Noradrenaline attenuates the natriuretic effect of atrial natriuretic factor in man

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- 1 The effects of noradrenaline ($0.025 \mu\text{g kg}^{-1} \text{min}^{-1}$) and atrial natriuretic factor ($0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$) alone, and in combination, were studied in eight healthy salt replete men.
- 2 Atrial natriuretic factor increased urinary sodium excretion and flow rate without changing glomerular filtration rate or systemic haemodynamics.
- 3 Noradrenaline decreased urinary sodium excretion without changing glomerular filtration rate, urinary flow rate or systemic haemodynamics.
- 4 When atrial natriuretic factor was administered against a background infusion of noradrenaline the natriuretic response to the peptide was significantly attenuated.
- 5 Further analysis showed that this attenuation was due to the additive antinatriuretic effect of noradrenaline rather than to a specific interaction between atrial natriuretic factor and noradrenaline.
- 6 The possible significance of this interplay between noradrenaline and atrial natriuretic factor is discussed in the context of experimental evidence for an important role of the sympathetic nervous system in modulating the renal effects of atrial natriuretic factor in animals.

Keywords noradrenaline atrial natriuretic factor sodium excretion

Introduction

There has been much interest in the intra-renal mechanisms of action of atrial natriuretic factor (ANF) (Ballerman & Brenner, 1986; Zeidel & Brenner, 1987). Most studies have investigated the glomerular and tubular sites of action of ANF but there has been relatively little investigation of possible interactions between ANF and other antidiuretic and antinatriuretic neuro-endocrine determinants of renal sodium and water excretion in man (Biollaz *et al.*, 1987; Cogan *et al.*, 1987; Leckie, 1987). One such influence on renal function is the sympathetic nervous system (SNS) (DiBona, 1977; Gill, 1979). In man there is evidence for a preferential interaction between ANF and noradrenergic blood pressure control mechanisms (Uehlinger *et al.*, 1986). There is also increasing evidence of a generalised interaction between ANF and the SNS (Holtz *et al.*, 1987; Kuchel *et al.*, 1987; Nakamaru & Inagami, 1986). In particular,

however, the renal SNS may modulate the effects of ANF (Hathaway & Solomon, 1984). ANF administration causes withdrawal of renal SNS activity (Thoren *et al.*, 1986). As the renal SNS is antinatriuretic this would be expected to facilitate the actions of ANF (DiBona, 1977; Gill, 1979). Conversely renal SNS stimulation blunts the natriuretic response to ANF (Morgan *et al.*, 1986). We have now studied the effect of noradrenaline on the renal effects of ANF in man.

Methods

Eight male volunteers aged 19 to 37 years (mean 24.6) were studied on four occasions with at least 7 days between each visit. All had a normal medical assessment including physical examination, biochemical and haematological profile, urinalysis and electrocardiogram (ECG). None

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had taken any regular medication in the 3 months prior to the study. Salt intake was not formally controlled though all subjects had a dietary assessment and timed urine collection to ensure they were salt-replete prior to study (see results). In addition, subjects were asked to adhere to their usual diet throughout the study period and, where possible, to maintain a similar pattern of meals prior to each investigational day. The study protocol was approved by the hospital committee on medical ethics and each volunteer gave written informed consent prior to investigation.

On each study day volunteers were asked to attend the clinical laboratory, fasted, at 08.30 h. They were seated and intravenous cannulae were placed in each forearm under local anaesthesia for later blood sampling and infusion. An oral water load of 15 ml kg⁻¹ was then given. Every 20 min thereafter subjects stood to void. On each occasion the volume of urine passed was measured and an aliquot saved for later analysis. An equal volume of water was given to drink. In this way a stable water diuresis was established over a 2 h period. The last 20 min clearance period of this stabilisation period was taken as baseline (B). At this point a first infusion of either placebo (5% (+)-glucose) or noradrenaline (Levophed, Winthrop Laboratories) 0.025 µg kg⁻¹ min⁻¹ in 5% (+)-glucose, was commenced and continued until the end of the experiment (Figure 1). After a further 20 min urinary collection period (period 1) a second infusion of either placebo, or ANF99-126 (Shire Pharmaceuticals Ltd, Andover, Hampshire, UK) 0.04 µg kg⁻¹ min⁻¹ (15 pmol kg⁻¹ min⁻¹) in 5% (+)-glucose, was commenced and continued for 15 min. Urine was collected at the end of this period (period 2) and for a further two collection periods (periods 3 and 4). Prior to the first infusion (B), prior to the second infusion

Figure 1 Protocol schema. Initial 2 h stabilisation phase. Each block thereafter represents a 20 min urinary clearance period (B = baseline period and P1–P4 infusion periods). Urine was voided at the end of each of these periods, the volume measured and an equal volume of water given to drink to start the next period. Blood pressure was recorded at the end of each period immediately prior to voiding. Horizontal arrows indicate nature and timing of the infusions. Vertical arrows indicate the timing of blood samples for measurement of plasma electrolytes, creatinine and hormones.

