The action of atriopeptin III on renal function in two models of chronic renal failure in the rat

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1 The natriuretic and diuretic effects of atriopeptin III (125, 250 and 500 ng kg⁻¹, i.v.) were studied in groups of rats anaesthetized with pentobarbitone which were either sham controls, unilaterally nephrectomized controls, adenine-fed or subtotal nephrectomy chronic renal failure models.

2 Atriopeptin III given at these doses to the sham control animals had no effect on blood pressure, renal blood flow or glomerular filtration rate but reversibly increased urine flow, between 46% to 54%, absolute sodium excretion, between 52% to 61%, and fractional sodium excretion, between 48% to 54% (all *P* values <0.05) from the lowest to the highest dose. The adenine-fed chronic renal failure group of rats had a reduced renal blood flow of between 30 and 75%, and glomerular filtration rate of approximately 20%, compared to the sham controls. Administration of atriopeptin at 125, 250 and 500 ng kg⁻¹ to the animals with renal failure increased water and sodium excretion to the same degree as observed in the sham group of rats.

3 In the group of unilaterally nephrectomized rats, atriopeptin III, at 125, 250 and 500 ng kg⁻¹ increased urine flow by 36%, 47% and 72%, respectively, absolute sodium excretion by 37%, 57% and 106%, respectively, and fractional sodium excretion by 46%, 45% and 102%, respectively. A similar pattern of responses was observed in the subtotal nephrectomy, chronic renal failure group in which filtration rate was approximately 4 times less than the controls. Although the magnitude of the urine flow and absolute sodium excretion responses were the same, the increases in fractional sodium excretion were all significantly larger than in the unilaterally nephrectomized control group.

4 These results show that in two different models of chronic renal failure, atriopeptin III still caused a natriuresis and diuresis. This suggests that the nephrons retain sensitivity to the atrial natriuretic peptides in diseases such as chronic renal failure and that these compounds may be useful in mobilizing body fluids in this situation.

Introduction

The mechanisms underlying the renal actions of the atrial natriuretic peptides whereby they increase the excretion of fluid by the kidney (Raine *et al.*, 1989) is unclear. At relatively high doses they cause a selective dilatation of the renal vasculature (Hintze *et al.*, 1985), causing an increase in both renal blood flow and glomerular filtration rate which, by increasing filtered load, could increase the excretion of water and sodium. Nevertheless, at low doses, diuresis and natriuresis occur even though there are no measurable alterations in renal haemodynamics (Johns & Rutkowski, 1989). Investigations have been carried out to assess the possible tubular sites of action of these peptides; reports using both whole kidney and micropuncture methodologies have shown that the proximal tubular sodium reabsorption is minimally affected (Vinay *et al.*, 1987). However, there is increasing evidence that the fluid reabsorption along the loop of Henle and the inner medullary regions of the collecting tubule may be inhibited (Schnermann & Briggs, 1987) which could lead to increased water and sodium excretion.

The importance of these peptides in pathological situations in which there is excessive fluid retention and hypertension has not been defined. There are reports that in congestive cardiac failure (Saito *et al.*, 1987) and essential hypertension (Kohn *et al.*, 1987; Matsubara *et al.*, 1987) the circulating levels of the peptides are raised but they do not appear to contribute sufficiently to mobilize and remove fluid. Another situation in which they may play some role is that of chronic renal failure in which the number of functional nephrons is

reduced and those which remain are hyperfiltering. In man, chronic renal failure is associated with increased plasma levels of atrial natriuretic peptide (Anderson *et al.*, 1986), hypertension and often volume expansion. The question arises as to whether the sensitivity of the remaining nephrons to the circulating atrial natriuretic peptide may be altered in some way. This problem was addressed in the present study by examining the effectiveness of a range of low doses of atrial natriuretic peptides in two different models of chronic renal failure. The first was induced by feeding high levels of adenine, which produces progressive blockage of nephrons, and the second was a subtotal nephrectomy in which the remaining nephrons underwent compensatory hypertrophy.

