PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **182**, 570–575 (1986)

THE BLOOD PRESSURE DECREASE-INDUCED SYMPATHETIC DISCHARGE FOLLOWING ATRIAL NATRIURETIC FACTOR ADMINISTRATION MAY OFFSET ITS NATRIURETIC ACTION

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Abstract. Conscious SHR and WKY rats were infused during 7 days with ANF (Arg 101-Tyr 126), 100 ng/hr/rat, by means of miniosmotic pumps and their basal blood pressure (BP), changes in sodium excretion and urinary catecholamines compared with those at the last day of the infusion. The SHR initial BP of 181 ± 3 mmHg gradually declined to 137 ± 5 mmHg. No significant change in blood pressure was observed in the ANF-infused WKY group. However, WKY rats exhibited an increased sodium excretion and urinary dopamine/norepinephrine ratio when compared to sham-infused rats. No such differences were observed in SHR. It is suggested that an ANF-induced withdrawal of the renal sympathetic tone permits the manifestation of its natriuretic action in WKY rats. When, however, a BP decrease predominates, as in SHR, this decrease results in a reflex sympathetic discharge with a renal sympathetic activity overriding the ANF induced natriuresis seen in WKY rats. Secondary sympathetic responses to the ANF-induced BP decrease have to be thus taken into account when a dissociation between the hypotensive and natriuretic action of ANF is observed in vivo.

Introduction. We have previously observed that a chronic infusion of low doses of ANF reduces blood pressure in conscious SHR without apparent changes in sodium excretion (1). This dissociation of the vascular and renal ANF action remained unexplained. We have recently presented some evidence that ANF can act as an inhibitory modulator of the increased sympathetic nervous activity in vivo (2, 3) and abnormally high synthesis of catecholamines in vitro (4). The natriuretic action of atrial extracts had been found to be absent in 6-OH-dopamine-sympathectomized rats (5). We wanted to test the hypothesis that a withdrawal of the renal sympathetic activity normally participating in the natriuretic action of ANF may be overriden by a blood pressure decrease-induced sympathetic discharge to the point that the natriuretic action of ANF could not materialize. With the high variability of plasma catecholamines in rats, the urinary catecholamine measurements offer a certain advantage in reflecting the overall sympathetic activity over the 24 hours urine collection. Some data are compatible with the possibility that the inhibitory action of ANF is mediated by inhibition of the dopamine-β-hydroxylase (3, 4) the enzyme involved in the conversion of dopamine to norepinephrine, two catecholamines with opposing actions. The urinary DA/NE ratio which was found to be suited to reflect the catecholamine relationship to natriuresis (6) was therefore chosen to monitor indirectly the ANF action on the renal sympathetic activity. We determined the BP, changes in sodium

0037-9727/86 $1.50

excretion and urinary dopamine and norepinephrine before starting the experiment and at the height of the 7 days infusion of low dose ANF in SHR and WKY rats.

Materials and Methods. Spontaneously hypertensive rats (SHR), 14-15 weeks old, and their normotensive Wistar-Kyoto controls (WKY), 14-15 weeks old, were purchased (Taconic Farms, Germantown, NY). Systolic blood pressure was measured indirectly by means of the tail cuff method (Narco Biosystems Inc., Texas, USA) in conscious, prewarmed (37°C for 10 min) rats. The animals were accomodated in metabolic cages 3 to 4 days before the experiments were started and were kept on regular rat chow and tap water ad libitum. Forty-eight hours after this initial period the animals were separated in four experimental groups. Under light ether anesthesia, one group each of SHR and WKY rats, was implanted subcutaneously in the neck with osmotic minipumps (model 2001, Alza, Palo Alto, CA) filled with synthetic ANF (Arg 101-Tyr 126) to release 100 ng/hr (35 pmol/hr) of the peptide. The pumps were connected to the left jugular vein by means of a polyethylene catheter (PE-60). A second group each of SHR and WKY, was similarly anesthetized and a piece of plastic tubing with the same size as the minipumps was implanted subcutaneously. The left jugular vein was cannulated with a blind PE-60 catheter.

