A study *in vitro* of the sodium pump in fulminant hepatic failure

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Summary

1. The mechanism underlying the raised leucocyte sodium content in fulminant hepatic failure was studied by measurement of sodium fluxes, \((\text{Na}^+ + \text{K}^+)\)-dependent adenosine triphosphatase activity, and leucocyte ATP content.

2. The rate constant for sodium efflux in the leucocytes was significantly reduced, and attributable to reduced activity of the enzyme \((\text{Na}^+ + \text{K}^+)\)-ATPase. Leucocyte ATP content was not significantly different from that of control cells.

3. Incubation of cells from patients in the sera of normal subjects resulted in a reversal of these changes. Inhibition of the leucocyte sodium efflux rate constants and \((\text{Na}^+ + \text{K}^+)\)-ATPase of normal cells was achieved by incubation in sera from patients.

4. We suggest that the raised sodium content of leucocytes in fulminant hepatic failure is attributable to a defective sodium pumping mechanism, possibly due to a circulating toxin.

Key words: adenosine triphosphate, \((\text{Na}^+ + \text{K}^+)\)-dependent adenosine triphosphatase, fulminant hepatic failure, leucocyte, sodium.

Abbreviations: ATP, adenosine triphosphate; \((\text{Na}^+ + \text{K}^+)\)-ATPase, \((\text{Na}^+ + \text{K}^+)\)-dependent adenosine triphosphatase.

Introduction

We have previously shown that the sodium content (mmol/kg cell dry wt.) and concentration of peripheral blood leucocytes (mmol/l of cell water) was increased up to threefold in fulminant hepatic failure (Alam, Wilkinson, Poston, Moodie & Williams, 1977). The sodium concentration of normal cells is maintained lower than that of the extracellular fluid by the membrane-bound sodium pump. At least 75% of the total sodium efflux from leucocytes is affected by an ouabain-sensitive component (Hilton & Patrick, 1973), identified with the \((\text{Na}^+ + \text{K}^+)\)-ATPase enzyme (EC 3.6.1.3), the remaining 25% being still unexplained. In our previous study we found that the raised leucocyte sodium content was usually accompanied by a diminished potassium content, suggesting inhibition of \((\text{Na}^+ + \text{K}^+)\)-ATPase, although this was not directly estimated. A malfunction of \((\text{Na}^+ + \text{K}^+)\)-ATPase could result from either direct inhibition of the enzyme or a low concentration of its substrate, ATP. A raised leucocyte sodium content could also result from an increase in the passive influx of sodium ions into the cell. We have therefore studied the sodium and potassium content and concentration, the rate of sodium influx, the \((\text{Na}^+ + \text{K}^+)\)-ATPase activity and the ATP content of leucocytes in fulminant hepatic failure. The reasons for studying the leucocyte rather than the more commonly used erythrocyte as a cell model have been stressed by other workers (Baron, 1972; Edmondson, Thomas, Hilton, Patrick & Jones, 1975).

Patients and methods

Twenty-eight patients with fulminant hepatic failure were studied: 14 with viral hepatitis, 12 with paracetamol (acetaminophen) overdose, one with halothane-associated hepatic failure, and one with acute fatty liver of pregnancy. At the time of
investigation 25 patients had grade IV, and three grade III, hepatic encephalopathy (Trey & Davidson, 1970).

Leucocytes were isolated from peripheral blood as described by Baron & Ahmed (1969), by differential sedimentation of erythrocytes with dextran. Handling of the blood from the control subjects and the patients was identical, and the blood was not stored.

The intracellular sodium and potassium content and concentration were estimated by the method previously described (Alam et al., 1977) in leucocytes isolated from 30 ml of whole blood.

**Sodium fluxes**

The method described by Hilton & Patrick (1973) was used for the determination of both leucocyte sodium influx and the sodium efflux rate constants.