(P1), during both infusions (P2) and after the second infusion had ended (P3 + 4) venous blood was collected. Samples (35 ml) were taken towards the end of each of the urinary clearance periods. Each sample was aliquoted into chilled tubes (volume, preservative) for measurement of noradrenaline (5 ml, lithium heparin), angiotensin II (10 ml, 0.05 M *o*-phenanthroline 2 g l⁻¹ neomycin, 0.125 M EDTA disodium salt and 2% ethanol solution), aldosterone (5 ml, potassium EDTA), ANF (10 ml, potassium EDTA) and electrolytes, creatinine and osmolality (5 ml, no preservative). All samples were placed on ice (except electrolytes etc., which were allowed to clot), centrifuged at 4° C and the plasma separated off and stored at –20° C (ANF, aldosterone) or –70° C (noradrenaline, angiotensin II) until assayed.

Blood pressure was recorded automatically every 20 min (Dinamap vital signs monitor 1846, Critikon, USA) during the study and an ECG was displayed continuously on an oscilloscope monitor (Hewlett Packard adult monitor, USA). No adverse effects were observed during the study.

Analytical methods

All samples for each individual (i.e. four study days) were measured together, in one assay run, for any given variable. Plasma noradrenaline was assayed by the double isotope radioenzymatic method of Brown & Jenner (1981). The intra-assay coefficient of variation (INCV) for this method in our laboratory is 8.0% and the interassay coefficient of variation (ITCV) 11.1%. Plasma aldosterone was measured with a commercially available radioimmunoassay kit (Serono Diagnostics, Ltd, UK). The INCV and ITCV for this method in our laboratory are 6.6% and 14.7%, respectively. Angiotensin II (ANGII) was also measured, after plasma extraction, by a commercially available radioimmunoassay kit (Immunodiagnosics Ltd, UK). The INCV and ITCV with this kit in our laboratory are 2.2% and 12.1% respectively. Plasma ANF levels were measured by radioimmunoassay (Amersham International Ltd, UK) after plasma extraction by the method of Richards *et al.* (1987). The INCV and ITCV, respectively, for this method in our laboratory are 7.8% and 4.9%. Serum and urinary sodium were measured by an ion specific electrode (Beckman E2A autoanalyser). Serum and urinary creatinine were measured by the modified Jaffe method on an auto-analyser (Cobas Bio, Roche Diagnostica).

The following indices were calculated according to standard criteria (Roberts & Daneshmend, 1981). Clearance (CL) was calculated as UV/P , where U = urinary concentration, V = urinary flow rate and P = plasma concentration. Creatine clearance (CL_{cr}) was used as an index of glomerular filtration rate (GFR).

Statistical analysis

The effect of treatment (dual placebo [absence of both treatments] ANF alone, noradrenaline alone, and the combination of both treatments) was assessed by analysis of variance (ANOVA) allowing for repeated measures. This analysis also tested for any interaction between ANF and noradrenaline (NA) for a given variable. Urinary

data were logarithmically transformed prior to analysis. Baseline (preinfusion) to post-infusion logarithmic ratios were compared. The hormonal data was assessed by Student's t -test using the Bonferroni correction. $P < 0.05$ was considered statistically significant. All data are presented as means $\pm$ s.e. mean. Percentage change in sodium excretion from baseline is presented in Figure 2 for illustrative clarity; statistical analysis was performed as stated above and not on percentages.

