DECREASED OUABAIN-SENSITIVE ADENOSINE TRIPHOSPHATASE ACTIVITY IN THE ERYTHROCYTE MEMBRANE OF PATIENTS WITH CHRONIC RENAL DISEASE

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SUMMARY

1. Ouabain-sensitive ATPase (adenosine triphosphatase) activity was measured in the erythrocyte membranes of twenty patients with chronic renal disease. Decreased activity was found in nineteen of the twenty patients. The average decrease was 38%.

2. In three patients erythrocyte sodium concentration exceeded 9.5 mmol/l of RBC and these patients had the most marked decreases in ouabain-sensitive ATPase activity.

3. By contrast, in only two of 100 patients admitted to a general medical ward was erythrocyte sodium concentration greater than 9.5 mmol/l of RBC.

4. Ouabain-insensitive and calcium-activated components of erythrocyte membrane ATPase were unaffected by chronic renal disease.

Key words: chronic renal disease, uraemia, calcium-activated ATPase, ouabain-sensitive ATPase, erythrocyte sodium.

The concentration of sodium within the erythrocyte is 20-fold less than that in the plasma. This steep concentration gradient is maintained by continued active transport of sodium out of the erythrocytes (Hoffman, 1966). The enzyme responsible for this active sodium efflux is a sodium,potassium-activated ouabain-sensitive component of the ATP-hydrolysing enzyme system (Katz & Epstein, 1968; Skou, 1965). Evidence is accumulating that another calcium-activated component of this enzyme system is responsible for calcium efflux from the erythrocyte (Schatzman & Vincenzi, 1969). Welt, Smith, Dunn, Czerwinski, Proctor, Cole, Balfe & Gitelman (1967) reported that in some uraemic patients erythrocyte sodium concentration was increased and this was coupled with a decrease in the rate constant for sodium efflux and a decrease in ouabain-sensitive ATPase (adenosine triphosphatase) activity in the erythrocyte membranes. The incidence of this defect in uraemia is uncertain. Initially it was estimated...
that 25% of patients with uraemia had an erythrocyte transport defect as indicated by a high erythrocyte sodium concentration ([\(\text{Na}_e\)]); later reports of a similar defect in three healthy Negro kindreds in North Carolina (Balfe, Cole & Welt, 1968) raised the possibility that the initial estimates of the frequency of a high [\(\text{Na}_e\)] in uraemia were falsely elevated by the inclusion in the original studies of Negro patients with a genetic form of erythrocyte transport defect. We have undertaken to survey the incidence of a high [\(\text{Na}_e\)] in a uraemic population and to compare this with the incidence in a large group of patients with a variety of other disease states.

Most of the research on erythrocyte cation transport in uraemia has focused on patients with an elevation of [\(\text{Na}_e\)]. Smith & Welt (1970) have suggested, however, that uraemic patients with a high [\(\text{Na}_e\)] may represent only one end of a positively skewed distribution curve for [\(\text{Na}_e\)], rather than a separate population of patients. The present paper reports on the assay of various components of ATPase in the erythrocyte membranes of uraemic patients in which [\(\text{Na}_e\)] falls within the normal range, as well as those with an elevation of [\(\text{Na}_e\)].

**METHODS**

*Patient selection*

Patients for this study were drawn from the wards and clinics of the Queen Mary Veterans Hospital and the Royal Victoria Hospital, Montreal, Quebec. An attempt was made to select a heterogeneous group of patients with chronic renal disease. Their ages ranged from 19 to 92, and serum creatinine concentrations from 3.0 to 14.2 mg/100 ml. The average time since chronic renal disease was first diagnosed ranged from 6 weeks to 5 years, with a mean of 2 years. Patients with acute renal failure were excluded from the study, as were patients receiving chronic dialysis or who had been recently transfused. The normal controls were laboratory personnel and house staff of both sexes, ranging in age from 23 to 46.

Blood was always drawn from the control within 5 min of the time it was drawn from the patient, and in all subsequent steps in the study, patient and control blood samples were treated identically.

