CLINICAL RESEARCH

Sodium, potassium, and rate constants for sodium efflux in leucocytes from hypertensive Jamaicans

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Abstract

Leucocyte sodium and potassium content and concentrations were measured along with ouabain-sensitive and ouabain-insensitive rate constants for sodium efflux in 14 controls and 20 black patients with essential hypertension. Leucocyte sodium content was significantly increased in the patients (mean 101.1 ± 7.8 mmol/kg dry solids v 74.5 ± 7.6 mmol/kg dry solids; $p < 0.05$), whereas the rate constants for sodium efflux were not significantly reduced. There was no difference between the two groups in cell potassium values.

The increase in leucocyte sodium content in the presence of normal rate constants for sodium efflux suggests an increase in membrane permeability to sodium, which might be important in the pathogenesis of essential hypertension.

Introduction

Specific disturbances in sodium metabolism occur in essential hypertension, and attention has been focused on their significance in the pathogenesis of hypertension. Eyer¹ reported that blood pressure does not rise with age in populations with a non-Westernised life style and a small dietary intake of sodium chloride, but Dahl and Love described a positive correlation between salt intake and the prevalence of hypertension in several populations.² They also showed a difference in the prevalence of hypertension in adults positively correlated with urinary excretion of sodium, and later developed the concept of a genetically determined sensitivity to the hypertensinogenic effect of salt by breeding salt-resistant and salt-sensitive strains of rats.^{3,4}

More recently increased erythrocyte membrane transport of potassium in patients with mild hypertension and a decrease in the transport of sodium in severe hypertension have been

described⁵; thus in mild or severe essential hypertension the ratio of sodium to potassium fluxes was always depressed. There were identical alterations in sodium and potassium flux ratios in non-hypertensive children of hypertensive parents. Other workers have reported increased erythrocyte sodium and lithium countertransport in patients with essential hypertension and also in first-degree relatives of such patients.⁶ Increased leucocyte sodium and cell water and a reduced rate constant for sodium efflux in patients with essential hypertension have also been described.⁷ It is thus becoming clear that there are differences in sodium metabolism in hypertensive patients and, more fundamentally, that these differences may be related to changes or abnormalities of membrane transport of ions.

All of the later studies mentioned were in white subjects. In black populations hypertension is more prevalent, more severe, and associated with relatively greater morbidity and mortality than in white populations. We have therefore studied leucocyte sodium, potassium, and rate constants for sodium efflux in black hypertensive Jamaicans to try to determine the presence and nature of any abnormalities in cellular sodium homeostasis.

Methods

Twenty patients with essential hypertension were chosen from the hypertension clinic at this hospital. Patients with secondary causes for hypertension or established renal impairment were excluded. Fourteen normotensive controls were selected from the staff of the hospital.

Blood for isolation of the leucocytes was collected in heparinised syringes by venepuncture. Leucocytes were isolated by a modification of the method of Baron and Ahmed.⁸ The isolated cells were loaded with ^{22}Na by incubating them for 20 minutes in tissue-culture fluid (TC-199; Wellcome) containing ^{22}Na 0.9 mCi/l ($^{22}\text{NaCl}$; Amersham). The rate constant for total sodium efflux was determined from the residual radioactivity in timed samples of leucocytes. That for ouabain-insensitive sodium efflux was determined in cells treated with ouabain before the beginning of the determination. The difference in rate constants between total and ouabain-insensitive sodium efflux gave the rate constant for ouabain-sensitive or active efflux.

Extracellular space was measured with an extracellular fluid space marker, ^{125}I -polyvinylpyrrolidone (Amersham). Cell sodium and potassium were extracted overnight in 0.1N HNO_3 and measured by internal standard flame photometry. Electrolytes in leucocytes were

Blood pressure, leucocyte sodium and potassium content and concentrations, cell water, and rate constants for sodium efflux in patients with essential hypertension and controls

