies indicate that acute functional adaptation to uninephrectomy partly occurs at the level of the proximal tubule; however, blockade of the proximal tubular handling of sodium by haloperidol failed to suppress the immediate natriuretic response to uninephrectomy.

INTRODUCTION

Reduction in renal mass is followed by a rapid functional adaptation and the initiation of a compensatory hypertrophy in the remaining kidney (Hayslett, 1979; Humphreys et al., 1985). Within one hour, unilateral nephrectomy (UNX) results in an increased electrolyte excretion by the contralateral kidney with no apparent change in volume or composition of the blood as well as renal hemodynamics. Part of this rapid response has been ascribed to a reflex phenomenon, with an afferent limb originating in carotid baroreceptors and (so far uncharacterized) renal receptors (Humphreys et al., 1985). In addition to this neural control, a role for an endogenous opioïd mediation (Ribstein and Humphreys, 1983) and the pituitary release of a peptide derived from the proopïomelanocortin molecule (Lin et al., 1987) was suggested. More recently, the acute natriuretic response to UNX was shown to be associated with an increase in plasma levels of atrial natriuretic peptide (ANP) and in urinary excretion of cyclic GMP; moreover, an important role for ANP in mediating the UNX-associated natriuresis was suggested by the demonstration that right atrial appendectomy, which suppressed the rise in plasma ANP and urinary cGMP following UNX, also prevented the increase in sodium excretion (Valentin et al., 1990).

Dopamine produced within the kidney may act as a natriuretic hormone (Lee et al., 1982). It was reported that pretreatment of rats with dopamine antagonists attenuated the diuretic and/or natriuretic response to isotonic volume expansion (Pelayo et al., 1983; Hansell et al., 1991) and to administration of crude atrial extracts (Marin-Grez et al., 1985) or synthetic ANP (Hansell et al., 1987). Since it has been suggested that the response to UNX by the remaining kidney may recruit efferent renal nerves (Humphreys et al., 1985), some of which possibly convey dopaminergic influxes (Bell et al., 1973), the possibility exists that dopamine acts as a mediator in the immediate natriuretic response to UNX.

The present studies were designed to test the hypothesis that the dopaminergic system may influence the immediate natriuretic response to unilateral renal ablation. In order to do this, the renal response to UNX was assessed in rats treated by the dopamine receptor antagonist haloperidol.

METHODS

Animal preparation

Experiments were carried out in male Sprague–Dawley rats (Charles-River, France) weighing 240–360 g, prepared as previously described (Valentin et al., 1990). Briefly, lithium chloride (0.5 mmol/kg) was given to animals by gavage ninety minutes prior to anesthesia (Inactin 100 mg/kg ip, Byk-Gulden, FRG). Anesthetized rats were placed on a temperature-regulated table to maintain rectal temperature at 37±0.5°C, and tracheostomized to allow spontaneous breathing. Catheters for blood pressure monitoring, blood collection and infusion of solutions were placed into the right carotid artery, a femoral artery and a jugular vein respectively. Urine was collected in preweight vials via a catheter inserted into the urinary bladder through a suprapubic incision. A solution of 3% bovine serum albumin in saline (amounting to 1.25% of body weight) was infused to replace fluid losses associated with anesthesia and surgery. After completion of the preparative procedures, bovine serum albumin was replaced by a solution of the radioactive tracers infused at a rate of 2.4 ml/h throughout the experiment. At least a 1-h equilibration was allowed prior to commencement of urine collections.

Experimental protocol

Two groups of rats were defined according to the treatments administered prior to a common protocol of either UNX or sham-intervention.

Untreated rats (n = 18)

After equilibration, three 20-min urine collections (control period) were obtained. At the end of this period, the right kidney was exposed by a dorsal approach and either removed (n = 8) or gently manipulated and left in place (n = 10). Following a 20-min period of equilibration, 5 urine collections of 20 min each were obtained (experimental period). At the midpoint of each clearance period, a 150–180 µl blood sample was drawn in heparinized glass capillary tubes. After centrifugation, plasma was saved and stored for future analysis; red blood cells were resuspended in an equal volume of normal saline and returned to the animal via the jugular vein.