Methods

Animal preparation

- (a) *Sham control* These animals were intact rats which were untreated prior to use and fed a normal diet (Pilsbury 41B small animal diet), *ad libitum*.
- (b) *Unilateral nephrectomy control* Male albino Sprague-Dawley rats (260–280 g) were anaesthetized with sodium pentobarbitone (60 mg kg⁻¹, i.p.), a 2–3 cm long incision was made on the right side of the dorsum, about 1 cm from the spine and caudally from the last rib, the right kidney was exposed and removed after ligation of its peduncle. The wound was closed in layers, and sutured with catgut for muscles and silk for skin. The animals were used 4–5 weeks later.

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- (c) *Chronic renal failure* Rats were taken at 270–280 g and fed a diet containing 0.75% adenine (weight for weight) for 4–5 weeks before use. Pellets of regular rat diet (Pilsbury 41B) were ground to a powder, the adenine (Sigma, U.K.) added and the mixture presented to the animals *ad libitum*. This diet has been shown to induce a pronounced reduction in renal function (Yokazawa *et al.*, 1986).
- (d) *Chronic renal insufficiency* This was induced as previously described (Rutkowski *et al.*, 1981). Rats, at 270–280 g, were anaesthetized with sodium pentobarbitone, 60 mg kg⁻¹, i.p., and subjected to a right nephrectomy (see (b) above). The left kidney was exposed, 3/5 of the cortex was removed; bleeding was minimized by the application of a sterispon haemostatic sponge. The kidney was returned to the abdominal cavity and the musculature and skin sutured as described above. The animals were used 4–5 weeks later.

Experimental procedure

Male albino Sprague-Dawley rats (370–420 g) were anaesthetized with sodium pentobarbitone (60 mg kg⁻¹, i.p.) and subjected to tracheostomy to provide clear airways. The right carotid artery was cannulated for measuring blood pressure (Statham P23Db pressure transducer linked to a Grass model 7 polygraph) and blood sampling. A cannula was inserted into the left jugular vein for saline infusion (NaCl 150 mmol) at 6 ml h⁻¹ which was continued for the duration of the experiment. The left kidney was exposed using a mid-line abdominal approach, the ureter cannulated for urine collection and the renal artery separated from the renal vein and surrounding tissues to allow an electromagnetic flow probe (Skalar or Carolina) to be fitted for direct measurement of renal blood flow (SE medic flowmeter or a Carolina flowmeter linked to the Grass polygraph). Renal blood flow was not measured in the chronic renal insufficiency rats because of extensive connective tissue growth in that area resulting from the sub-total nephrectomy (see below). On completion of surgery, 2 ml of a solution containing 10 mg ml⁻¹ inulin saline was given i.v. over 1 min and the infusion changed to this same solution for the remainder of the experiment (Johns, 1988). Measurements were begun 2 h later. Blood samples (0.6 ml) were removed, centrifuged, the plasma stored, while the cells were resuspended in an equal volume of saline and reinfused intra-arterially.

Experimental protocol

The experimental protocol consisted of 5 clearance periods each of 15 min duration, two before (basal) and two following

(recovery) a period in which atriopeptin III (rat atrial natriuretic peptide 5-28 Bachem UK, Essex) was administered as a bolus dose of 0.3 ml, i.v., at the start of the urine collection. The two recovery clearances after the dose of atriopeptin III were taken 15 min following the end of the experimental period and therefore were used as the control clearances for the second dose of drug. Three doses of atriopeptin III were given, 125, 250 and 500 ng kg⁻¹ in random order to each animal.

Renal blood flow was measured directly, glomerular filtration rate was estimated as the clearance of inulin (Johns *et al.*, 1976). Plasma and urinary sodium and concentrations were measured with a Corning flame photometer (410C).

Statistics

The changes in each variable were assessed by taking a mean of the two control clearances and the two recovery clearances and comparing it to the experimental period when the peptide was given. The absolute and percentage changes expressed in the tables and figures represent the means of the individual changes recorded in each animal. Mean values $\pm$ s.e. are used. Statistical analysis was undertaken using the paired Student's *t* test within groups and the unpaired Student's *t* test between groups. Differences were taken to be statistically significant when *P* < 0.05.