Isolated leucocytes were resuspended in a tissue culture medium (TC 199, Wellcome Reagents Ltd), the sodium concentration of which was adjusted to 134–136 mmol/l and potassium to 5.4–5.8 mmol/l respectively and the pH to 7.3–7.4. The sodium concentration of the medium was not adjusted to that of the patients' plasma, which was often lower than 134 mmol/l, as the rate of leucocyte sodium efflux has been shown to be unaltered by a sodium concentration as low as 103 mmol/l (Hilton & Patrick, 1974). Leucocyte sodium influx, being a passive process, is proportional to the external sodium concentration. However, the error introduced by bathing the cells in a medium of physiological sodium concentration (approximately 10 mmol/l greater than that of the patients) would be at the most a few per cent of the total calculated influx. Leucocyte sodium influx is, however, considerably affected by small changes in the osmolality of the external medium (Hilton & Patrick, 1974) and the osmolality of the TC 199 was therefore carefully adjusted to that of the patient's plasma by using choline chloride.

**Sodium efflux.** To the leucocytes isolated from 60 ml of whole blood, 20 μCi of 22NaCl (The Radiochemical Centre, Amersham, Bucks., U.K.) was added to the cells and incubated at 37°C for 20 min. After centrifugation (room temperature, 160 g, 3 min), the leucocytes were washed twice in TC 199 and after the final centrifugation were resuspended in a further 8 ml of medium. Ouabain was added to half the cells at zero time to final concentration 0.1 mmol/l. Aliquots of the cells were subsequently removed at 4 and 12 min into specially prepared, preweighed 'lay flat' polythene tubes (Baron & Ahmed, 1969), which were immediately immersed in ice and then centrifuged (0°C, 160 g, 2 min). After careful removal of the supernatant, the tubes were heat-sealed and counted for radioactivity in an auto-scintillation spectrometer (Packard model 578). After radioactivity counting the seal on the tube was broken and the cells were dried to a constant weight at 100°C.

Hilton & Patrick (1973) have determined that the efflux of radioactive sodium from 22Na-loaded leucocytes falls off exponentially over 20 min. The rate constant for sodium efflux is thus the slope of the relationship between ln(c.p.m.) and time. By sampling cells every 4 min over 20 min, we have confirmed this exponential relationship, both in leucocytes from six healthy control subjects (e.g. Fig. 1) and in those from four patients with fulminant hepatic failure. The correlation coefficient (r) for the decay curve was greater than 0.99 in all cases. In view of this linearity Hilton & Patrick (1973) suggested that only two points are necessary to calculate the efflux rate constant, and consequently in most cases in this study leucocytes were removed and counted for radioactivity at 4 and 12 min only. Rate constants were calculated for the total sodium efflux ($k_1$), and the efflux in the presence of ouabain ($k_2$). The rate constant for the ouabain-sensitive component of sodium efflux ($k_s$) is therefore given by ($k_1-k_2$).

**Sodium influx.** At zero time, 5 μCi of 22NaCl was added to the leucocyte suspension isolated from 20 ml of whole blood. At 7½ min the specimen was immersed in ice and then centrifuged (0°C,
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160 g, 1 min). An aliquot of the supernatant was removed for radioactivity counting and the leucocytes were washed once in ice-cold TC 199. After transfer to a preweighed 'lay flat' polythene tube, the suspension was centrifuged (0°C, 160 g, 1 min) and the cells were counted and dried as described above. According to Hilton & Patrick (1973) influx is assumed to terminate when the cell plug forms, some 30 s after the onset of centrifugation, and therefore 8 min after addition of the isotope. The influx of sodium may be calculated from the uptake of $^{22}\text{Na}$ from the medium over this period. Taking into account the active efflux of sodium occurring during that time, this may be calculated by substitution in the equation

$$m = \frac{k_1 x}{1 - e^{-k_1 t}}$$

in which $m$ = sodium influx (mmol h$^{-1}$ kg$^{-1}$ cell dry wt.), $x$ = observed uptake of sodium (mmol/kg cell dry wt.), $t$ = time in hours (0·133 in present experiments) and $k_1$ = rate constant for total sodium efflux (h$^{-1}$).