Haloperidol-infused rats (n = 17)

In these experiments the dopamine receptor antagonist haloperidol (Janssen Laboratories, France) was added to the radioactive tracers and infused at a rate of 20 µg/kg/min for the duration of the experiment. In this group, 9 rats were subjected to uninephrectomy, whereas the remaining 8 animals underwent sham intervention.

In preliminary studies, it was observed that this dose of haloperidol entirely blocked the diuretic and natriuretic response to a test dose (150 µg/kg bolus) of iv dopamine (Laboratoires Lucien, France).

Analytical methods

Hematocrit (Hct) was determined in triplicate on each blood sample by spinning blood at 12,000 rpm in a microfuge (Hettich Haematokrit, Germany). Plasma protein concentration was measured by refractometry (Atago, Japan). Plasma and urine sodium and potassium were determined by flame photometry. Lithium in plasma and urine was determined by atomic absorption spectrophotometry. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated by clearances of ^{99m}Tc-diethylenetriaminepenta-acetic acid (DTPA) and sodium ^{131}I-orthoiodohippurate, respectively. Renal blood flow was calculated as ERPF/(1-Hct) and renal vascular resistance as mean arterial pressure (MAP)/renal blood flow. Clearances of sodium (CNa) and potassium (CK) were calculated as usual, and fractional excretions of Na and K were calculated as (CNa/GFR)×100 and (CK/GFR)×100, respectively. The fractional excretion of lithium (CLi/GFR)×100 was used as an index of whole kidney proximal tubular reabsorption (Koomans et al., 1989). Fractional distal reabsorption of sodium was calculated as (1–(CNa/CLi))×100.

Statistical analysis

Since in previous experiments (Ribstein and Humphreys, 1983) no difference was observed between separate renal function and between kidney weights measured at the end of the present experiments, pre-UNX and pre- and post-sham intervention values were expressed for a single kidney by halving total kidney function. The multiple data collected before and after the experimental maneuver were averaged to provide a single value for each of the control and experimental periods. Data are expressed as mean±SEM. Two-way analysis of variance and Student's *t*-test were used to assess significance between and among groups. A p value of 0.05 was considered the minimum level of significance.

RESULTS

In all experimental protocols, the sham intervention produced no significant change in systemic hemodynamics and renal function, indicating that the experimental preparation was stable for the duration of studies (Tables 1 and 2).

TABLE 1

Effect of unilateral nephrectomy or sham operation on single kidney function, systemic hemodynamics in untreated rats and in haloperidol treated rats

BW (g)	MAP (mm Hg)		HR (beats/min)		GFR (ml/min)		ERPF (ml/min)		RVR (mm Hg·min/ml)		FF (%)	
	CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP
Untreated rats, Sham nephrectomy (n=10)												
278	109	106	370	366	1.22	1.15	4.64	4.34	14.8	14.9	27.5	26.8
±9	±4	±5	±13	±17	±0.12	±0.12	±0.48	±0.40	±1.8	±1.7	±1.9	±1.7
Untreated rats, Unilateral nephrectomy (n=8)												
284	106	111	367	358	1.12	1.14	4.95	4.78	15.4	15.8	26.2	26.2
±8	±4	±3	±9	±10	±0.12	±0.06	±0.85	±0.68	±2.6	±1.7	±3.4	±2.8
Haloperidol treated rats, Sham nephrectomy (n=8)												
318	106	106	334	330	1.32	1.43	5.15	5.50	16.2	15.5	26.8	27.7
±12	±9	±8	±11	±9	±0.22	±0.22	±0.94	±0.96	±3.6	±3.0	±1.0	±1.1
Haloperidol treated rats, Unilateral nephrectomy (n=9)												
287	103	100	332	322	1.38	1.50	5.17	5.26	13.3	11.2	26.6	28.5*
±13	±4	±4	±11	±5	±0.22	±0.19	±0.50	±0.35	±1.9	±1.2	±2.9	±2.9

Values are means±SEM of 3 to 5 clearance periods for one kidney during control period (CTL) then after the experimental maneuver (EXP) either unilateral nephrectomy or sham operation. BW, body weight; MAP, mean arterial pressure; HR, heart rate; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; RVR, renal vascular resistance; FF, filtration fraction. *P<0.05 between CTL and EXP.

