CLINICAL RESEARCH

Failure of renal dopamine response to salt loading in chronic renal disease

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Abstract

Eight patients with chronic glomerulonephritis and five age-matched normal volunteers were given additional sodium chloride by mouth under conditions of metabolic balance. Whereas in the normal volunteers plasma renin activity was suppressed and urinary excretion of free dopamine increased, in the patients dopamine was not mobilised and plasma renin activity was not completely suppressed.

Abnormal retention of sodium and water in glomerulonephritis may be due partly to a failure to mobilise dopamine in the kidney. Specific renal dopamine agonists may be natriuretic and hypotensive in chronic glomerulonephritis.

Introduction

The mechanisms responsible for the hypertension in patients with chronic renal disease have long been disputed. In most of these patients hypertension responds to restriction of sodium and fluids,¹ and an increased extracellular sodium and water content correlating with diastolic blood pressure has been reported.² In patients with chronic glomerulonephritis plasma

renin activity may be close to normal, but this may be inappropriately high for the state of sodium balance.³⁻⁵ Although sodium retention appears to be the primary event, the reason for this is not clear. In a few patients plasma renin activity is appreciably increased; in these patients blood pressures do not fall when salt and water are restricted.^{1, 6}

Recently it has become apparent that the catecholamine dopamine may play an important part in salt handling by the kidney⁷ and may initiate the natriuretic cascade.⁸ Renal dopamine is probably mostly produced within the kidney tubules, after uptake of filtered L-dopa, and then secreted into the tubular lumen. There is evidence for a dopaminergic innervation of the kidney,⁹ but the contribution of the renal nerves to total urinary dopamine excretion appears to be small¹⁰ and their importance in sodium excretion is not clear. Renal production of dopamine increases in response to loading with sodium chloride.^{11, 12} Moreover, dopamine infused into the renal artery causes natriuresis.¹³ Both these observations have led to the suggestion that endogenous dopamine is an intrarenal natriuretic hormone.

We therefore carried out a study to determine whether the urine dopamine response to oral loading with sodium chloride was normal in patients with chronic renal disease.

Patients and methods

We selected for study eight men with varying degrees of renal impairment (seven had glomerulonephritis proved at biopsy) and five age-matched normal male volunteers. Patients were excluded if they had proteinuria in excess of 5 g a day, inappropriate salt loss, or rapidly progressive renal failure. Patients and controls were admitted to the metabolic unit at Leeds General Infirmary or St James's Hospital, where they received a diet that yielded the same amount of energy as their usual food intake but contained roughly 40 mmol(mEq) sodium a day. In cases in which it was considered safe to do so all drugs were stopped two days before admission to hospital (one week before the start of the study).

Subjects were weighed daily and their blood pressure (lying and standing) measured twice daily. All urine was collected daily for estimation of sodium, creatinine, and dopamine excretions. On selected days a fasting recumbent blood sample was taken for measurement of plasma creatinine and electrolyte concentrations, packed cell volume, and plasma renin activity. A period of four days was allowed

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for patients to become used to the ward routine and achieve balance with the diet. The controls, after voluntary salt restriction as outpatients, spent two and a half days on the metabolic unit to achieve sodium balance. Blood and urine samples were collected over the next three days. Dietary supplements of Slow Sodium tablets (Ciba) were then given to increase the dietary sodium intake to roughly 220 mmol a day for a further nine days. At the end of this period the patients, but not the controls, reverted to the low-sodium diet for four days before being discharged from hospital, so that most of any retained sodium could be excreted.

Laboratory methods—Urine was collected into acid to prevent oxidation of dopamine. Dopamine was assayed by a radioenzymatic method¹⁴ after prior extraction from urine with alumina¹⁵; interassay variation was 14% and intra-assay variation 5%. Urine and plasma electrolyte and creatinine concentrations were measured by standard laboratory techniques. Plasma renin activity was measured by radioimmunoassay¹⁶; interassay variation was 8.0% and intra-assay variation 6.4%. Packed cell volume was determined by the Hawksley micro-haematocrit method.

Statistical methods—Comparisons were made between the patients and the controls while they were taking the low- and high-sodium diets, and between the low- and high-sodium diets in each group, by analysis of variance.¹⁷ The cumulative sodium balance at the end of the study was compared by Wilcoxon's two-sample test.

Ethical approval—The protocol was approved by the ethical committees of the Leeds eastern and western districts. Informed written consent was obtained from the subjects.