Subject	Blood pressure (mm Hg)		Sodium content (mmol/kg dry solids)	Sodium concentration (mmol/l cell water)	Potassium content (mmol/kg dry solids)	Potassium concentration (mmol/l cell water)	Cell water (l/kg wet weight)	kOA _s	kOA _i
	Systolic	Diastolic							
Hypertensives									
1	170	108	45.5	20.7	247	112	2.20	1.06	0.44
2	184	154	70.8	50.2	224	159	1.41	1.51	0.01
3	166	120	90.3	45.8	376	191	1.97	2.26	0.66
4	188	130	49.0	22.8	326	152	2.15	0.87	0.50
5	148	112	144.2	89.6	240	149	1.61	0.95	1.35
6	156	116	95.6	38.7	301	122	2.47	0.51	2.94
7	166	116	120.6	57.9	298	143	2.08	1.71	0.56
8	200	126	95.5	75.8	344	273	1.26	2.38	0.45
9	160	108	93.4	44.3	337	160	2.11	1.80	0.16
10	180	110	129.0	58.4	351	159	2.21	2.26	0.52
11	110	92	125.0	36.7	398	131	3.40	3.00	0.61
12	213	146	78.7	35.1	344	153	2.24	2.74	1.07
13	160	112	81.1	37.0	445	203	2.18	1.45	1.06
14	160	120	154.6	62.2	353	142	2.48	2.28	0.80
15	158	130	125.8	43.6	405	140	2.89	3.20	0.03
16	158	118	61.2	29.4	392	189	2.08	4.51	0.14
17	148	124	109.5	54.2	302	150	2.02	1.16	2.84
18	183	132	173.3	63.5	238	87	2.73	4.65	0.46
19	160	90	70.0	32.0	346	157	2.19	2.73	0.71
20	170	110	108.0	49.3	383	175	2.20	1.45	0.09
Mean ± SEM	166.9 ± 4.8*	118.8 ± 3.6*	101.1 ± 7.8†	47.4 ± 3.9	332.0 ± 13.6	158.0 ± 8.9	2.19 ± 0.11	2.12 ± 0.25	0.77 ± 0.18
Controls									
21	120	70	79.5	39.8	335	168	2.00	2.26	0.63
22	124	72	108.0	54.2	333	167	1.99	1.19	0.82
23	130	80	113.6	51.6	336	152	2.20	4.07	0.58
24	126	80	89.8	37.1	366	151	2.42	3.27	0.51
25	128	82	73.9	33.0	357	159	2.24	1.19	0.01
26	136	80	125.8	68.7	277	151	1.83	3.49	0.18
27	98	78	35.4	14.1	388	154	2.52	2.30	0.12
28	138	84	89.7	82.1	373	189	1.07	3.63	0.68
29	132	76	78.1	49.4	407	258	1.58	2.51	0.68
30	130	68	56.7	21.1	317	132	2.40	2.76	1.01
31	110	72	40.5	20.4	256	129	1.99	3.33	0.84
32	124	86	59.0	29.4	357	177	2.01	3.50	0.83
33	124	78	43.6	25.5	327	209	1.71	2.81	0.64
34	130	84	49.7	25.1	358	181	1.98	2.67	0.54
Mean ± SEM	125.0 ± 1.5*	77.9 ± 1.5*	74.5 ± 7.6†	39.4 ± 5.3	341.0 ± 10.8	170.0 ± 8.8	2.00 ± 0.10	2.78 ± 0.23	0.58 ± 0.08

kOA_s = Ouabain-sensitive rate constant for sodium efflux.
kOA_i = Ouabain-insensitive rate constant for sodium efflux.

*p < 0.0001.

†p < 0.05.

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

expressed as content (mmol/kg dry solids) and concentration (mmol/l cell water).

Results are expressed as means ± SEM. Significance of differences between values was measured by Student's *t* test.

Results

The mean age of the controls was 38.1 years (range 22-55) and of the hypertensive patients 38.5 years (range 21-54). The mean blood pressures of the two groups were 125/78 mm Hg and 167/119 mm Hg, respectively (table).

Leucocyte sodium content in the controls was 74.5 ± 7.6 mmol(mEq)/kg dry solids and in the hypertensive patients 101.1 ± 7.8 mmol/kg dry solids (*p* < 0.05). Sodium concentration was also higher in the patients than in the normotensive controls (47.4 ± 3.9 *v* 39.4 ± 5.3 mmol/l cell water).

Leucocyte potassium contents were closely similar in the controls and hypertensive patients (341.0 ± 10.8 *v* 332.0 ± 13.6 mmol(mEq)/kg dry solids), as were leucocyte potassium concentrations (170.0 ± 8.8 *v* 158.0 ± 8.9 mmol/l cell water). Amounts of cell water were similar in the controls and hypertensives (2.00 ± 0.10 *v* 2.19 ± 0.11 l/kg wet weight).

There was no significant difference in the rate constants for total sodium efflux, ouabain-insensitive, or ouabain-sensitive efflux between the two groups.

Discussion

In the only other reported study of this type, Edmondson *et al*⁷ found an increase in leucocyte sodium content and cell water, a reduction in leucocyte potassium concentration, similar contents of leucocyte potassium, but a reduction in total and active sodium efflux rate constants. They suggested that a defect

in the sodium pump was the underlying cause of hypertension in English patients.

Increased concentrations of sodium in smooth muscle have been linked theoretically with increased peripheral resistance by several authors,^{9,10} and abnormalities in leucocyte sodium homeostasis have been regarded as important by assuming that those leucocyte defects are shared by smooth-muscle cells.