TABLE 2

Effect of unilateral nephrectomy or sham operation on single kidney electrolyte excretion in untreated rats and in haloperidol treated rats

UV (µl/min)		$U_{Na}V$ (µEq/min)		FENa (%)		FELi (%)		FDRNa (%)		UKV (µEq/min)		FEK (%)	
CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP	CTL	EXP
Untreated rats, Sham nephrectomy (n=10)													
6.5	5.8	0.76	0.73	0.48	0.48	28.7	27.4	98.1	98.1	1.46	1.44	28.6	29.4
±0.9	±0.9	±0.17	±0.20	±0.10	±0.12	±3.0	±3.4	±0.4	±0.4	±0.17	±0.16	±3.6	±2.9
Untreated rats, Unilateral nephrectomy (n=8)													
7.7	15.6	0.82	2.02*	0.50	1.43*	31.0	41.7*	98.4	96.9*	1.40	2.57*	28.9	55.4*
±2.0	±5.4	±0.24	±0.44	±0.29	±0.12	±3.8	±6.7	±0.4	±0.4	±0.12	±0.26	±2.6	±7.1
Haloperidol treated rats, Sham nephrectomy (n=8)													
11.9	15.5	0.84	0.95	0.44	0.51	27.9	26.8	98.4	98.3	1.68	1.72	27.2	26.9
±4.6	±6.1	±0.26	±0.27	±0.12	±0.15	±6.8	±5.1	±0.3	±0.3	±0.36	±0.37	±3.9	±6.5
Haloperidol treated rats, Unilateral nephrectomy (n=9)													
9.3	11.0	0.83	2.23*	0.62	1.36*	30.8	32.8	98.7	97.5*	1.62	2.44*	23.4	39.0*
±2.5	±1.9	±0.18	±0.63	±0.20	±0.52	±2.8	±3.1	±0.4	±0.6	±0.25	±0.24	±4.2	±6.5

Values are means±SEM of 3 to 5 clearance periods for one kidney during control period (CTL) then after the experimental maneuver (EXP) either unilateral nephrectomy or sham operation. UV, urine flow; UNaV and UKV, urinary sodium and potassium excretion; FENa, FELi and FEK, fractional excretion of sodium, lithium and potassium; FDRNa, fractional distal reabsorption of sodium. P<0.05 between CTL and EXP.

Effect of UNX in the untreated group

UNX was associated with a consistent increase in sodium and potassium excretion of 199±65 and 104±22% respectively (both $P<0.05$; Table 2) and no significant change in mean arterial pressure (MAP), ERPF and GFR (Table 1). Increments in both the absolute and the fractional excretion of sodium and potassium were thus observed (Table 2). Both the clearance and the fractional excretion of lithium increased significantly (by 31.7±9.8 and 37.5±9.6% respectively). In addition, the fractional distal reabsorption of sodium decreased from 98.4±0.4 to 96.9±0.4% ($P<0.002$). Although hematocrit and plasma protein concentration slightly decreased after UNX (from 43.8±1.3 to 42.4±1.4% and from 5.47±0.13 to 4.83±0.09 g/dl, respectively), changes were similar to those observed in sham-uninephrectomized rats (from 43.7±0.9 to 43.3±0.8% and from 5.50±0.04 to 4.73±0.15 g/dl, respectively).

Influence of haloperidol on the response to UNX

Baseline renal function and MAP were similar in haloperidol-treated rats when compared to untreated rats. However, heart rate was slightly lower in haloperidol treated rats as compared to untreated rats (333±8 versus 369±8 beats/min, $p<0.05$).

In haloperidol treated rats, the natriuretic response to UNX was not affected when compared to untreated animals (+183±60 versus +199±65%, P = NS). Although no significant change in GFR or ERPF was observed, filtration fraction slightly increased after UNX. As depicted in Table 2 and Fig. 1, haloperidol treatment entirely inhibited the increase in fractional excretion of lithium associated with UNX. By contrast, the fall in fractional distal reabsorption of sodium was similar in haloperidol treated rats (from 98.7±0.5 to 97.6±0.6%; $P<0.02$) and untreated rats. In addition, the increase in fractional excretion of potassium was attenuated when compared to untreated animals (Fig. 1). Changes in hematocrit and plasma protein concentration following UNX or sham-UNX were similar in haloperidol treated rats and in untreated rats.

