The profile of plasma rubidium concentrations after oral rubidium administration is not altered in manic patients. This suggests that the increased rate of rubidium uptake into erythrocytes occurs only into a small intracellular volume, since a more generalised increase in tissue rubidium uptake ought to lead to an observable increase in the rate of clearance of rubidium from the plasma. Hence, the changes we have found in erythrocyte $Na^+$, $K^+$-ATPase activity cannot be assumed to reflect changes occurring in any other specific organ, including the brain. The direct study of cation transport *in vivo* in neurons is obviously desirable but must await the development of suitable and sensitive non-invasive techniques, such as nuclear magnetic resonance spectroscopy.

## Conclusions

We have found an increase in the rate of uptake of rubidium into erythrocytes *in vivo* in unmedicated patients suffering from an acute manic illness. These patients fulfilled strict diagnostic criteria for acute mania, were suffering a significant symptomatic illness at the time of testing, and had received no medication before being studied. The changes we have found suggest that there is an increase in the *in-vivo* activity of $Na^+$,$K^+$-ATPase in the erythrocyte membrane in acute manic illness. This *in-vivo* model offers an extension of the *in-vitro* measurements of $Na^+$,$K^+$-ATPase activity used in previous studies. However, our data suggest that changes demonstrated in the erythrocyte membrane *in vivo* cannot necessarily be extrapolated to infer any similar changes in cation transport in the brain.

For acknowledgements, references and authors' details, see the following paper, on pp. 504–510

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# The Effect of Lithium on Cation Transport Measured *in vivo* in Patients Suffering from Bipolar Affective Illness

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We have investigated cation transport *in vivo* in patients being treated with lithium for bipolar affective illness by studying the disposition of rubidium after an oral load of rubidium chloride. The rate of erythrocyte cation transport was increased in the patients when compared with matched healthy volunteers. However, the rate of *in-vivo* erythrocyte rubidium accumulation in the euthymic treated patients was significantly lower than in a matched group of unmedicated manic patients. The regulation of specific pathways for cation transport may be altered in individuals predisposed to affective illness.

The specific therapeutic activity of lithium salts was first described in a group of manic men by Cade (1949). His discovery was made as a result of chance observations, and, despite almost 40 years of investigation of the effects of lithium on many aspects of neuronal biochemistry and neurotransmitter function, the pharmacological actions crucial to its well established clinical effects are not yet known (Wood & Goodwin, 1987).

One area of interest has been the changes in the transport of cations across cell membranes which occur in patients suffering from affective illness. Alterations in the activity of the sodium-pump enzyme $Na^+$,$K^+$-ATPase have been described *in vitro*

by many groups of investigators in both the manic and depressive poles of bipolar illness. Most studies of depressed patients have shown reduced $Na^+,K^+$-ATPase activity during periods of illness. However, *in-vitro* studies in acute manic illness have been much less clear. Early studies suggested decreased $Na^+,K^+$-ATPase activity in periods of mania, but more recent studies have demonstrated increased enzyme activity in this group (Naylor *et al*, 1973; Hokin-Neaverson *et al*, 1974; Naylor *et al*, 1976; Hesketh *et al*, 1977; Sengupta *et al*, 1980). Our own *in-vivo* study has recently demonstrated an increase in erythrocyte $Na^+,K^+$-ATPase in patients suffering from an acute manic illness (Wood *et al*, 1987, and see preceding paper).

The potential importance of these changes in cation transport to the treatment of bipolar affective illness has also been investigated (for a review see Wood, 1987). The effect of lithium salts on cation transport via $Na^+,K^+$-ATPase was first studied *in vitro* by Naylor *et al* (1974), who showed an increase in the activity of $Na^+,K^+$-ATPase in the erythrocyte membranes of patients taking lithium salts (in a double-blind comparison with inactive placebo). Other investigators have also shown an increase in $Na^+,K^+$-ATPase activity *in vitro* in erythrocyte and platelet membranes from patients on long-term lithium therapy (Hokin-Neaverson *et al*, 1976; Hesketh *et al*, 1978; Sengupta *et al*, 1980). Furthermore, in one study there was demonstrated an inverse correlation between the degree of stimulation of $Na^+K^+$-ATPase by lithium and the risk of subsequent clinical relapse (Johnston *et al*, 1980). However, some workers have failed to show any effect of lithium on $Na^+,K^+$-ATPase *in vitro* (Nurnburger *et al*, 1982; Dagher *et al*, 1984; Thakar *et al*, 1985).

When studies of this sort are conducted on patients responding to and subsequently being maintained on lithium, it is impossible to say whether the observed change in sodium-pump activity is a *direct* action of lithium on $Na^+,K^+$-ATPase, or whether it is a *secondary* consequence of a change in the patient's mental state mediated by some other mechanism. This difficulty can be avoided by studying the effect of lithium on cation transport in healthy volunteers (in whom no change in mental state would be expected after lithium administration). In the single *in-vitro* study of the effect of lithium on $Na^+,K^+$-ATPase activity in healthy volunteers, Naylor *et al* (1977) showed no change in erythrocyte $Na^+,K^+$-ATPase activity after 14 days of lithium treatment. However, we have used a technique for studying $Na^+,K^+$-ATPase activity *in vivo*, and have found a stimulation of the activity of erythrocyte $Na^+,K^+$-ATPase in volunteers who had received lithium for 21 days, suggesting that there is a *direct* stimulatory effect of lithium on the activity of erythrocyte $Na^+,K^+$-ATPase *in vivo* (Wood *et al*, 1986).