(\(\text{Na}^+ + \text{K}^+\))-ATPase activity

Leucocyte (\(\text{Na}^+ + \text{K}^+\))-ATPase activity was evaluated in 16 patients in the leucocytes isolated from 40 ml of whole blood, and run concurrently with the study of fluxes and of ATP content. The final leucocyte suspension was equally divided between two preweighed tubes. After centrifugation (room temperature, 1000 g, 3 min), the wet weight of each leucocyte isolate was determined. The cells were then lysed by hypotonic shock (1 ml of distilled water, 3 min) and isotonicity was restored with 3 ml of quadruple-strength Hartmann's solution. This leucocyte isolate, rather than a purified membrane fraction, was used for ATPase estimation in order to avoid removal of a possible loosely bound inhibitor. One aliquot was resuspended in 4·4 ml of an incubation medium designed by Bonting, Simon & Hawkins (1961) for optimum ATPase activity, the concentrations of ATP and Mg$^{2+}$ being in excess of those likely to be found in vivo (ATP 2 mmol/l, Mg$^{2+}$ 1 mmol/l, K$^+$ 5 mmol/l, Na$^+$ 58 mmol/l, CN$^-$ 10 mmol/l, EDTA 0·1 mmol/l, Tris 92 mmol/l, osmolality 314 mmol/kg, pH 7·5). The second aliquot was resuspended in 4·4 ml of the same medium, but with ouabain added to a final concentration of 0·1 mmol/l. The addition of ATP to the medium and adjustment of the pH were carried out immediately before the experiment, as ATP was found to dissociate within a few days if left in solution. The addition of cyanide to the incubation media was designed to abolish any alkaline phosphatase activity which might occur at pH 7·5. After incubation for 1 h at 37°C all enzyme activity was abolished by precipitation of protein with 0·2 ml of 71% perchloric acid added to each tube. The precipitated protein was removed after centrifugation (room temperature, 1000 g, 3 min) and estimation of orthophosphate in the supernatant carried out by Bartlett's (1959) modification of the colorimetric method of Fiske & Subbarow (1925). Leucocyte ATPase activity was expressed as µmol of inorganic phosphate (P$_i$) released h$^{-1}$ g$^{-1}$ cell wet wt. and the (\(\text{Na}^+ + \text{K}^+\))-ATPase component of the total ATPase activity calculated as the difference in the ATPase activity in the ouabain-free and the ouabain-rich medium.

Cross-incubation studies

We studied the possibility that a circulating toxin may play a role in the pathogenesis of the observed leucocyte abnormalities by incubating the leucocytes from 90 ml of whole blood from healthy control subjects in the serum of patients with fulminant hepatic failure for 120 min at 37°C, during which the suspension was repeatedly agitated by pipette. The pH of the incubation sera did not change appreciably during this period. After washing once in TC 199, the rate of sodium influx, the sodium efflux rate constants, and the (\(\text{Na}^+ + \text{K}^+\))-ATPase component of the total ATPase activity were measured. Similarly, leucocytes from patients with fulminant hepatic failure were incubated in serum from healthy subjects over 120 min and, after washing in TC 199, the sodium fluxes and the (\(\text{Na}^+ + \text{K}^+\))-ATPase activity were evaluated.

As a control for this cross-incubation study the sodium fluxes and (\(\text{Na}^+ + \text{K}^+\))-ATPase activity were measured in normal leucocytes previously incubated for 120 min in the serum of a different control subject, and also in leucocytes from patients with fulminant hepatic failure which had been incubated over the same period in the patients' own serum.