Results

Sham control rats

The results from this group of animals fed a normal diet are given in Table 1. Administration of atriopeptin III over this dose range had no effect on either blood pressure, renal blood flow or glomerular filtration rate. However, the doses of 125, 250 and 500 ng kg⁻¹, atriopeptin III produced significant reversible increases in urine flow of 47%, 46% and 54% (all *P* values < 0.05), respectively, absolute sodium excretion, of 52%, 56% and 61% (all *P* values < 0.01), respectively, and fractional sodium excretion, of 48%, 57% and 54% (all *P* values < 0.05), respectively.

Chronic renal failure

Administration of the adenine diet caused a marked change in the appearance of the kidneys which was reflected in the left

Table 1 Effect of atriopeptin III (125, 250 and 500 ng kg⁻¹) on blood pressure and renal function in sham control rats (*n* = 7)

	125 ng kg ⁻¹			250 ng kg ⁻¹			500 ng kg ⁻¹		
	Basal	Exptl	Recovery	Basal	Exptl	Recovery	Basal	Exptl	Recovery
Blood pressure (mmHg)	126 ± 8	131 ± 3	123 ± 7	129 ± 6	130 ± 7	120 ± 11	128 ± 6	124 ± 8	122 ± 9
Renal blood flow (ml min ⁻¹ kg ⁻¹)	13.2 ± 1.3	13.1 ± 1.5	13.4 ± 1.2	12.9 ± 1.4	12.5 ± 1.1	12.5 ± 1.1	11.9 ± 0.9	11.6 ± 1.0	11.8 ± 1.0
Glomerular filtration rate (ml min ⁻¹ kg ⁻¹)	2.5 ± 0.2	2.6 ± 0.2	2.6 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	2.4* ± 0.3	2.3 ± 0.3
Urine flow (μ l min ⁻¹ kg ⁻¹)	41.3 ± 6.3	60.8* ± 8.6	44.8 ± 9.5	37.6 ± 6.7	56.0* ± 7.8	40.7 ± 6.4	40.5 ± 6.8	60.6* ± 10.0	39.9 ± 7.0
Absolute sodium excretion (μ mol min ⁻¹ kg ⁻¹)	7.2 ± 1.5	10.9* ± 2.0	8.1 ± 2.2	5.9 ± 1.5	8.8* ± 1.6	6.5 ± 1.5	6.8 ± 1.6	10.3* ± 2.1	6.7 ± 1.7
Fractional sodium excretion (%)	1.87 ± 0.35	2.66* ± 0.46	1.98 ± 0.54	1.71 ± 0.36	2.72* ± 0.59	2.01 ± 0.57	2.05 ± 0.58	2.96* ± 0.80	2.04 ± 0.67

The *P* values represent a comparison between the mean of the two basal and recovery periods with the value obtained during atriopeptin III administration (Exptl) * *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

Figure 1 Comparison of the baseline levels of systemic blood pressure (BP), renal blood flow (RBF), glomerular filtration rate (GFR), urine flow (UV), absolute sodium excretion (U_{Na} V) and fractional sodium excretion (FE_{Na}) in sham control (open columns), adenine-fed chronic renal failure (hatched columns), unilateral nephrectomised control (solid columns) and subtotal nephrectomy chronic renal insufficiency (stippled columns) rats. The *P* values represent the significance levels using the unpaired Student's *t* test between groups.

kidney weight, of 3.58 ± 0.34 g compared with the sham of 1.43 ± 0.06 g, and in their functional characteristics as shown in Figure 1. Compared with the sham rats, the adenine-treated animals had a significantly elevated blood pressure (164 ± 14 versus 122 ± 6 mmHg, $P < 0.05$) and reduced renal blood flow (7.5 ± 1.1 versus 12.9 ± 1.1 ml min⁻¹ kg⁻¹, $P < 0.01$) and glomerular filtration rate (0.4 ± 0.1 versus 2.4 ± 0.2 ml min⁻¹ kg⁻¹, $P < 0.001$). Although urine flow was significantly greater in the adenine-treated group (75.2 ± 13 versus 38.3 ± 6.7 μl min⁻¹ kg⁻¹, $P < 0.05$), absolute sodium excretion was not changed statistically, but fractional sodium excretion was markedly increased (15.0 ± 3.5 versus $1.7 \pm 0.3\%$, $P < 0.001$).