When data from all rats undergoing UNX were pooled, a significant correlation between UNX-associated changes in FEK and FELi was obtained ($n = 17$, $r = 0.75$, $p<0.05$).

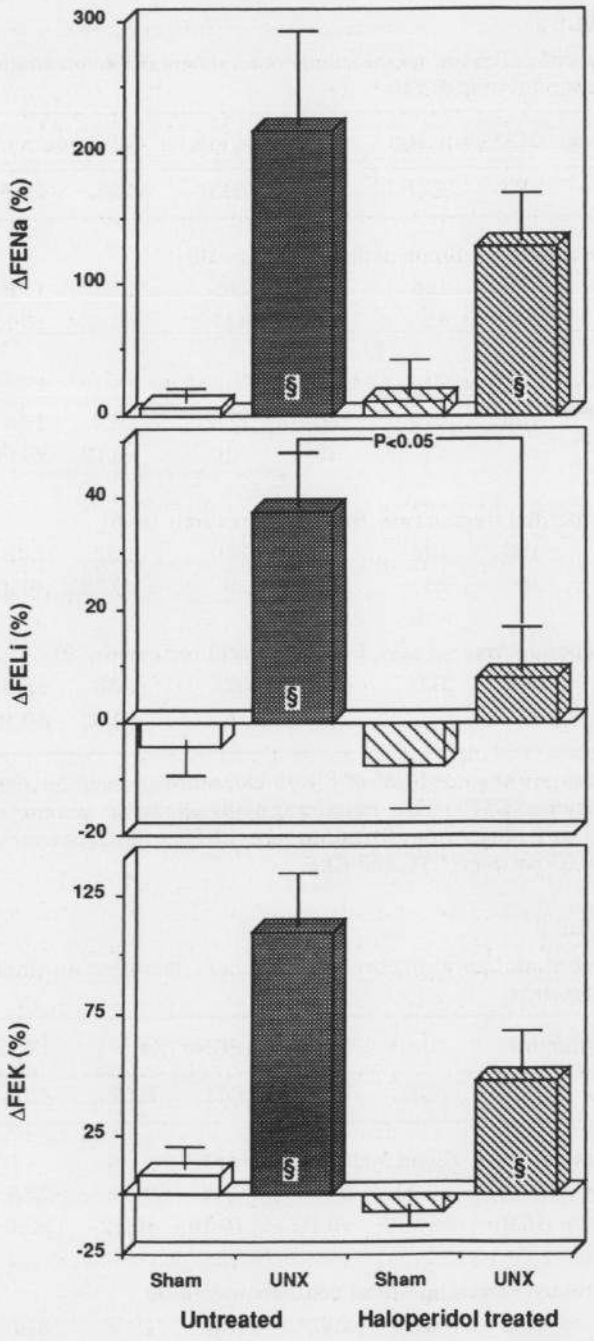

Fig. 1. Effect of haloperidol treatment on the relative changes (mean±SEM) in fractional excretion of sodium (FENa), lithium (FELi) and potassium (FEK) associated with unilateral nephrectomy (UNX) or sham nephrectomy (Sham) in anesthetized euvolemic rats. §$p<0.05$ between UNX and Sham within each treatment.

DISCUSSION

In the present studies, it was shown that the immediate natriuretic response to uninephrectomy was associated with no change in renal hemodynamics and with a substantial increase in the fractional excretion of lithium. Since in euvolemic rats, changes in the tubular handling of lithium closely reflect changes in the proximal tubular handling of sodium (Koomans et al., 1989), the present findings suggest that the immediate natriuretic response to a controlateral nephrectomy results at least in part