Leucocyte ATP content

To measure leucocyte ATP content a weighed aliquot of leucocytes isolated from 30 ml of whole blood was lysed by hypotonic shock (distilled water, 2 min). The sample was then deproteinized in ice-cold 10% perchloric acid. ATP was determined with an ATP test combination kit, designed for measurements in whole blood [Boehringer Corporation (London) Ltd], 1 ml of the leucocyte
Table 1. Electrolyte estimations and sodium flux rate constants

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Plasma electrolyte concentration (mmol/l)</th>
<th>Leucocyte electrolyte content (mmol/kg cell dry wt.)</th>
<th>Leucocyte sodium efflux rate constants (h⁻¹)</th>
<th>Sodium influx (mmol h⁻¹ kg⁻¹ cell dry wt.)</th>
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<td>K</td>
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<td>K</td>
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<td>26/F</td>
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<tr>
<td>20</td>
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<td>18/F</td>
<td>135</td>
<td>3.1</td>
<td>153</td>
<td>370</td>
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</tbody>
</table>

Mean ± SEM  
154 ± 14 355 ± 8 2.92 ± 0.12 1.61 ± 0.10 1.27 ± 0.07 235 ± 15

Mean control value ± SEM  
80 ± 1 385 ± 2 3.80 ± 0.06 2.79 ± 0.07 1.01 ± 0.03 294 ± 10

P (patient vs control value)  
<0.001 <0.005 <0.001 <0.001 <0.005 <0.005

Results

Leucocyte sodium, potassium and water content

In agreement with the previously published study (Alam et al., 1977), the leucocyte sodium content in our patients was significantly higher, at 154 ± 14 mmol/kg cell dry wt., than the value (80 ± 1 mmol/kg cell dry wt.) in the control subjects (P < 0.001, Table 1). The sodium concentration was also raised at 55 ± 4 mmol/l of cell water, compared with 30 ± 0.2 in the control subjects (P < 0.001, Table 1). Conversely, the leucocyte potassium content was lower than that of the control group (355 ± 8 mmol kg⁻¹ cell dry wt. compared with 385 ± 2 for control subjects; P < 0.005, Table 1), as was the potassium concentration (130 ± 4 mmol/l of cell water compared with 144 ± 0.6 for control subjects, P < 0.001, Table 1).

In the group of 24 healthy individuals (13 female, 11 male, aged 22–38 years) the leucocyte sodium and potassium contents were 80 ± 1 mmol/kg cell dry wt. and 385 ± 2 mmol/kg cell dry wt. respectively, and the sodium and potassium concentrations were 30 ± 0.2 mmol/l of cell water and 144 ± 0.6 mmol/l of cell water respectively. The cell water content of the control group was 2.67 ± 0.70 l/kg cell dry wt. These figures agree closely with those reported by Edmondson, Thomas, Hilton, Patrick & Jones (1974).
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Leucocyte sodium fluxes

The rate constant for total sodium efflux was significantly reduced in the patients (2.92 ± 0.12 h⁻¹) as compared with control values (3.80 ± 0.06 h⁻¹) (P < 0.001, Table 1, Fig. 2). This appeared to be entirely due to a reduced ouabain-sensitive component (1.61 ± 0.10 h⁻¹, compared with control value 2.79 ± 0.07 h⁻¹; P < 0.001), since the quantitatively less-important ouabain-insensitive efflux was significantly raised (1.27 ± 0.07 h⁻¹ as compared with the control value of 1.01 ± 0.03 h⁻¹; P < 0.005).

The present results were also analysed with respect to renal failure (arbitrarily defined as a plasma creatinine concentration of >0.02 mmol/l). There was no difference in the ouabain-sensitive sodium efflux between the two groups (1.59 ± 0.10 h⁻¹ for eight patients with renal failure and 1.62 ± 0.15 h⁻¹ for the 16 patients without renal failure).

The mean value for the rate of sodium influx in the patient group was significantly reduced (235 ± 15 mmol h⁻¹ kg⁻¹ cell dry wt. as compared with the control value 294 ± 10 mmol/l, a slightly lower value than that reported by Hilton & Patrick (1973) (359 ± 37 mmol h⁻¹ kg⁻¹ cell dry wt.).