The responses to atriopeptin III of these adenine-treated rats are given in Table 2 and show that the peptide had no effect on blood pressure or renal blood flow at these dose levels but increased glomerular filtration rate at 250 ng kg⁻¹, by 22% ($P < 0.05$). However, atriopeptin III significantly increased urine flow by 30% ($P < 0.01$) and 23% ($P < 0.05$) at 250 and 500 ng kg⁻¹, respectively. In these adenine-treated

Figure 2 A comparison of the effects of atriopeptin III (APIII) at 125, 250 and 500 ng kg⁻¹ on absolute sodium excretion (U_{Na} V) (a) and fractional sodium excretion (FE_{Na}) (b) in sham control rats (●) and adenine-fed chronic renal failure rats (○). The asterisks represent the significance levels using Student's *t* test comparisons within each group of rats. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

rats, atriopeptin III at 125, 250 or 500 ng kg⁻¹ significantly increased absolute sodium excretion by 18%, 34% and 30% (all P values < 0.01), respectively, and fractional sodium excretion, by 13%, 12% and 12% (all P values < 0.05), respectively. A comparison of the changes in absolute and fractional sodium excretions caused by atriopeptin III in the sham and chronic renal failure rats are presented in Figure 2 and show that the responses in absolute sodium excretion were very similar. The increases in fractional sodium excretion in the failure rats were larger with greater variability than in the sham animals and the differences just failed to reach statistical significance.

Table 2 Effect of atriopeptin III (125, 250 and 500 ng kg⁻¹) on blood pressure and renal function in chronic renal failure (adenine) rats ($n = 5$)

	125 ng kg ⁻¹			250 ng kg ⁻¹			500 ng kg ⁻¹		
	Basal	Exptl	Recovery	Basal	Exptl	Recovery	Basal	Exptl	Recovery
Blood pressure (mmHg)	168 ± 13	174 ± 14	173 ± 17	160 ± 18	160 ± 18	158 ± 17	168 ± 18	163 ± 18	168 ± 16
Renal blood flow (ml min ⁻¹ kg ⁻¹)	7.7 ± 1.2	7.6 ± 1.2	7.9 ± 1.3	7.2 ± 0.8	7.2 ± 1.0	6.2 ± 0.5	7.7 ± 1.4	7.8 ± 1.5	7.9 ± 1.0
Glomerular filtration rate (ml min ⁻¹ kg ⁻¹)	0.38 ± 0.09	0.42 ± 0.09	0.44 ± 0.12	0.39 ± 0.06	0.47* ± 0.10	0.37 ± 0.08	0.34 ± 0.07	0.40 ± 0.09	0.35 ± 0.08
Urine flow (μl min ⁻¹ kg ⁻¹)	78.1 ± 9.7	96.5 ± 15.2	91.7 ± 13.2	80.3 ± 12.6	99.8** ± 17.2	73.5 ± 12.9	91.6 ± 11.5	109.0* ± 13.0	84.7 ± 10.1
Absolute sodium excretion (μmol min ⁻¹ kg ⁻¹)	8.4 ± 1.3	11.3** ± 2.1	10.7 ± 2.1	8.9 ± 2.1	11.9** ± 2.6	9.0 ± 2.1	10.6 ± 2.0	13.3** ± 2.4	10.0 ± 1.8
Fractional sodium excretion (%)	15.9 ± 2.8	19.1* ± 4.2	17.9 ± 4.3	16.9 ± 4.8	19.0* ± 5.1	17.8 ± 5.1	21.0 ± 2.9	23.3* ± 3.8	21.0 ± 5.0

The *P* values represent a comparison between the mean of the two basal and recovery periods with the value obtained during atriopeptin III administration (Exptl) * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 3 Effect of atriopeptin III (125, 250 and 500 ng kg⁻¹) on blood pressure and renal function in unilaterally nephrectomized rats (*n* = 6)