Contrary to Edmondson *et al*, we found no significant difference in the rate constants for sodium efflux, nor in cell water and leucocyte potassium concentration. The increased leucocyte sodium content in the presence of normal rate constants for sodium efflux (ouabain sensitive and insensitive) suggests that a defect in the sodium pump does not underlie the disturbance in cellular sodium homeostasis. Since the two important variables which determine cell sodium are the rates of influx and efflux, the rate of sodium influx is apparently responsible for the increase in leucocyte sodium content, the influx rate having exceeded the efflux rate. Thus an abnormally enhanced membrane permeability to sodium ion must exist in leucocytes from our black hypertensive patients.

It is not surprising that the leucocyte potassium content was similar in the controls and hypertensive patients. Reportedly, after acute reduction of the rate constant for sodium efflux, the efflux rate (*k* × [Na]) falls as well but returns to normal when the intracellular sodium concentration increases enough to offset the fall in rate constant.¹¹ During the period of acute reduction in efflux rate of sodium there is a similar reduction of influx rate of potassium, and, indeed, potassium content might fall if efflux exceeds influx. After sodium efflux returns to normal, however, potassium inclusion by the same pump also increases, thus returning cell potassium to normal. In leucocytes from our hypertensive patients the primary insult which resulted in the increase in sodium was not a reduction in rate constant but

presumably an increase in membrane permeability to sodium. Regardless of the initiating factor, however, the next steps are identical—namely, increased sodium efflux and potassium influx leading to a return to normal of cell potassium.

The significance of the disturbances in cellular sodium homeostasis is not clear, but if we assume that the changes in the sodium content of leucocytes are found in other cells then our findings may be relevant to the production or maintenance of hypertension. Increased sodium in smooth muscle has long been thought to cause the increase in peripheral resistance which is uniformly found in hypertension. Our findings indicate that there may be a different pattern of derangement of cellular sodium homeostasis in black patients with hypertension.

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Effect of naftidrofuryl on the metabolic response to surgery

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Abstract

In a randomised study of 34 patients undergoing elective operations of moderate severity naftidrofuryl infusion significantly improved postoperative nitrogen balance. The control group excreted 26.2 ± 2.7 g nitrogen in the first three postoperative days. A group treated with naftidrofuryl excreted 18.0 ± 1.6 g nitrogen in the same period ($p < 0.0005$). The preoperative nutritional state of patients treated with naftidrofuryl did not differ from that of the controls.

Though hormonal changes causing an improvement in nitrogen balance could not be excluded by this study, the results show that naftidrofuryl infusion may stimulate postoperative catabolism of endogenous carbohydrate and fat, thus sparing tissue protein.

Introduction

Increased urinary excretion of nitrogen and reduced synthesis of tissue protein are accepted features of the metabolic response to injury.^{1 2} It is widely recognised that this alteration in protein metabolism leads to increased morbidity and mortality in injured patients, and hyperalimentation with protein and energy sources has been advocated as a means of improving prognosis after surgery.^{3 4} Though intensive nutritional support may

improve nitrogen balance postoperatively, the evidence that it will significantly alter outcome remains unconvincing. Several workers have suggested that inhibition of intracellular metabolic pathways may be the basis of abnormal protein metabolism after injury.⁵⁻⁷ Pharmacological stimulation of cellular metabolism may therefore be a more specific means of improving nitrogen balance. Naftidrofuryl (Praxilene) may stimulate cellular metabolism after injury. We decided to investigate the possibility that this drug might modify postoperative nitrogen metabolism.

Patients and methods

Informed consent was obtained from 34 patients undergoing elective operations of moderate severity. Only patients who reported no preoperative weight loss were considered for study. They were weighed and their skinfold thicknesses measured in the four positions described by Durnin and Rahaman.⁸ These measurements were used to derive fat-free mass. They were then randomised into a control group or a treatment group according to the last digit of their hospital case number. On the morning of operation a 24-hour urine collection was started, and daily collections were continued for the study period, which was three days. Total urinary nitrogen was estimated by the method of Fleck.⁹ Plasma urea and electrolyte concentrations were measured daily.

Both groups received similar amounts of blood in the perioperative period and a standard fluid regimen consisting of isotonic dextrose and saline for three days postoperatively. Only water was permitted by mouth. During the study the treatment group received twice-daily infusions of 200 mg naftidrofuryl given over one to two hours. The first infusion began with the induction of anaesthesia. A standard anaesthetic technique was used throughout.

Results

The 19 control patients undergoing operations of moderate severity excreted 26.2 ± 2.7 g (mean $\pm$ 2 SEM) of nitrogen in the three days

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