Results

Prestudy screening showed 24 h sodium excretion was 150 ± 23 mmol. Initial blood pressure and

Table 1 Heart rate (HR, beats min^{-1}), systolic blood pressure (SBP, mm Hg) and diastolic blood pressure (DBP, mm Hg) on each of the 4 study days. P = placebo (5% (+)-glucose), NA = noradrenaline $0.025 \mu\text{g kg}^{-1} \text{min}^{-1}$ and ANF = atrial natriuretic factor $99\text{--}126\text{--}0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$. B = baseline collection period and P1–P4 = periods 1 to 4 as described in text. All data are presented as means $\pm$ 1 s.e. mean

		B	1	2	3	4
HR (beats min^{-1})	P + P	67 ± 3	65 ± 3	66 ± 3	67 ± 2	68 ± 3
	NA + P	61 ± 2	60 ± 3	61 ± 2	62 ± 2	61 ± 3
	P + ANF	65 ± 2	63 ± 2	67 ± 3	63 ± 2	66 ± 2
	NA + ANF	61 ± 2	60 ± 3	64 ± 3	61 ± 3	65 ± 3
SBP (mm Hg)	P + P	117 ± 4	117 ± 4	118 ± 4	119 ± 4	122 ± 4
	NA + P	123 ± 4	118 ± 4	119 ± 4	121 ± 3	116 ± 3
	P + ANF	114 ± 3	119 ± 3	115 ± 3	119 ± 4	118 ± 4
	NA + ANF	121 ± 5	122 ± 5	124 ± 5	125 ± 6	123 ± 5
DBP (mm Hg)	P + P	73 ± 4	69 ± 4	67 ± 4	66 ± 4	71 ± 4
	NA + P	68 ± 3	69 ± 3	68 ± 3	72 ± 3	68 ± 3
	P + ANF	68 ± 4	66 ± 4	66 ± 4	69 ± 4	69 ± 4
	NA + ANF	68 ± 2	71 ± 3	71 ± 3	71 ± 3	74 ± 3

Table 2 Urinary sodium excretion ($U_{Na}V$, $\mu\text{mol min}^{-1}$) [geometric mean], urinary flow rate (V , ml min^{-1}) and creatinine clearance (CL_{cr} , ml min^{-1}) on each of the four study days (abbreviated as in Table 1). B = baseline collection period and P1–P4 = periods 1 to 4 as described in text. * $P < 0.01$, ** $P < 0.001$, + $P < 0.05$ P + ANF vs NA + ANF

		B	P1	P2	P3	P4
$U_{Na}V$ ($\mu\text{mol min}^{-1}$)	P + P	91 ± 32	87 ± 26	83 ± 25	80 ± 25	79 ± 29
	P + ANF	57 ± 55	56 ± 51	$82 \pm 65^*$	$110 \pm 84^{**}$	$80 \pm 66^*$
	NA + P	105 ± 67	100 ± 60	93 ± 50	$82 \pm 42^*$	$82 \pm 41^*$
	NA + ANF ⁺	83 ± 31	78 ± 29	$107 \pm 37^*$	$118 \pm 48^{**}$	$104 \pm 43^*$
V (ml min^{-1})	P + P	13.2 ± 0.8	12.9 ± 0.8	12.6 ± 0.8	12.4 ± 0.8	12.1 ± 0.8
	P + ANF	11.6 ± 1.5	11.6 ± 1.3	$13.1 \pm 1.4^*$	$14.5 \pm 1.4^{**}$	$13.4 \pm 1.3^*$
	NA + P	14.1 ± 1.2	13.9 ± 1.3	13.4 ± 1.1	12.8 ± 1.1	12.5 ± 0.9
	NA + ANF	12.9 ± 1.1	12.7 ± 1.1	$14.2 \pm 1.2^*$	$14.8 \pm 1.2^{**}$	$14.3 \pm 1.3^*$
CL_{cr} (ml min^{-1})	P + P	109 ± 6	106 ± 4	110 ± 4	107 ± 5	107 ± 3
	P + ANF	102 ± 6	104 ± 6	113 ± 8	111 ± 6	98 ± 8
	NA + P	108 ± 6	109 ± 4	107 ± 4	104 ± 4	106 ± 2
	NA + ANF	113 ± 6	108 ± 4	111 ± 5	110 ± 5	111 ± 4

heart rate were similar on all 4 study days (Table 1). Creatinine clearance was also similar on all 4 days and did not change significantly on any study day (Table 2).

ANF increased $U_{Na}V$ ($P < 0.001$) and urinary flow rate ($P < 0.001$). Noradrenaline decreased $U_{Na}V$ ($P < 0.05$) but did not affect urinary flow rate. NA blunted the rise in sodium excretion due to ANF when the two substances were given concomitantly ($P < 0.05$). In fact the peak response (i.e. the maximum natriuresis occurring during period 3) was reduced by $67 \pm 30\%$ when ANF was given against a background infusion of NA (Figure 2, Table 2).