	125 ng kg ⁻¹			250 ng kg ⁻¹			500 ng kg ⁻¹		
	Basal	Exptl	Recovery	Basal	Exptl	Recovery	Basal	Exptl	Recovery
Blood pressure (mmHg)	142 ±7	144 ±7	138 ±4	143 ±6	148 ±4	144 ±4	143 ±7	138 ±5	133 ±5
Renal blood flow (ml min ⁻¹ kg ⁻¹)	22.7 ±1.6	22.7 ±1.9	23.1 ±1.7	23.8 ±1.4	21.8 ±1.6	22.8 ±1.6	23.8 ±1.4	21.8 ±1.1	21.9 ±1.1
Glomerular filtration rate (ml min ⁻¹ kg ⁻¹)	3.7 ±0.5	3.4 ±0.5	3.5 ±0.4	3.6 ±0.5	3.9 ±0.5	3.4 ±0.5	3.5 ±0.7	3.6 ±0.7	3.5 ±0.6
Urine flow (μl min ⁻¹ kg ⁻¹)	41.7 ±7.3	64.8* ±13.8	49.1 ±8.7	55.0 ±11.1	80.0* ±13.2	62.1 ±12.5	37.2 ±8.9	64.2* ±11.5	42.5 ±8.9
Absolute sodium excretion (μmol min ⁻¹ kg ⁻¹)	5.8 ±1.9	9.4* ±2.5	7.4 ±2.0	10.0 ±2.6	15.5* ±3.6	11.9 ±3.1	5.4 ±2.0	11.3* ±3.5	7.0 ±2.3
Fractional sodium excretion (%)	1.01 ±0.31	1.75* ±0.40	1.27 ±0.26	1.65 ±0.39	2.66* ±0.55	2.24 ±0.51	0.94 ±0.28	1.93* ±0.44	1.19 ±0.31

The *P* values represent a comparison between the mean of the two basal and recovery periods with the value obtained during atriopeptin III administration (Exptl) * *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

Unilateral nephrectomized rats

In this group of animals in which one kidney had been removed and the remaining kidney had undergone hypertrophy (kidney weight 2.93 ± 0.1 g) blood pressure was similar to the sham animals. Both renal blood flow (12.9 ± 1.1 versus 23.0 ± 0.3 ml min⁻¹ kg⁻¹) and glomerular filtration rate (3.5 ± 0.4 versus 2.4 ± 0.2 ml min⁻¹ kg⁻¹) were significantly (*P* < 0.01 and *P* < 0.05, respectively) greater than the sham control rats but urine flow, absolute and fractional sodium excretions were very similar in the two groups.

Table 3 shows that administration of atriopeptin III had no effect on either systemic blood pressure, renal blood flow or glomerular filtration rate at any dose tested. However, atriopeptin III, at 125, 250 and 500 ng kg⁻¹ given to the unilaterally nephrectomized animals, caused significant, reversible increases in urine flow, of 36%, 47% and 72% (all *P* values < 0.05), respectively, absolute sodium excretion, of 37%, 57% and 106% (all *P* values < 0.05), respectively and fractional sodium excretion of 46%, 45% ± 102% (all *P* values < 0.05), respectively.

Chronic renal insufficiency

These animals had a much reduced renal mass (1.72 ± 0.04 g) compared to the unilateral nephrectomized rats and it was not feasible to measure renal blood flow due to extensive scarring from the preliminary surgery. Figure 1 shows that in comparison to the unilaterally nephrectomized control rats, blood pressure was higher (165 ± 5 versus 140 ± 5 mmHg, *P* < 0.001), glomerular filtration rate was lower (0.8 ± 0.1 versus 3.5 ± 0.4 ml min⁻¹ kg⁻¹, *P* < 0.01) and while there were increased levels of urine flow (80 ± 18 versus

41 ± 7 μl min⁻¹ kg⁻¹, *P* < 0.05) and fractional sodium excretion (7.0 ± 1.6 versus $1.0 \pm 0.3\%$, *P* < 0.001) the absolute rate of sodium excretion was slightly but not significantly greater.

Table 4 presents the responses to atriopeptin III in the chronic renal insufficiency rats. Administration of the atriopeptin III had no measurable effect on either systemic blood pressure or renal haemodynamics at any dose tested. However, administration of atriopeptin III, at 125, 250 and 500 ng kg⁻¹ caused significant reversible increases in urine flow, of 29%, 58% and 57% (all *P* values < 0.005), respectively, absolute sodium excretion, of 31%, 73% and 78% (all *P* values < 0.05), respectively, and fractional sodium excretion, of 16%, 51% and 71% (all *P* values < 0.05), respectively. Figure 3 presents a comparison of the absolute changes induced by atriopeptin III in the unilaterally nephrectomized and the chronic renal failure rats. It shows that the changes in absolute sodium excretion were not significantly different at any dose level, although the response in the failure rats was slightly higher at the largest dose of atriopeptin III, but the increases in fractional sodium excretion were significantly (all *P* values < 0.001) greater at every dose in the failure rats compared with the control unilaterally nephrectomized animals.