Results

Mean ages were comparable between the two groups (patients $44 \pm \text{SD } 11$ years, controls 43 ± 13 years). Proteinuria in the patients averaged 1.8 g/24 h. Seven patients had proliferative glomerulonephritis confirmed by biopsy and one a good history of post-streptococcal nephritis. Two patients were normotensive and were not taking any drugs before the study. Three patients who were hypertensive stopped their treatment before the study, while three others continued with their drugs throughout (one was taking frusemide and Slow-K; one allopurinol, bendrofluazide, Slow-K, propranolol, and methyl dopa; and one frusemide, chlorthalidone,

metoprolol, prazosin, 1 α -hydroxycholecalciferol, chlorpheniramine, and calcium supplements).

The figure shows urinary excretion of free dopamine and plasma renin activity. There was a highly significant ($p < 0.001$) difference in excretion of free dopamine between the patients and the controls and a significant ($p < 0.001$) change in excretion of free dopamine over time (that is, on salt loading). The group $\times$ time interaction was also significant ($p < 0.01$), indicating that the change in urinary excretion of dopamine over time was different between the two groups and implying that the effect of sodium chloride loading differed between the two groups. Plasma renin activity was measured in three of the controls; there was no overall difference between patients and controls, but there was a significant change over time ($p < 0.001$) and a significant group $\times$ time interaction ($p < 0.05$) (that is, the change in plasma renin activity on salt loading was different between patients and controls).

Table I shows the mean body weight, packed cell volume, plasma sodium and chloride concentrations, sodium excretion, creatinine clearance, and blood pressure in the patients and controls. Mean arterial pressure was calculated as mean diastolic pressure (from two standing and two lying recordings) plus one-third of the mean difference between systolic and diastolic pressures (from two standing and two lying recordings).

Mean blood pressure over the three days on which a low-salt diet was taken was 86 mm Hg in the controls and 99 mm Hg in the patients; this rose to 87 mm Hg in the controls and 102 mm Hg in the patients when a high-salt diet was taken. These blood pressures, however, were not significantly different, and the rise on sodium chloride loading was not significant. There was no group $\times$ time interaction. Packed cell volume was not significantly different overall between the groups, but there was a significant change over time ($p < 0.001$) and a significant group $\times$ time interaction ($p < 0.05$). Plasma sodium concentration was significantly ($p < 0.01$) greater in patients than controls and rose significantly on sodium loading ($p < 0.001$), but this change was not significantly different between the groups. Plasma chloride concentration was also greater in patients than controls ($p < 0.05$) and rose significantly on sodium chloride loading ($p < 0.001$). The rise in plasma chloride concentration was significantly different between the two groups ($p < 0.05$). Creatinine clearance, as expected, was different between the groups, but there was no change with time and no group $\times$ time interaction. It is difficult, however, to identify significant differences between groups

TABLE I—Clinical variables in patients and controls taking 40 mmol (2.3 g) sodium chloride for three days and 220 mmol (12.9 g) for nine days (values expressed as means ($\pm$ SEM))