Urinary volume, water intake and indirect blood pressure were measured daily; urinary catecholamines and sodium at days-2 and 7. Urinary catecholamines were determined radioenzymatically (7), urinary sodium by flame photometry and creatinine colorimetrically. The main metabolites of DA-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and methoxytyramine (MT) were determined by HPLC (8). The data were analyzed by a two-way analysis of variance with repeated measures separately for SHR and WKY rats to compare the response to saline with that to ANF. The same analysis was also performed for individual va-

TABLE I

BLOOD PRESSURE, RENAL INDICES AND CATECHOLAMINE EXCRETION IN WKY RATS IN THE CONTROL PERIODS AND FOLLOWING ANF (REAL OR SHAM) ADMINISTRATION (MEAN ± SE)

	CONTROL PERIOD		CONTROL PERIOD	
BP mmHg	116	± 2.5	120	± 3.2
U volume ml/24h	5	± 0.7	3.9	± 0.7
U creatinine mg/24 h	4.8	± 0.7	3.3	± 0.5
U Na^+ mmol/24 h	2.5	± 0.7	1.3	± 0.5
Urinary DA µg/mg creat.	1.1	± 0.14	0.64	± 0.02
Urinary NE µg/mg creat.	0.38	± 0.04	0.31	± 0.02
Urinary DA:NE ratio	2.8	± 0.34	1.9	± 0.2
	SHAM ANF		**ANF ADMINISTRATION**	
BP mmHg	115	± 3	120	± 5
U volume ml/24 h	2.3	± 0.5	3.9	± 0.8
U creatinine mg/24 h	3.3	± 0.5	4.7	± 0.2
U Na^+ mmol/24 h	1 6	± 0.4 —*—	3.7	± 1.2**
U DA µg/mg/creat.	0.5	± 0.1	0.73	± 0.17
U NE µg/mg/creat.	0.25	± 0.02	0.2	± 0.03
Urinary DA:NE ratio	1.9	± 0.3 —*—	3.2	± 0.6**

* Different when sham and ANF administrations are compared ($p < 0.05$).
** Different when ANF or sham administration compared with the respective control period ($p < 0.05$).

TABLE II

BLOOD PRESSURE, RENAL INDICES AND CATECHOLAMINE EXCRETION IN SHR IN THE CONTROL PERIODS AND FOLLOWING ANF (REAL OR SHAM) ADMINISTRATION (MEAN ± SE)

	CONTROL PERIOD	CONTROL PERIOD
BP mmHg	175 ± 4.5 †	181 ± 3.0 †
U volume ml/24h	4.3 ± 0.7	6.1 ± 0.8
U creatinine mg/24h	4.5 ± 0.2	3.8 ± 0.5
U Na^+ mmol/24h	0.85 ± 0.12†	0.97 ± 0.15†
Urinary DA µg/mg creat.	1.04 ± 0.02	1.2 ± 0.1
Urinary NE µg/mg creat.	0.13 ± 0.01	0.19 ± 0.02
Urinary DA:NE ratio	7.6 ± 0.7 †	6.9 ± 0.7 †
	SHAM ANF	**ANF ADMINISTRATION**
BP mmHg	163 ± 2.6 †——— * ———	137 ± 4.7**†
U volume ml/24h	5.2 ± 0.8	4.5 ± 1.1
U creatinine mg/24h	3.1 ± 0.4	2.7 ± 0.35
U Na^+ mmol/24h	0.8 ± 0.1 †	0.7 ± 0.1 †
Urinary DA µg/mg creat.	1.21 ± 0.04	1.32 ± 0.2
Urinary NE µg/mg creat.	0.23 ± 0.02	0.25 ± 0.05
Urinary DA:NE ratio	5.9 ± 0.45†	5.6 ± 0.4 †

* Different when sham and ANF administrations are compared ($p < 0.05$).
** Different when ANF or sham administration compared with the respective control period ($p < 0.05$).
† Different from corresponding values in WKY rats listed on Table 1 ($p < 0.05$).

riables separately for saline and ANF infusion to compare SHR and WKY rats. To diminish the variability of some indices we made also the same analysis on values comparing in percentage the changes occuring between day -2 and 7 of the infusion of ANF, saline respectively.

Results. As can be seen on Table 1 and 2 the mean systolic BP baseline and following sham-infusion and ANF infusion was higher in SHR than WKY rats. The BP did not change following ANF infusion in WKY rats but decreased in SHR. During all conditions (baseline, sham infusion, ANF infusion) the urinary Na^+ excretion was significantly lower but DA/NE ratio higher in SHR than in WKY rats. None of the urinary volume and creatinine excretion values was significantly different when the effect of the sham infusion or ANF infusion was considered separately or compared between sham infusion and ANF. Urinary sodium excretion did not change in sham or ANF-infused SHR or sham-infused WKY rats but significantly increased in ANF-infused WKY rats. The urinary DA and NE excretions, corrected for creatinine had a wide variation. In general, urinary DA was higher and NE lower in SHR than WKY rats in the control period but none of these differences was significant. The same was true also for the sham infusion- or ANF-induced changes in DA or NE excretion. When the urinary DA:NE ratio was used, the higher values of this ratio in SHR than in WKY rats were significant not only during baseline conditions, but also following sham or ANF infusion. As shown on Figure 1, the ANF-induced changes were significantly different from the sham infusion-induced changes only in urinary Na^+ excretion and the DA/NE ratio in WKY rats (both $p < 0.05$) and the BP decrease induced by ANF in SHR but not WKY rats ($p < 0.01$). There were no significant differences between water intake, between urinary excretions of epinephrine DOPAC, HVA and MT between WKY rats and SHR as well as be-