Discussion

The objective of this investigation was to define the action of the atrial natriuretic peptide, atriopeptin III, on renal haemodynamic and tubular function in chronic renal failure. This pathological situation is one in which the number of functioning nephrons may be severely reduced and in which the remaining nephrons are hyperfiltering with the consequence that their reabsorptive properties are severely disturbed

Table 4 Effect of atriopeptin III (125, 250 and 500 ng kg⁻¹) on blood pressure and renal function in chronic renal insufficiency rats (*n* = 6)

	125 ng kg ⁻¹			250 ng kg ⁻¹			500 ng kg ⁻¹		
	Basal	Exptl	Recovery	Basal	Exptl	Recovery	Basal	Exptl	Recovery
Blood pressure (mmHg)	171 ±7	171 ±6	163 ±5	166 ±8	169 ±6	166 ±5	156 ±6	160 ±4	161 ±7
Glomerular filtration rate (ml min ⁻¹ kg ⁻¹)	0.79 ±0.10	0.89 ±0.11	0.91 ±0.16	0.77 ±0.12	0.89 ±0.10	0.82 ±0.10	0.87 ±0.16	0.90 ±0.19	0.74 ±0.13
Urine flow (μl min ⁻¹ kg ⁻¹)	91.1 ±25.0	114.9* ±28.3	85.9 ±20.2	71.5 ±18.7	117.9* ±22.8	86.1 ±15.0	72.9 ±15.8	125.6* ±29.4	87.5 ±16.8
Absolute sodium excretion (μmol min ⁻¹ kg ⁻¹)	9.6 ±3.0	12.7* ±3.8	9.1 ±2.9	6.7 ±2.0	13.8* ±3.4	9.7 ±1.8	8.5 ±2.2	16.0* ±4.1	10.9 ±3.1
Fractional sodium excretion (%)	8.4 ±2.6	9.5* ±2.6	6.6 ±1.6	5.3 ±1.4	10.1* ±2.0	7.6 ±1.1	7.4 ±2.4	14.0* ±4.1	12.6 ±5.4

The *P* values represent a comparison between the mean of the two basal and recovery periods with the value obtained during atriopeptin III administration (Exptl) * *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

Figure 3 A comparison of the effects of atriopeptin III (APIII) at 125, 250 and 500 ng kg⁻¹ on absolute sodium excretion ($U_{Na} V$) (a) and fractional sodium excretion (FE_{Na}) (b) in unilaterally nephrectomized control rats (●) and subtotal chronic renal insufficiency rats (○). The *P* values represent Student's unpaired *t* test comparisons between the two groups while the asterisks represent the significance levels using the Student's paired *t* test comparison within each group of animals. * *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

(Hostetter *et al.*, 1981). Two different models of chronic renal failure were used in the present study, firstly, that arising from feeding adenine, and secondly, that consequent to subtotal nephrectomy.

Feeding adenine for 4–5 weeks caused an increase in kidney mass and was associated with a greatly reduced filtration rate, similar to that found by Yokazawa *et al.* (1986). These authors found that there was deposition of small crystals in the proximal tubular lumens, causing tubular obstruction, while in the plasma there were marked increases in the levels of urea nitrogen and uric acid. It was of interest that the adenine-fed rats had sodium excretion which were the same as in rats with normal renal function; thus, the greatly decreased filtration rate resulted in an extremely high fractional sodium excretion indicating that the reabsorption of water and sodium by the epithelial cells was much reduced.

Administration of atriopeptin III over the dose range studied in the sham control rats had no effect on renal haemodynamics but reversibly increased the excretion of water and sodium at every dose. The magnitude and pattern of these excretory responses were very similar to those observed by Luft *et al.* (1986b) using bolus administration of atriopeptin III over the same dose range in intact rats and most likely represented an action on tubular reabsorptive processes. There are now many studies using larger doses of these peptides which have reported much larger increases in water and sodium excretion, up to 10–15 times (Goetz, 1988), but under these circumstances there were often increases in glomerular filtration rate which, by increasing filtered load, could also have contributed to the natriuretic and diuretic response.