Serial measurements of leucocyte sodium fluxes and the leucocyte sodium content in four patients showing improvement in both liver-function tests and level of consciousness in the days subsequent to their initial study showed gradual improvement towards normality (Table 2). The leucocyte sodium content was initially high in all but one patient, and the ouabain-sensitive sodium efflux rate constant was low in all. During the subsequent week, these abnormalities returned towards normal, the changes in sodium efflux being parallel to the expected alterations in leucocyte sodium content. The total leucocyte count ranged from 3.5 x 10⁹/l to 30.0 x 10⁹/l with polymorphonuclear cells from 65 to 93%. There was, however, no significant correlation between the percentage polymorphonuclear count and the leucocyte sodium content (r = 0.07).

Leucocyte (Na⁺ + K⁺)-ATPase activity and ATP content

The mean value for the leucocyte lysate (Na⁺ + K⁺)-ATPase was significantly lower in the 16 patients than in the 13 control subjects (6.9 ± 2.0 μmol of P, h⁻¹ g⁻¹ cell wet wt. and 20.3 ± 1.2; P < 0.001, Fig. 4). There was no significant correlation between the ouabain-sensitive sodium efflux rate constant and the leucocyte (Na⁺ + K⁺)-ATPase activity in the patients (r = 0.15).
TABLE 2. Serial measurements of leucocyte sodium content and ouabain-sensitive sodium flux rate constants in four patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Time after admission (days)</th>
<th>Grade of encephalopathy</th>
<th>Leucocyte sodium (mmol/kg cell dry wt.)</th>
<th>Ouabain-sensitive sodium efflux rate constant (h⁻¹)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>IV</td>
<td>93</td>
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<tr>
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<td>7</td>
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<td>38</td>
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<tr>
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<td>III</td>
<td>65</td>
<td>1.80</td>
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<td>2</td>
<td>8</td>
<td>0</td>
<td>74</td>
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</table>

The mean value for leucocyte (Na⁺ + K⁺)-ATPase activity in the 13 healthy control subjects (20.3 ± 1.2 μmol of P₁ h⁻¹ g⁻¹ cell wet wt.) is comparable with a value of 73 ± SD 17 μmol of P₁ g⁻¹ cell dry wt. reported by Block & Bonting (1964), the wet weight of leucocytes being approximately four times their dry weight. The mean value for (Na⁺ + K⁺)-ATPase activity was almost ten times that obtained for erythrocytes in an equivalent study by Bonting et al. (1961). This is not unexpected since the total leucocyte sodium flux rate may be up to 15 times greater than that of erythrocytes (Hilton & Patrick, 1973).

The mean value for the ATP content of the leucocytes for the 15 healthy control subjects was 1.49 ± 0.05 mg of ATP/g cell wet wt. In a study of leucocyte ATP in children with malnutrition, Yoshida & Metcoff (1967) found the control value for leucocyte ATP to be 4.82 ± 0.67 μmol/g of protein. Preliminary studies have shown that the protein content of wet leucocytes prepared as above is approximately 20% of their weight (unpublished observations). The values obtained in this study are therefore within the same range, though slightly higher than those of Yoshida & Metcoff (1967).

Cell-incubation studies

The incubation of leucocytes from healthy control subjects with the serum from patients with fulminant hepatic failure markedly inhibited both the ouabain-sensitive sodium efflux rate constant (1.15 ± 0.27 h⁻¹, n = 5) and the (Na⁺ + K⁺)-ATPase activity (4.6 ± 1.3 μmol of P₁ h⁻¹ g⁻¹ cell wet wt., n = 6). These changes were similar to those obtained when leucocytes from patients were incubated for a similar 2 h period in their own serum (ouabain-sensitive sodium efflux rate constant 1.55 ± 0.24 h⁻¹, n = 4) and (Na⁺ + K⁺)-ATPase activity 3.2 μmol of P₁ h⁻¹ g⁻¹ cell wet wt., n = 5).