However ANOVA showed that this reduction in sodium excretion was no more than expected from an additive effect of two opposite influences i.e. net sodium excretion reflected the sum of the antinatriuretic action of NA alone and the natriuretic action of ANF alone. In other words, there was no evidence of a synergistic interaction between the two treatments. Similarly no evidence of an interaction between NA and ANF was found for urinary flow rate.

The hormonal measurements are shown in Table 3. Initial hormonal levels did not differ between study days. NA infusion caused comparable and significant increases in circulating levels on the NA + P and NA + ANF days. ANF infusion caused comparable and significant increases in circulating levels on the P + ANF and NA + ANF days. ANF infusion also caused a significant fall in aldosterone levels on the P + ANF and NA + ANF days. Aldosterone levels

did not change significantly on the other study days and ANGII did not change on any of the investigational days.

Blood pressure and heart rate did not change significantly on any study day and did not differ between days (Table 1).

Figure 2 Percentage change ($\% \pm$ s.e. mean) in sodium excretion ($U_{Na}V$) from baseline on the 4 study days as indicated. P = placebo ($5\% (+)$ -glucose), NA = noradrenaline $0.025 \mu\text{g kg}^{-1} \text{min}^{-1}$ and ANF = atrial natriuretic factor $99-126 \text{ } 0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$. Horizontal arrows at bottom of figure indicate nature and timing of infusions (for duration see text). * $P < 0.05$ (t -test after ANOVA).

Table 3 Noradrenaline (NA, nmol l^{-1}), angiotensin II (ANGII, pmol l^{-1}), aldosterone (ALDO, nmol l^{-1}) and atrial natriuretic factor (ANF, pmol l^{-1}) levels on each of the 4 study days (abbreviated as in Table 1). B = baseline collection period and P1–P4 = periods 1 to 4 as described in text. * $P < 0.01$ (paired t -test), ** $P < 0.001$ (paired t -test)

		B	P1	P2	P3	P4
NA (nmol l^{-1})	P + P	3.38 ± 0.44	3.59 ± 0.48	—	3.98 ± 0.57	—
	P + ANF	4.02 ± 0.42	4.63 ± 0.88	—	4.22 ± 0.77	—
	NA + P	3.52 ± 0.16	$5.29 \pm 0.44^{**}$	—	$5.12 \pm 0.28^{**}$	—
	NA + ANF	3.19 ± 0.22	$5.55 \pm 0.51^{**}$	—	$5.59 \pm 0.69^{**}$	—
ANGII (pmol l^{-1})	P + P	32.1 ± 3.7	31.1 ± 3.2	31.6 ± 3.2	34.2 ± 3.5	—
	P + ANF	38.2 ± 9.3	37.1 ± 8.3	38.8 ± 10.6	36.6 ± 8.0	—
	NA + P	33.7 ± 5.2	31.0 ± 4.3	29.1 ± 3.6	31.4 ± 4.8	—
	NA + ANF	30.2 ± 3.1	33.1 ± 6.3	29.6 ± 3.0	27.5 ± 2.8	—
ALDO (nmol l^{-1})	P + P	0.41 ± 0.08	0.43 ± 0.07	0.48 ± 0.07	0.44 ± 0.07	± 0.07
	P + ANF	0.55 ± 0.11	0.57 ± 0.12	0.57 ± 0.12	$0.33 \pm 0.06^{*}$	$0.33 \pm 0.08^{*}$
	NA + P	0.34 ± 0.09	0.41 ± 0.08	0.44 ± 0.09	0.49 ± 0.09	0.43 ± 0.12
	NA + ANF	0.38 ± 0.05	0.36 ± 0.06	0.34 ± 0.05	$0.21 \pm 0.04^{**}$	$0.18 \pm 0.04^{**}$
ANF (pmol l^{-1})	P + P	9.2 ± 2.4	5.7 ± 2.0	8.4 ± 3.6	10.7 ± 3.8	—
	P + ANF	10.2 ± 3.8	14.9 ± 7.4	$131.7 \pm 30.2^{**}$	23.5 ± 6.9	—
	NA + P	5.4 ± 1.9	3.5 ± 1.7	4.8 ± 1.7	6.7 ± 4.5	—
	NA + ANF	8.6 ± 3.0	9.4 ± 4.0	$106.7 \pm 27.8^{**}$	18.9 ± 4.1	—

Discussion

This study has two major findings. Firstly it shows that low dose NA is antinatriuretic in man and that this effect occurs without any change in systemic blood pressure or GFR. Secondly, we have shown that this dose of NA blunts the natriuretic response to ANF.