*Measurement of intracellular electrolytes*

Fresh heparinized blood (10 ml) was centrifuged at 7500 rev./min in a refrigerated centrifuge at 4°C for 5 s, the plasma and buffy coat were aspirated, and the erythrocytes washed three times with approximately 10 vol of ice-cold tetramethylammonium chloride. Following the last wash, sufficient wash solution was added to adjust the packed cell volume (PCV) of the erythrocyte suspension to approximately 0.5, and the PCV of the suspension was determined in triplicate. The erythrocytes were then lysed, diluted with lithium diluent, and sodium was measured on an IL flame photometer. Intracellular sodium was expressed as concentration of sodium per litre of erythrocytes ('mmol/l of RBC'). All determinations were done in duplicate. Plasma trapping with this procedure, determined with inulin, was found to be less than 0.05% after three washes. Repeat determinations of erythrocyte sodium concentration on the same control revealed a variation of less than 1 mmol/l of RBC.

*Preparation of erythrocyte membranes*

Erythrocyte membranes were prepared by adding packed erythrocytes from which plasma
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anduffy coat had been removed, to 10 vol of ice-cold distilled water containing Tris buffer (5 mmol/l) at pH 7-6. The resulting haemolysate was stirred rapidly for 20 min at 4°C. The membranes from both the patient and the control were sedimented in the same refrigerated centrifuge (20 000 g for 20 min) and washed three times with a solution containing NaCl (0-017 mol/l) and Tris (5 mmol/l; pH 7-5). The membranes were then washed three times with Tris (5 mmol/l; pH 7-5), resuspended in 6 vol of Tris (5 mmol/l), and stored overnight at -20°C. The weight of the membrane suspension was determined on a Cahn electrobalance after 24 h of drying at 80°C in a vacuum oven.

ATPase assay was performed on both the control and patient membranes the morning after preparation.

**ATPase assay**

ATPase activity was assayed by incubating 0-5 ml of membrane suspension for 90 min in a shaking water bath at 37°C with ATP (disodium salt; 1 mmol/l; Sigma Chemical Co.), Tris (25 mmol/l; pH 7-45), magnesium (1 mmol/l) and appropriate concentrations of sodium, potassium and calcium. The enzyme reaction was stopped with ice-cold 7-5% trichloroacetic acid, the membranes were precipitated by centrifuging at 20 000 g for 15 min in a refrigerated centrifuge, and the inorganic phosphorus (Pi) released was measured by an AutoAnalyzer modification of the Lowry–Lopez technique (Lowry & Lopez, 1946). Enzyme activity was expressed as Pi released h⁻¹ (mg dry wt. of membrane suspension)⁻¹.

It was previously shown that sodium (75 mmol/l) and potassium (25 mmol/l) caused maximal activation of erythrocyte Na⁺, K⁺-activated ATPase (Cole & Dirks, 1971). Consequently, ouabain-sensitive ATPase activity was calculated as the difference between Pi released in a medium which contained sodium (75 mmol/l), potassium (25 mmol/l), Tris (25 mmol/l), magnesium (1 mmol/l), ethanedioxybis(ethylamine)-NN'-tetra-acetic acid (EGTA; 0-1 mmol/l) and ATP (1 mmol/l), and in a medium which contained ouabain (1 mmol/l), sodium (75 mmol/l), potassium (25 mmol/l), Tris (25 mmol/l), magnesium (1 mmol/l), EGTA (0-1 mmol/l) and ATP (1 mmol/l).

Maximal calcium activation of ATPase was obtained with calcium (0-15 mmol/l) present in the incubation medium. Calcium-activated ATPase activity was calculated as the difference in Pi released between a medium which contained ouabain (1 mmol/l), Tris (25 mmol/l), magnesium (1 mmol/l), EGTA (0-1 mmol/l), calcium (0-15 mmol/l) and ATP (1 mmol/l), and a similar medium from which calcium was omitted.

Blanks consisting of boiled membrane suspension were included with each experiment. All determinations were done in duplicate.