Conversely, when leucocytes from the patients were incubated with serum from healthy control
subjects, the ouabain-sensitive sodium efflux rate constant (2.67 ± 0.21 h⁻¹, n = 5) and the (Na⁺ + K⁺)-ATPase activity (18.8 ± 3.8 μmol of P₄ h⁻¹ g⁻¹ cell wet wt., n = 5) returned to approximately 95% of the values obtained for the control group. Furthermore, these values did not differ significantly from those in a control study in which leucocytes from control subjects were incubated in the serum of another healthy control subject: ouabain-sensitive sodium efflux rate constant 2.88 ± 0.13 h⁻¹ (n = 4) and (Na⁺ + K⁺)-ATPase activity 18.1 ± 1.9 μmol of P₄ h⁻¹ g⁻¹ cell wet wt. (n = 7).

Discussion

As we wished to study the cell-membrane sodium pump, measurements of the (Na⁺ + K⁺)-ATPase activity in an isolated membrane fraction, rather than that of a crude leucocyte lysate, might have been preferable. However, in a study of erythrocyte sodium transport in uraemia, Kramer, Gospodinov & Kruck (1976) found that a loosely bound inhibitor of sodium transport was removed in the vigorous purification of the membrane fraction. We therefore used the crude leucocyte lysate so that such an inhibitory substance might remain bound. Since the (Na⁺ + K⁺)-ATPase activity thus measured was therefore not exclusively cell-membrane (Na⁺ + K⁺)-ATPase, the absence of a correlation between the observed (Na⁺ + K⁺)-ATPase activity and the ouabain-sensitive sodium efflux rate constant (a direct measurement of membrane function) was not unexpected. The reduction in rate constant for total sodium efflux suggests that the raised leucocyte sodium content in fulminant hepatic failure is due to inhibition of the active transport system for sodium. As might have been predicted from previous observations that the raised leucocyte sodium is often accompanied by a reduced potassium content (Alam et al., 1977), the impaired component of sodium efflux was that due to the (Na⁺ + K⁺)-ATPase. Moreover, the (Na⁺ + K⁺)-ATPase activity in the leucocyte lysate was reduced in the patients, even though the enzyme activity was assayed under conditions of excess substrate concentration. Leucocyte (Na⁺ + K⁺)-ATPase activity in fulminant hepatic failure is therefore inhibited independently of substrate availability.

In control subjects the mean total efflux rate calculated as the product of the rate constant k, and the intracellular sodium content, was 304 ± 7.31 mmol h⁻¹ kg⁻¹ cell dry wt. This is comparable with 294 ± 10 mmol h⁻¹ kg⁻¹ cell dry wt. for the influx rate. When the total efflux rate was calculated in the same way for the patients, a mean value of 450 ± 42 mmol h⁻¹ kg⁻¹ cell dry wt. was found, approximately twice that for the influx (235 ± 15 mmol h⁻¹ kg cell dry wt.). This implies that the cells from the patients were not in a steady state during the course of the experiment. Consequently the values for influx and efflux must be treated with caution. As patients' cells improved towards normality when incubated in normal serum, it is possible that removal of the patients' cells into standard tissue culture fluid initiates an increase in the efflux rate constant above that which existed in vivo, leading to an overestimation of the sodium efflux rate. The raised intracellular sodium concentration represents that which occurs in vivo, but the flux measurements may have moved away from these values during the incubation. Alternatively, it is possible that the increase in intracellular sodium represented an increase in a non-exchangeable or slowly exchangeable compartment of sodium which was not present in control leucocytes, and which would not equilibrate with ²²Na on incubation. Calculation of the total sodium efflux, using the total cellular sodium content, would therefore give inappropriately high values.