While we did not directly investigate the effects of renal SNS stimulation during ANF administration, it is well recognised that NA infusion has qualitatively similar effects (DiBona, 1977; Johnson & Barger, 1981). Thus our findings are comparable with those of Morgan *et al.* (1986) who found that low level renal SNS stimulation, which itself tended to be antinatriuretic, limited the natriuretic effects of ANF in the rat. Our results therefore suggest that NA, and perhaps the SNS, can also modulate the renal effects of ANF in man. At the doses of both substances used in this study we were unable, however, to identify any specific interaction; the net natriuresis on the NA + ANF study day appeared to simply reflect the addition of two opposite effects.

How might these two hormones have exerted their effects? Neither substance affected GFR suggesting a possible interplay between them at tubular level. It is known that both NA and ANF have direct tubular actions (Bello-Reuss, 1980; Biollaz *et al.*, 1987). Alternatively an indirect tubular action could have occurred by way of changes in intrarenal blood flow. Renal blood flow (RBF) may have been reduced by NA and, if filtration fraction (FF) rose, no alteration in GFR would have occurred (Werko *et al.*, 1951). The changes in peritubular physical forces resulting from such perturbations might, however, have enhanced proximal tubular reabsorption of sodium. This could explain the tubular antinatriuretic effect of NA we observed. These hormones could also have acted by redistributing blood flow to different nephron sub populations. By increasing blood flow to 'salt-conserving' nephrons, NA could exert one effect while ANF could produce the other by increasing flow to 'salt-losing' nephrons. We did not, however, measure total renal blood flow in these experiments and it is not possible to reliably detect changes in the distribution of intra-renal blood flow in man in this type of study. We cannot therefore say with certainty whether the tubular effects of either hormone, or their interplay, were direct or indirect. NA does, however, antagonise the vascular actions of ANF more than other vasoconstrictor hormones (Bolli *et al.*, 1986; Takeshita *et al.*, 1987) suggesting the possibility of an intra-renal haemodynamic interaction.

In contrast to the effects on sodium excretion

NA did not cause a significant fall in urinary flow rate. Consequently it was not surprising that NA did not affect the diuretic response to ANF.

The results of this experiment, in conjunction with the findings from experimental animals, have several interesting implications. It is a long-standing observation that atrial distension is associated with a natriuresis and diuresis and, it is now known, release of ANF (Karim *et al.*, 1972; Knapp *et al.*, 1986). Prior cardiac (vagal afferent) denervation abolishes the renal effects of this manoeuvre but not the release of ANF (Karim *et al.*, 1972; Knapp *et al.*, 1986). This initially puzzling observation might be at least partially explained by the adrenergic-ANF interplay suggested above. Atrial dilatation is also associated with reflex renal SNS withdrawal, probably via a cardiac vagal afferent pathway (Thoren *et al.*, 1986). Cardiac denervation prevents this reflex adrenergic withdrawal (though not release of ANF) and this may prevent any facilitation of the action of ANF. Indeed, ANF itself may stimulate afferent cardiac vagal transmission (Thoren *et al.*, 1986).

A second area of relevance is in certain pathological salt retaining conditions such as nephrotic syndrome and congestive heart failure (CHF). These conditions are associated with heightened adrenergic activity and a reduced response to exogenous ANF (Koepke *et al.*, 1987). Recently it has been shown that renal denervation in nephrotic rats almost completely restores the natriuretic response to administered ANF (Koepke *et al.*, 1987). This suggests that renal (and possibly systemic) sympathetic overactivity in these conditions blunts the renal effects of ANF. In this context both our infusion rates of NA and ANF produced circulating levels within the range typifying CHF (Levine *et al.*, 1982). Our findings suggest that the circulating levels of NA, *per se*, found in patients with CHF, may limit the actions of ANF in this condition. We did, however, only look at the effects of short term infusions and there are many other reasons why patients with heart failure may be refractory to ANF, e.g. because of receptor down regulation, renin-angiotensin system overactivity and reduced renal perfusion pressure. In summary, we have shown that low dose infusion of NA is antinatriuretic and that this dose of NA blunts the effect of ANF on sodium excretion at a tubular level in man. We suggest that this may be further evidence of a reciprocal interplay between ANF and the SNS in the control of sodium-volume homeostasis.

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