Plasma diffusible calcium was measured on an atomic absorption spectrophotometer after high-pressure ultrafiltration of the plasma at constant pH, Pco₂, and temperature (Gonda, Morgan & Beck, 1963).

**RESULTS**

**Intracellular sodium concentration in uraemia**

The concentration of sodium within the erythrocyte ([Na₃]) was measured in twenty patients with uraemia and in twenty controls. The results are shown in Fig. 1. The mean [Na₃] in the twenty patients was 7·2±0·6 (SEM) mmol/l of RBC and in the twenty controls 5·6±0·3
(SEM) mmol/l of RBC. In three of the twenty patients $[Na_c]$ was more than three standard deviations above the mean of the control values.

Intracellular sodium concentration in other disease states

A high $[Na_c]$ has now been reported in several disease states other than uraemia. In order to determine the incidence of a high $[Na_c]$ in a general medical population, we studied 100 consecutive admissions to the general medical ward of a veterans' hospital. The majority of these patients were over the age of 70 and had disease involving multiple organ systems. Patients who had chronic renal disease, as indicated by elevation of the blood urea nitrogen or plasma creatinine, were excluded from this part of the study. The distribution of $[Na_c]$ in these 100 patients is shown in Fig. 2. In two of the patients $[Na_c]$ was more than three standard deviations above the mean in the control series.

![Fig. 1. Erythrocyte sodium concentration $[Na_c]$ in twenty patients with uraemia and twenty control subjects. $\bar{x}$ is the mean value.](image)

Ouabain-sensitive ATPase activity in uraemia

Measurements were made of the ouabain-sensitive ATPase activity in the erythrocyte membranes of twenty patients with uraemia. A control was included with each assay and all results were expressed as a patient/control ratio. The mean patient/control ratio for ouabain-sensitive ATPase activity in the entire uraemic group was 0.62. This ratio was significantly different from 1.00 with a probability less than 0.001 ($t = 7.4$). Nineteen of the twenty uraemic subjects had a ouabain-sensitive ATPase activity in their erythrocyte membranes which was lower than that of the control value (Table 1). In uraemic patients with $[Na_c]$ exceeding
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9.5 mmol/l of RBC the mean ouabain-sensitive ATPase patient/control ratio was 0.53, compared with 0.64 in patients with [Na\textsubscript{e}] less than 9.5 mmol/l of RBC (Fig. 3). The mean ouabain-sensitive ATPase activity in the erythrocyte membrane of the twenty patients with uraemia was 65±10 (SEM) nmol of P\textsubscript{i} h\textsuperscript{-1} (mg dry wt. of membrane suspension)\textsuperscript{-1}.

Clinical correlation

Various routine biochemical and haematological measurements were made in the patients at the time of the study, as well as careful note being made of any medication. No significant correlation was found (\(P>0.05\) in all instances) between the extent of the decrease in ouabain-sensitive ATPase and the serum sodium, potassium, chloride, blood urea nitrogen, or creatinine, the CO\textsubscript{2} combining power, or the serum calcium or phosphorus. There was a weak correlation (0.02 < \(P<0.05\)) between the PCV and the extent of the decrease in ouabain-sensitive ATPase. Most of the patients were receiving multiple medications, but no pattern could be seen between any particular drug and the extent of the decrease in ouabain-sensitive ATPase activity.

Other components of ATPase

Other components of the ATP-hydrolysing enzyme system were also examined. The ouabain-insensitive component of ATPase is not associated with active sodium or potassium transport. The ouabain-insensitive ATPase activity in the erythrocyte membranes of the twenty patients was 29±5 (SEM) nmol of P\textsubscript{i} h\textsuperscript{-1} (mg dry wt. of membrane suspension)\textsuperscript{-1}. This was not significantly different (\(t=1.11\); \(P>0.10\)) from the ouabain-insensitive ATPase activity in the erythrocyte membranes of the twenty controls of 36±4 (SEM) nmol of P\textsubscript{i} h\textsuperscript{-1} (mg dry wt. of membrane suspension)\textsuperscript{-1}.

