An attempt to predict daily erythrocyte lithium fluctuations

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SUMMARY

Erythrocyte lithium concentration, which is a better predictor of brain lithium levels than plasma lithium concentrations, possesses the disadvantage of precise hourly determination following the last intake. The variability in RBC lithium accumulation increases as the extracellular lithium concentration increases. This increase is also time dependent and it would be very useful if the pharmacokinetic rate constant were known. Unfortunately, low lithium levels do not allow measurements within confidence intervals.

In this work, we tried to determine, in vitro, the kinetic rate constants in erythrocytes of healthy volunteers.

Different high lithium loaded plasma-like media were used for an extrapolation procedure of constants allowing the determination of an erythrocyte load constant namely $K_0 = 0.0161 \pm 0.0005 \text{ h}^{-1}$ at corresponding plasma lithium concentrations.

The abnormalities of lithium transport determined by in vitro procedures would be very useful in understanding the etiology of affective illness. Lithium flux pre-controls corrected with this rate constant would be very helpful in enlarging laboratory time management.

INTRODUCTION

It is now well known that erythrocyte lithium concentrations are better predictors of brain lithium levels than plasma lithium concentrations (1–9). The variability in RBC lithium accumulation increases as the extracellular lithium concentration increases, so that differences between subjects become more evident with the use of higher extracellular lithium concentrations (10).

This work aims to determine, in vitro, erythrocyte loading rates for lithium by using high lithium loaded plasma-like media. Then these rates can be extrapolated for low lithium plasma values. Following a background correction, these extrapolated values could be very useful to predict RBC lithium accumulation at varying times. This study will be followed by an attempt to determine the influence of countertransport phenomena in low lithium containing plasma media.

MATERIALS AND METHODS

Determination of lithium ratio in vitro

Venous blood of 20 healthy volunteers was collected in sodium heparin. The blood was centrifuged at
Table I: High lithium loaded plasma-like media (five cases four each block).

<table>
<thead>
<tr>
<th>5 mM Li⁺</th>
<th>10 mM Li⁺</th>
<th>20 mM Li⁺</th>
<th>40 mM Li⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCl (5 mM)</td>
<td>KCl (5 mM)</td>
<td>KCl (5 mM)</td>
<td>KCl (5 mM)</td>
</tr>
<tr>
<td>*LiCl (5 mM)</td>
<td>*LiCl (10 mM)</td>
<td>*LiCl (20 mM)</td>
<td>*LiCl (40 mM)</td>
</tr>
<tr>
<td>Na₂HPO₄ (1 mM)</td>
<td>Na₂HPO₄ (1 mM)</td>
<td>Na₂HPO₄ (1 mM)</td>
<td>Na₂HPO₄ (1 mM)</td>
</tr>
<tr>
<td>Tris HCl (10 mM)</td>
<td>Tris HCl (10 mM)</td>
<td>Tris HCl (10 mM)</td>
<td>Tris HCl (10 mM)</td>
</tr>
<tr>
<td>Glucose (10 mM)</td>
<td>Glucose (10 mM)</td>
<td>Glucose (10 mM)</td>
<td>Glucose (10 mM)</td>
</tr>
<tr>
<td>Adenosine (10 mM)</td>
<td>Adenosine (10 mM)</td>
<td>Adenosine (10 mM)</td>
<td>Adenosine (10 mM)</td>
</tr>
<tr>
<td>*NaCl (125 mM)</td>
<td>*NaCl (120 mM)</td>
<td>*NaCl (110 mM)</td>
<td>*NaCl (90 mM)</td>
</tr>
</tbody>
</table>

2000 g for 15 min. Separated cells were washed twice for 10 min at 37°C with 10 volumes of cold 115 mM MgCl₂ solution, at a pH adjusted to compensate for the change in temperature.

The incubations were performed at 37°C on washed cells which were in different high lithium loaded (5 mM, 10 mM, 20 mM, 40 mM) plasma-like media (Table I).

The suspension was incubated at 37°C and at pH = 7.4 with orbital shaking (30 rpm) for 24 h during which samples were taken at different intervals. Cells and plasma were separated, washed with isotonic MgCl₂ and analyzed.

**Analytical procedures**

Lithium concentrations in red cell lysate plasma were determined by flame emission photometry (11).

**RESULTS**

Assuming that the potential across the RBC is constant and that Li⁺ is transported passively across the cell membrane, the intracellular concentration of Li⁺ will also increase when extracellular Li⁺ is raised. The results which were obtained at different hours are shown in Table II. The graphic presentation of these values are given in Figure 1.

The following zero order kinetic constants (K₀) were determined for the different lithium concentrations:

\[
K₀ (5 \text{ mM}) = 0.084 \pm 0.011 \\
K₀ (10 \text{ mM}) = 0.156 \pm 0.024 \\
K₀ (20 \text{ mM}) = 0.343 \pm 0.027 \\
K₀ (40 \text{ mM}) = 0.643 \pm 0.021 
\]

These values show a linear tendency \( K₀ = f (\text{mM}) \).