	Low-sodium diet			High-sodium diet								
Days:	1	2	3	4	5	6	7	8	9	10	11	12
	Body weight (kg)											
Patients	76.9 (14.0)	76.9 (13.9)	76.8 (14.0)	76.8 (13.8)	77.0 (13.9)	77.1 (13.5)	76.9 (13.5)	76.9 (13.5)	76.7 (13.2)	76.5 (13.2)	76.4 (13.1)	76.3 (12.9)
Controls	68.7 (5.4)	68.7 (5.4)	68.7 (5.3)	68.8 (5.3)	69.2 (5.2)	69.7 (5.2)	69.2 (5.2)	69.3 (5.2)	69.0 (5.2)	69.3 (5.2)	69.0 (5.2)	68.8 (5.1)
	Packed cell volume											
Patients	0.443 (0.029)	0.436 (0.03)	0.441 (0.031)		0.424 (0.03)		0.413 (0.03)		0.415 (0.031)		0.409 (0.031)	0.408 (0.03)
Controls	0.452 (0.02)	0.444 (0.023)	0.442 (0.019)		0.426 (0.021)		0.424 (0.021)		0.434 (0.018)		0.432 (0.019)	0.438 (0.019)
	Plasma sodium (mmol/l)											
Patients	139.0 (0.7)	137.9 (0.6)	138.6 (0.9)		140.5 (0.4)		143.4 (1.2)		143.8 (1.2)		144.8 (1.4)	144.2 (1.5)
Controls	137.0 (0.6)	138.4 (0.5)	138.7 (0.6)		139.6 (0.4)		140.9 (0.7)		139.4 (0.6)		140.7 (0.4)	140.3 (0.6)
	Plasma chloride (mmol/l)											
Patients	102.8 (1.2)	103.5 (1.0)	103.0 (1.2)		106.8 (1.6)		108.3 (1.8)		110.2 (2.3)		110.0 (2.4)	110.7 (2.4)
Controls	99.6 (0.5)	99.5 (0.7)	100.9 (0.8)		104.3 (0.4)		102.2 (1.4)		103.5 (1.2)		103.7 (1.2)	101.9 (1.1)
	Sodium excretion (mmol/24 h)											
Patients	50 (7)	50 (6)	42 (6)	75 (8)	148 (7)	210 (14)	222 (11)	226 (11)	211 (9)	225 (11)	218 (12)	217 (11)
Controls	38 (8)	32 (7)	24 (4)	92 (17)	157 (18)	266 (8)	212 (5)	239 (16)	188 (9)	243 (20)	236 (11)	163 (21)
	Creatinine clearance (ml/min)											
Patients	57 (11)	58 (12)	59 (11)		73 (15)		66 (13)		67 (12)		68 (15)	63 (12)
Controls	117 (14)	120 (11)	102 (8)		101 (11)		114 (13)		107 (3)		111 (12)	114 (18)
	Blood pressure (mm Hg)											
Patients	101 (7)	101 (6)	96 (6)	101 (6)	100 (6)	104 (6)	104 (6)	101 (6)	102 (6)	98 (7)	103 (7)	104 (7)
Controls	87 (2)	83 (2)	88 (4)	87 (2)	91 (2)	87 (2)	86 (4)	84 (3)	87 (4)	87 (2)	87 (4)	88 (3)

Conversion: SI to traditional units—Sodium and chloride: 1 mmol = 1 mEq.

with numbers as small as these when there is a wider distribution of creatinine clearance in the patients than in the controls.

Table II shows the cumulative sodium balance on the final day of sodium chloride loading in each subject with the mean plasma creatinine concentration throughout the study. The difference in cumulative sodium balance between patients and controls was significant ($p < 0.01$). When all subjects were taken together the cumulative sodium balance on the final day of sodium chloride loading correlated positively with the mean plasma creatinine concentration ($r = 0.70$, $p < 0.01$, Spearman's coefficient of rank correlation).

Mean ($\pm$ SEM) urinary excretion of free dopamine (plotted as histogram) and plasma renin activity ($\bullet$ — $\bullet$) in patients and controls during three days of 40 mmol (2.3 g) sodium chloride diet and nine days of 220 mmol (12.9 g) sodium chloride diet.

Conversion: SI to traditional units—Dopamine excretion: 1 $\mu\text{mol}/24\text{h} \approx 190\text{ }\mu\text{g}/24\text{h}$. Plasma renin activity: 1 $\text{mmol}/\text{l}/\text{h} \approx 1.3\text{ ng}/\text{ml}/\text{h}$.

Discussion

The observation that the cumulative sodium balance in the patients was greater than that in the controls after nine days of a high-sodium diet is in keeping with observations that total body sodium is increased in patients with renal disease.¹⁸ Retention of sodium was greatest in those patients with the highest plasma creatinine concentration. Koomans *et al*¹⁹ showed that the sensitivity of blood pressure to salt increases with decreasing creatinine clearance, so it seems that not only are patients with poor renal function more likely to retain sodium but that their blood pressure will rise further in response to this. In our study, although mean blood pressure increased more on salt loading in patients than controls, the effect was not pronounced. Possibly over a longer period of sodium loading the blood pressure might have risen further to reduce the positive cumulative sodium balance by producing a pressor natriuresis.²⁰ The sodium retention was not, however, reflected by greater increase in body weight in the patients, probably because dietary estimates of the patients' energy intakes were underestimated and the patients lost weight gradually throughout the study.

The more pronounced rise in plasma sodium (and also

TABLE II—Cumulative sodium balance on last day of 220 mmol (12.9 g) sodium chloride diet and mean plasma creatinine concentration in each subject

Controls (case No)	Cumulative sodium balance (mmol)	Mean plasma creatinine ($\mu\text{mol}/\text{l}$)	Patients (case No)	Cumulative sodium balance (mmol)	Mean plasma creatinine ($\mu\text{mol}/\text{l}$)
1	182	67	6	338	89
2	203	86	7	230	103
3	35	83	8	253	117
4	185	105	9	313	143
5	119	113	10	272	147
			11	252	332
			12	408	358
			13	379	627
Mean (SEM)	145 (31)	91 (8)		306 (23)	240 (66)

Conversion: SI to traditional units—Sodium: 1 $\text{mmol} = 1\text{ mEq}$. Creatinine: 1 $\mu\text{mol}/\text{l} \approx 11.3\text{ }\mu\text{g}/100\text{ ml}$.

chloride) concentrations in the patients suggests either an impairment of the osmoreceptors responsive to raised plasma osmolarity or, more probably, a relative failure of the kidneys to respond to antidiuretic hormone. Packed cell volume tended to fall further in patients than controls, indicating that more water was retained, increasing the intravascular volume, a factor that may contribute to any rise in blood pressure.