from a decrease in the proximal reabsorption of sodium. Most of the previous studies on the functional adaptation to UNX failed to demonstrate a significant increase in glomerular filtration rate within the first hours following UNX (Hayslett, 1979; Ribstein and Humphreys, 1983; Humphreys et al., 1985; Lin et al., 1987; Valentin et al., 1990). Different authors reported on the early occurrence of changes in tubular reabsorption of sodium. In the dog, micropuncture studies indicated that proximal sodium reabsorption is depressed within 2 h after clamping of the controlateral renal artery (Dirks and Wong, 1978); however, it must be noted that an increase in urinary sodium excretion did not constantly occur in these experiments (Dirks and Wong, 1978). In the rat, fractional proximal reabsorption was shown to decrease within 2 h following a partial renal infarction in chronically uninephrectomized rats (Allison et al., 1973). In addition, clearance studies performed in water diuresing Brattleboro rats showed a reduction in calculated proximal fractional reabsorption of sodium 1–2 h after ligation of the controlateral renal pedicle (Shirley and Skinner, 1978). In man, lithium clearance was used to show a decrease in fractional reabsorption of sodium 5 days after uninephrectomy; the fractional clearances of β2-microglobulin, albumin and immunoglobulin G increased as well within this time-period (Strangaard et al., 1988). Taken together, the present data suggest that, following UNX, a change in proximal tubular function may precede the increase in glomerular filtration rate.

Pretreatment by the dopamine receptor antagonist haloperidol did not influence the magnitude of the natriuretic response to uninephrectomy. However, haloperidol entirely blocked the increase in clearance and fractional excretion of lithium associated with uninephrectomy. Such findings indicate that in haloperidol-treated animals, the natriuretic response to uninephrectomy entirely results from a decrease in the distal reabsorption of sodium. Moreover, changes in proximal tubular function do not seem to be a prerequisite for the occurrence of the natriuretic response to uninephrectomy.

At the dose used, haloperidol is a non specific dopamine inhibitor, acting on both DA_1 and DA_2 receptors. In the rat, haloperidol has proved to be a potent inhibitor of the renal effects of dopamine (Marin-Grez et al., 1985), although most of the vascular and tubular actions of dopamine are probably mediated by receptors of the DA_1 subtype (Felder et al., 1989). Dopamine may inhibit proximal reabsorption of sodium by acting on DA_1 receptors located on both the basolateral and the brush border membranes of proximal tubules (Felder et al., 1989). The present observation that the post-uninephrectomy increase in fractional excretion of lithium is inhibited by haloperidol suggests that the decreased proximal tubular reabsorption of sodium associated with uninephrectomy may be in part under dopaminergic control. Whether this dopaminergic effect is direct or interrelated with the ANP system is open to discussion. In fact, it has been proposed that ANP, in addition to its well documented inhibition of distal sodium reabsorption (Zeidel, 1990), may also decrease proximal tubular reabsorption of solutes such as phosphate (Hammond et al., 1985), bicarbonate (Hammond et al., 1985) or lithium (Burnett et al., 1984). Other studies indicated that the natriuretic (Marin-Grez et al., 1985; Hansell and Fasching, 1987) as well as the phosphaturic (Ortola et al., 1989) action of ANP could be attenuated by dopaminergic blockade, a finding that not all studies could confirm (Allen et al., 1988; Murphy et al., 1988). More recently, it was proposed that ANP inhibits Na^+-H^+antiport at the brush border membrane indirectly by enhancing availability of intrarenal dopamine and directly by potentiating dopamine action on the proximal tubule (Winaver et al., 1990). However, in keeping with our findings, it appears that most of the natriuretic effect of ANP results from a distal, rather than a proximal, tubular effect (Johnston et al., 1989; Zeidel, 1990). It should be noted that, conceivably, the dopaminergic effect observed in the present studies may belong to the efferent neural pathway of the neurohumoral mechanisms contributing to the acute natriuretic response to uninephrectomy, as previously described (Humphreys, 1985). However, additional studies would be required to support a specific neural-mediated dopaminergic effect, since dopamine formed within the kidney appears to originate from circulating DOPA, mostly at the level of renal tubular cells, and only to a lesser extent in renal nerves (Lee, 1982).

CONCLUSION

In conclusion, the present studies indicate that acute functional adaptation to uninephrectomy partly occurs at the level of the proximal tubule; however, blockade of the proximal tubular handling of sodium by haloperidol failed to suppress the immediate natriuretic response to uninephrectomy.

ACKNOWLEDGMENTS

Part of this work was supported by a grant from the Club des Jeunes Hypertensinologues. Dr Jean-Pierre Valentin was supported by a fellowship from the French Society of Hypertension. The authors would like to thank Françoise Mollet and André Hernandez for their excellent technical assistance.

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