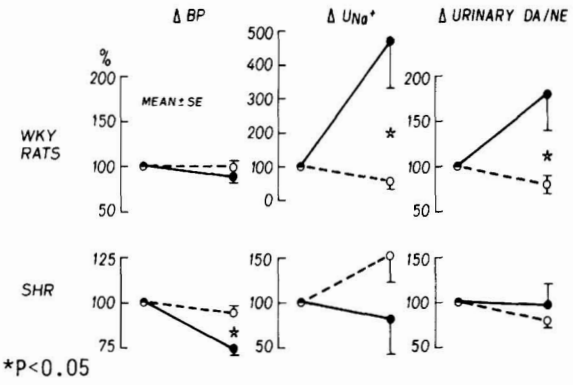

Figure 1 The percentage changes in systolic BP (Δ BP) urinary sodium excretion ($\Delta U\ Na^+$) and urinary DA/NE ratio following ANF ●——● or sham o------o infusion in WKY rats and SHR (mean ± SE).

tween the sham infusion and ANF infusion-induced changes in these indices in WKY rats and SHR (data not shown).

Discussion. It is well established that the regulation of the changes in sodium excretion results from an interaction of several neuronal and humoral mechanisms involving among other changes in the sympathetic nervous activity (9) and probably release of ANF (10). The administration of pharmacological doses of ANF with an overwhelming direct vasorelaxant activity (11) is apparently more effective in SHR having an elevated peripheral vascular tone than in normotensive WKY rats (12). In accordance with our previous studies (1), ANF induced a decrease in BP in SHR but not in WKY rats. Whether this decrease was due to vasorelaxation or decreased stroke volume (13) can not be decided from our studies.

As far as ANF-induced changes in sodium excretion are concerned, the present study compares the endpoint of a chronic ANF-infusion with baseline values. Under those conditions, the excretory values for Na^+ were lower in SHR than in WKY rats. When comparing water and food consumption, there was no difference between the two groups of rats suggesting that rather excretory mechanisms are responsible for differences in the changes in sodium excretion. The role of catecholamines in the regulation of natriuresis is postulated in several studies (9, 14). The great variability in the urinary excretions of the two main catecholamines, DA and NE, even if expressed per mg creatinine, makes a meaningful conclusion difficult. However, catecholamine changes, whether primary or secondary to ANF, are apparently better reflected by the urinary DA/NE ratio for reasons previously outlined. The direction of the change from the baseline towards the end of the ANF infusion probably reflects changes occuring in the renal sympathetic nervous system under the influence of ANF. The coincidence of the ANF-induced natriuresis and increase in the DA/NE ratio in WKY rats may thus reflect the natriuretic action of ANF at least partially mediated by an inhibitory action of ANF on the sympathetic nervous activity (3, 4) directly or indirectly via vagal afferent stimulation (15). In the presence of the considerable hypotensive action of ANF in SHR there is a reflex activation of the sympathetic nervous activity (16) which may offset this inhibitory action and the natriuretic effect of ANF diminishes or entirely disappears. Such an interpretation is in accordance with the finding that with minimal BP decrease after acute administration of ANF in WKY rats there is a cardiosuppression reflected by a decrease in pulse rate; this does not occur however in SHR when the BP decrease is much more profound and a reflex sympathetic discharge apparently obscures the initial cardiosuppression (17). These data suggest that the sympathetic nervous response to ANF infusion may be a factor deter-

mining the presence or absence of natriuresis following ANF, dependent on the degree to which secondary sympathetic responses to an ANF-induced BP decrease modify this sympathetic response. This is in accordance with Homer Smith's statement in 1957: "Where multiple controls are superimposed on a function such as sodium excretion it is conceived that normal regulatory mechanisms may be obscured by compensatory reactions" (18).

Acknowledgements. This study was supported by the Medical Research Council of Canada, the National Research Council of Canada and the Ministère de la Science et de la Technologie du Québec. We wish to thank, Mrs. Sylvie Ouellet for secretarial help, to Mrs. Dominique Chevalier, Carmen Savard, Suzanne Diebold and Suzanne Olivieri for technical help and Mr. François Bellavance for statistical collaboration.

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Received May 2, 1986.
P.S.E.B.M. 1986, Vol. 182.
Accepted June 20, 1986.