In this study we showed that the kidneys of patients with glomerulonephritis do not respond in a normal manner. Urine dopamine excretion during a low-salt diet was much lower in the patients than the controls and did not rise significantly in the patients on salt loading. Although plasma renin activity in the patients was suppressed on sodium loading, this change was not as pronounced (or as rapid) as that in the controls, in keeping with the proposal of other workers that plasma renin activity is inappropriately high in chronic renal disease. The ratio of plasma renin activity to renal dopamine production may be important in regulating sodium excretion.⁷

According to the intact nephron hypothesis, when any part of the nephron is damaged the whole unit will stop functioning. As a result, in glomerulonephritis many renal tubules (the probable source of dopamine in the kidney) will stop functioning and the contribution of the tubules to urine dopamine excretion will be much reduced. Also, since the source of renal dopamine is probably circulating L-dopa²¹ then as glomerular filtration rate and renal plasma flow fall less L-dopa will be delivered to the tubules and dopamine excretion might be expected to decrease. Our unpublished observations in outpatients with a wide range of impaired renal function support this. In patients with a plasma creatinine concentration greater than 180 $\mu\text{mol}/\text{l}$ (2 $\text{mg}/100\text{ ml}$) urine dopamine excretion was much reduced and appeared to depend on glomerular filtration rate, whereas in patients with more normal renal function urine dopamine excretion was independent of glomerular filtration rate. Itskovitz and Gilberg²² showed that with increasing degrees of renal failure urinary free dopamine diminished and almost disappeared when plasma creatinine concentration was greater than 530 $\mu\text{mol}/\text{l}$ (6 $\text{mg}/100\text{ ml}$). In chronic renal disease, therefore, it seems that dopamine is inappropriately low and renin inappropriately high when compared with total body sodium.

Oral administration of levodopa results in increased renal plasma flow, glomerular filtration rate, and sodium and potassium excretion, effects that may be brought about by conversion to dopamine.²³ Normally the L-dopa supplied to the kidney is in excess of that required for production of dopamine, and it is probably the filtered load of sodium that controls the conversion of L-dopa to dopamine⁷ until renal plasma flow is low.

Until recently the idea of dopamine as an intrarenal natriuretic agent had no practical importance outside intensive care and renal units. However, specific renal dopamine agonists that may be administered by mouth are now becoming available^{24 25}: ibopamine (diisobutyl *N*-methyl dopamine) increases renal blood flow (and produces natriuresis) in patients with chronic renal failure.²⁵ These agents may come to have an important

therapeutic role in the management of oedema and hypertension in chronic renal disease.

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Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction

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Abstract

The effect of intravenous atenolol on ventricular arrhythmias in acute myocardial infarction was assessed in 182 patients admitted within 12 hours of the onset of chest pain. Ninety-five patients were randomised to receive 5 mg intravenous atenolol followed immediately by 50 mg by mouth and 50 mg 12 hours later, then 100 mg daily for 10 days; 87 patients served as controls. The treated patients had significantly fewer ventricular extrasystoles; 58 control patients (67%) had R-on-T

extrasystoles compared with only 25 treated patients (26%) ($2p < 0.0001$); repetitive ventricular arrhythmias were detected in 64 control patients (74%) and 55 treated patients (58%) ($2p < 0.05$). Heart rate was significantly reduced from 77 ± 1 beats/min at entry to 65 ± 1 beats/min ($2p < 0.001$) in the first hour after intravenous atenolol, and in addition the rate was significantly different from that in the control group. There was no difference in the incidence of heart failure, but fewer patients in the treated group received other antiarrhythmic agents or digoxin.

These results show that early intravenous atenolol prevents ventricular arrhythmias in suspected acute myocardial infarction.

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Introduction

Beta-adrenergic-blocking drugs reduce the incidence, frequency, and severity of ventricular arrhythmias after experimental coronary artery occlusion,¹⁻³ and an increase in the ventricular fibrillation threshold associated with myocardial ischaemia has