A calcium-activated component of ATPase, which has been reported to be associated with calcium transport in the erythrocyte, was also assayed. The mean calcium-activated ATPase
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<th>Patient</th>
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<th>Blood urea nitrogen (mg/100 ml)</th>
<th>Creatinine (mmol/l)</th>
<th>Sodium (mmol/l)</th>
<th>Potassium (mmol/l)</th>
<th>Chloride (mmol/l)</th>
<th>CO₂ combining power (mmol/l)</th>
<th>Calcium (mg/100 ml)</th>
<th>Phosphorus (mg/100 ml)</th>
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\(\bar{x} \quad 65 \quad 104 \quad 0.62\)

SEM \(10.8 \quad 13 \quad 0.05\)

(1) Expressed as nmol of P₄ h⁻¹ (mg dry wt. of membrane suspension)⁻¹.
activity in the erythrocyte membranes of the twenty uraemic patients was 64±11 (SEM) nmol of P_i h^{-1} (mg dry wt. of membrane suspension)^{-1}, a value which was not significantly different (t = 1.06; P>0.10) from the corresponding control value of 81±11 (SEM) nmol of P_i h^{-1} (mg dry wt. of membrane suspension)^{-1}.

No correlation was found between the calcium-activated ATPase activity in the patients and total plasma calcium, plasma diffusible calcium (measured in eight of the patients) or alkaline phosphatase.

![Graph](image)

**Fig. 3.** Mean patient/control ratio for ouabain-sensitive ATPase activity in seventeen uraemic patients with [Na\_i] less than 9.5 mmol/l of RBC, and in three uraemic patients with [Na\_i] greater than 9.5 mmol/l of RBC.

**DISCUSSION**

Abnormalities in erythrocyte cation transport in uraemia were first reported by Welt, Sachs & McManus (1964). Subsequent investigations revealed that 25% of patients with uraemia had a higher than normal concentration of sodium within their erythrocytes coupled with a decrease in the rate constants for sodium efflux and potassium influx, and a decrease in the ouabain-sensitive component of ATPase in the erythrocyte membrane (Welt et al., 1967). Villamil, Retton & Kleeman (1968) have reported a 14% decrease in the rate constant for sodium efflux in the erythrocytes of uraemic patients, and an increased gain of sodium by the erythrocyte during cold storage.

In the present study we have found that nineteen out of twenty patients with a creatinine amount over 3.0 mg/100 ml had a decrease in the ouabain-sensitive ATPase activity of their erythrocyte membranes. Three of the twenty patients had [Na\_i] greater than 9.5 mmol/l of RBC.
Severe hyponatraemia and hypokalaemia can result in alterations in erythrocyte sodium transport, and consequently in changes in intracellular sodium (Levin, Rector & Seldin, 1972). The majority of our patients had serum sodium and potassium values within the normal range at the time of our study (Table 1) and in none did the serum sodium or potassium concentrations approach those studied by Levin et al. (1972).

Levin et al. (1972) have also shown that, in vitro, low bicarbonate results in a decreased rate of sodium flux into the erythrocyte, and consequently a decreased intracellular sodium concentration. Twelve of our twenty patients had a CO₂ combining power less than 24 mmol/l. There was no significant difference in the decrease of erythrocyte membrane ouabain-sensitive ATPase activity between these patients and the eight patients with a CO₂ combining power over 24 mmol/l. There was, however, a statistically significant difference ($t = 2.41; P < 0.02$) in [Na⁺] between these two groups of patients. The mean [Na⁺] in the twelve patients with a CO₂ combining power less than 24 mmol/l was 6.0 mmol/l of RBC, while in the remaining eight patients the mean [Na⁺] was 9.0 mmol/l of RBC. At this point, it cannot be determined whether the decrease in the erythrocyte membrane ouabain-sensitive ATPase in the uraemic patients with a low CO₂ combining power is a consequence of a decrease in sodium influx resulting from acidosis, or if it is the result of an unknown uraemic toxin causing a primary decrease in ouabain-sensitive ATPase. The latter hypothesis is favoured for two reasons. In a previous study we have shown that incubation of normal erythrocytes in buffered uraemic plasma induces a defect in ouabain-sensitive ATPase activity in the normal erythrocytes (Cole, Balfe & Welt, 1968). In the present study a decrease in ouabain-sensitive ATPase activity in the erythrocyte membrane is noted both in patients with normal and with low CO₂ combining power. Thus we would suggest that a decrease in erythrocyte membrane ouabain-sensitive ATPase is one of the primary manifestations of the uraemic state. In those patients who exhibit acidosis, there is an additional decrease in erythrocyte sodium influx, so that in these patients [Na⁺] tends not to be elevated.