In the adenine-fed chronic renal failure rats, atriopeptin III induced increases in water and sodium excretion very similar in pattern or magnitude to those observed in the sham control rats and therefore these failing kidneys were still sensitive to

the peptides. These observations support those of Hildebrandt & Banks (1988) in rats with nephrotic syndrome, induced with aminonucleoside, and those of Sterzel *et al.* (1987), using rats with antiglomerular basement membrane nephritis, who found atrial natriuretic peptides were still able to increase the excretion of water and sodium. In this latter report there were concomitant increases in glomerular filtration rate. The increases in fractional sodium excretion which occurred in response to the atrial natriuretic peptide were not statistically different in the sham control rats as compared to the chronic renal failure rats. The baseline levels of fractional sodium excretion in the adenine-fed rats were larger compared to the sham animals, consequently the change in fractional sodium excretion to the atrial peptide in proportionate terms was smaller and therefore it is not possible to conclude whether a change in tubular sensitivity had occurred. Nonetheless, it is clear that in the adenine-induced chronic renal failure model, atrial natriuretic peptides at low, non-vasodilator levels, could still cause a natriuresis and diuresis.

In an attempt to study the chronic insufficiency model of renal failure the unilaterally nephrectomized rat was used as the appropriate control. The remaining kidney of this control was heavier and had greater blood flow and glomerular filtration rate compared with the kidney of the sham control rats but responded to all doses of atriopeptin III by increasing water, absolute and fractional sodium excretions to a similar degree to the sham control rats. Renal blood flow could not be measured in this insufficiency model, because of extensive scarring around the remnant kidney and although glomerular filtration rate was greatly reduced, water and sodium output were similar or slightly higher compared to the unilaterally nephrectomized controls. The consequence of these differences was that fractional sodium excretion was greatly elevated in the chronic renal insufficiency model. Infusion of atriopeptin III into the chronic renal insufficiency rats had no effect on glomerular filtration rate but significantly increased urine flow and sodium output, which in size and pattern were almost identical to those found in the unilaterally nephrectomized controls. The increases in fractional sodium excretion were significantly larger in absolute terms in the insufficiency rats than the control rats at every dose tested, and one interpretation would be that there was an increased sensitivity to the peptide. Together these results show that the insufficiency animals remain responsive to the peptides and these observations are consistent with and support those of Luft *et al.* (1986a), who used a similar model of chronic renal insufficiency, and with the adenine-fed model described above using comparable doses of atriopeptin III.

It would seem that in both models of chronic renal failure, adenine feeding and subtotal nephrectomy, the nephrons retained or possibly increased their sensitivity to the atrial natriuretic peptide as its action on many fewer nephrons elicited the same magnitude of response. This apparent increase in sensitivity to atriopeptin III in these states of sodium and water retention is similar to that previously reported in DOCA-salt induced hypertension (Johns & Rutkowski, 1989) in which fluid expansion also exists. However, it is important to recognise that, although the same dose of peptide was given to both control and failure rats, in the latter groups the metabolism of the peptide may have been slower and its action prolonged as has been suggested by Predel and co-workers (1987) in progressive renal failure in man. Indeed, Luft *et al.* (1986b) have shown that the kidney accounts for almost 60% of the clearance by atriopeptin III from the plasma. The consequence of this would be an apparent equivalence of action in both control and failure rats which might not accurately reflect the sensitivity of the nephrons to the peptide.

This investigation has examined the changes in renal function which occur when atriopeptin III was given to two different models of chronic renal failure, one induced by feeding adenine, one resulting from subtotal nephrectomy. The dose levels of atriopeptin III used had no effect on blood pressure

or renal haemodynamics in either the control or renal failure groups of rats but it did increase water and sodium output at every dose tested. The magnitudes of the natriuresis and diuresis following atriopeptin III were similar in both the control and chronic renal failure groups which indicated that the nephrons present within the failing kidneys retained or even increased their sensitivity to the peptides. These findings suggest that administration of atrial natriuretic peptides may

be useful in mobilizing body fluids in those patients who have chronic renal failure.

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