The inhibition of the sodium-transport mechanism may be due to a circulating toxin, since incubation of hitherto normal leucocytes in the serum of patients with fulminant hepatic failure resulted in gross abnormalities of the cells' sodium transport system, very similar to those seen in the patients' cells. The inhibition of the sodium efflux rate constant may therefore be effected by an abnormal plasma constituent. This substance appears to be a reversible inhibitor, as it may be removed from affected cells by incubation in normal sera.

Depletion of ATP did not appear to contribute to the low sodium efflux rate constant, as the ATP content was not significantly lower than in the control subjects and bore no relationship to the observed inhibition of the total sodium efflux rate constant. Leucocyte ATP did, however, correlate with the serum phosphate concentration, which was generally low in the patients studied. This low serum phosphate in fulminant hepatic failure confirms an earlier report from this laboratory (Knell, Pratt, Curzon & Williams, 1972). Thus hypophosphataemia may be a direct result of the intravenous administration of glucose during the patients' illness, as the serum phosphate concentration can fall profoundly with prolonged
parenteral nutrition (Sheldon & Gazyb, 1975; Tovey, Benton & Lee, 1977). Sheldon & Gazyb (1975) reported a correlation between serum inorganic phosphate and whole blood ATP concentrations in patients with hypophosphataemia and their ATP concentrations tended to be low.

A similar fall in the ouabain-sensitive efflux rate constant has been reported in both erythrocytes (Welt, Sachs & McManus, 1964; Kramer et al., 1976) and leucocytes from patients with chronic renal failure (Edmondson et al., 1975). Low sodium efflux rate constants have been described in essential hypertension (Edmondson et al., 1975), cystic fibrosis (Balfé, Cole & Welt, 1968), hyperthyroidism (Smith & Samuel, 1970) and in cases of severe burning (Proctor, Smith, Cole & Welt, 1967). Specific inhibition of (Na++K+)-ATPase has been reported in a variety of diseases (Balfé et al., 1968; Proctor et al., 1967), including chronic renal failure (Welt et al., 1964; Cole, 1973; Kramer, Backer & Kruck, 1974), and in renal failure this has also been attributed to the effect of a toxic metabolite, possibly one of the aromatic hydroxy acids (Kramer, Gospodinov & Kruck, 1972). In our study the secondary acute renal failure in eight out of 21 patients was not the explanation for the observed inhibition of sodium transport, which is to be expected as Francavilla, Albano, Mastrangelo, Coratelli, Palasciano & Amerio (1972) showed that inhibition of the (Na++K+)-ATPase occurred only in chronic as opposed to acute renal failure. The ouabain-insensitive component of the total sodium efflux rate constant was stimulated, which has not previously been described in any of the disease stages mentioned above in which leucocyte sodium is elevated. However, Kramer et al. (1976) have demonstrated an increased ouabain-insensitive efflux rate constant in the erythrocyte in uraemia, but this has not been described in a similar study by Welt et al. (1964). The stimulus for the raised ouabain-insensitive efflux rate constant may thus be some extrinsic factor. Bittar & Tallitsch (1976) have demonstrated that aldosterone stimulates both the ouabain-sensitive and -insensitive components of sodium transport in the barnacle muscle. The plasma aldosterone concentration is almost invariably raised in fulminant hepatic failure (Bernardi, Wilkinson, Poston, Wernze, Spech & Williams, 1977), so aldosterone may be responsible for the increased ouabain-insensitive efflux rate constant. On the basis of studies in the kidney tubules of the adrenalectomized rat, Schmidt, Schmid, Schmid & Dubach (1975) have suggested that aldosterone acts on the (Na++K+)-ATPase component of sodium transport alone. However, the effect of aldosterone in the ouabain-insensitive efflux rate constant in leucocytes is not yet known. This study involves leucocytes only and we do not imply that the abnormality is widespread amongst other tissues.

References


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Sodium pump in hepatic failure