Active sodium transport defects in the erythrocyte have been identified in an increasingly lengthy list of disease states, including such diverse entities as cystic fibrosis (Balfe et al., 1968), third-degree burns (Proctor, Smith, Cole & Welt, 1967), metastatic malignancy (Welt et al., 1967), hyperthyroidism (Smith & Samuel, 1970) and haemolytic anaemia (Zachowsky, Oski, Shaafi, Shahet & Nathan, 1968). The incidence of an erythrocyte sodium transport defect, which in its most severe form is indicated by a high [Na⁺], has not previously been studied systematically in a general medical population. In the present study we measured [Na⁺] in 100 consecutive admissions to the general medical ward of a Canadian veterans’ hospital. In only two of these patients was [Na⁺] greater than 9.5 mmol/l of RBC. Neither of these patients had any of the specific diseases enumerated above. One patient died with a cerebrovascular accident a few days after [Na⁺] was measured. The other patient, with alcoholism, chronic bronchitis and pneumonia, recovered and was lost to follow-up.

The current study was restricted to Caucasian patients. It has been reported that in 13% of the Negro population in North Carolina [Na⁺] is greater than 10.5 mmol/l of RBC (Balfe, Cole, Smith, Graham & Welt, 1968). This hereditary form of sodium transport abnormality was apparently unassociated with any disease state, and can be separated from the pathological form of erythrocyte transport defect by detailed sodium transport studies. In the last 5 years, we have measured [Na⁺] in over 200 healthy Caucasian controls and never recorded a value greater than 9.5 mmol/l of RBC.
Metabolic abnormalities in the erythrocyte in uraemia have been identified by many investigators (Zachowsky et al., 1968; Desforges, 1970; Theil, Brodine, Doolan & Martinez, 1961). The relationship between these abnormalities and the decrease in ouabain-sensitive ATPase reported here remains to be elucidated. Other components of the ATP-hydrolysing enzyme system in the erythrocyte membrane, specifically the ouabain-insensitive and the calcium-activated components, were found to be unchanged in uraemia. The latter component of ATPase has been shown to be associated with calcium efflux in the erythrocyte (Schatzman & Vincenzi, 1969). In view of the abnormalities of calcium metabolism which are known to occur in uraemia, it was speculated that abnormalities in calcium transport might occur in the erythrocyte and be revealed as changes in the activity of calcium-activated ATPase. No such changes could be identified in the present study.

Sodium transport abnormalities in uraemia are not limited to the erythrocyte. Tyler (1970) has suggested that defects in the Na⁺-K⁺ ion pump in cerebral cells may be responsible for the numerous metabolic changes seen in uraemic encephalopathy. Minkoff, Gaertner, Darab, Mercier & Levin (1972) have demonstrated decreased Na⁺,K⁺-activated ATPase activity in brain tissue from uraemic rats. Bricker and others have identified a toxic factor in uraemic plasma that depresses proximal tubular sodium reabsorption (Bricker, 1972).

In view of the widespread occurrence of Na⁺,K⁺-activated ATPase in many tissues, it may well be that many of the abnormalities in sodium transport in uraemia result from a decrease in the activity of this enzyme system.

ACKNOWLEDGMENT

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REFERENCES