In the present study we have used this *in-vivo* technique to study cation transport in patients with manic–depressive illness. We have compared the results in a group of euthymic patients receiving long-term treatment with lithium as prophylaxis for bipolar affective illness with those in a group of untreated acutely manic patients, in order to investigate further the effect of lithium on cation transport *in vivo* and in order to assess the possible relevance of any change in cation transport *in vivo* to the therapeutic properties of the drug.

## Methods

### Subjects

#### *Lithium-treated patients*

We recruited ten patients (six men, four women) from the specialist lithium clinic in Oxford. All were receiving lithium for the prophylaxis of an affective illness, which had included at least one manic episode (hence bipolar affective illness), and had been taking lithium for at least six months before the study. All were being seen regularly for assessment of their symptoms and for monitoring of their lithium treatment, and all had stable serum lithium concentrations within the range 0.4–1.0 mmol/l, suggesting good compliance with therapy. All were out-patients at the time of testing, and were taking no other drugs. Symptoms of depression were rated clinically using the Beck or Hamilton rating scales (Hamilton, 1960; Beck *et al*, 1961). The symptoms of mania were also assessed using the Young Mania Rating Scale (Young *et al*, 1978).

#### *Acutely manic patients*

For the purposes of comparison, as detailed in the results section, we have included data from five patients with an acute manic illness, who were recruited to a separate study. This group was recruited shortly after their admission to hospital. The diagnosis according to the DSM–III criteria (American Psychiatric Association, 1980) was agreed by two psychiatrists. The patients received no psychotropic medication before or during testing. The symptoms of mania were assessed during the test period using the Young Mania Rating Scale (Young *et al*, 1978). A full description of this study is published elsewhere (Wood *et al*, 1987, and see preceding paper). The Young ratings were in the range 22–31 for the five patients.

#### *Controls*

Comparison was made with healthy volunteers matched for age, sex, and weight, who had no history of affective illness, and who were taking no drugs at the time of the study.

**Study protocol**

On the day of the study all the subjects received a loading dose of rubidium, according to the protocol of Boon *et al* (1984) (and see previous paper for details). All tests started at 9 a.m. Samples of venous blood were taken immediately before the first dose and at one hour and five hours after the last dose of RbCl for the measurement of plasma and erythrocyte rubidium concentrations.

In order to assess the linearity of uptake of rubidium into erythrocytes in the presence of lithium, three of the patients took a second rubidium load (at least six months after the first). On the second occasion blood samples were taken hourly between one hour and five hours after the rubidium load, and rubidium concentrations were measured in the usual way.

The patients were taking a variety of lithium carbonate formulations and continued to take their lithium according to the prescribed schedule before and throughout the day of the test. The 12-hour serum lithium concentration was measured on the day of the rubidium test, both to assess continued compliance with therapy and to confirm that lithium concentrations were within the accepted therapeutic range.

TABLE I

*Demographic data and the results of* in-vivo *cation transport assay in 10 patients receiving long-term lithium as prophylaxis for bipolar affective illness, and in matched controls*

| | *Euthymic patients* | *Controls* |
|---|---|---|
| Number | 10 | 10 |
| Age: years (means range) | 45 (23–66) | 44 (26–67) |
| Weight: kg (means range) | 74 (61–90) | 69 (60–95) |
| Serum Li conc.: mmol/l (means range) | 0.82 (0.5–1.08) | |
| Symptom assessment (medians, range) | | |
| Beck scale | 4 (0–11) | |
| Hamilton scale | 4 (1–5) | |
| Young scale | 0 (0–2) | |
| Increment in plasma Rb conc.: μmol/l | | |
| 1 hour | 10.18 (1.65) | 11.52 (2.44) |
| 5 hours | 5.29 (1.28) | 7.69 (4.29) |
| Increment in erythrocyte Rb conc.: μmol/l | | |
| 1 hour | 26.07 (7.61) | 27.69 (6.15) |
| 5 hours | 43.68 (10.5) | 42.40 (7.73) |
| Pseudo-rate constant: $h^{-1}$ medians (IQR), range | 0.35 (0.30–0.38) | 0.24 (0.17–0.34)* |
| Potassium conc. mmol/l (means, s.d.) | | |
| plasma | 4.93 (1.01) | 4.80 (0.67) |
| erythrocytes | 81.92 (4.14) | 84.17 (4.16) |
| Sodium conc. mmol/l (means, s.d.) | | |
| plasma | 140.8 (5.62) | 141.9 (5.65) |
| erythrocytes | 10.01 (4.61) | 8.01 (0.67) |

*$P<0.02$.

The concentrations of sodium and potassium in both the plasma and erythrocytes were also measured, in blood taken immediately before the adminstration of rubidium. The method of data analysis was as detailed in the previous paper (p. 501).

## Results

The demographic details of the euthymic patients and the matched healthy volunteers are shown in Table I. There were no significant differences in ages or weights between the two groups, and all the subjects had normal blood pressures measured by sphygmomanometry (data not shown). No patient was rated as currently suffering from a significant affective episode by clinician-rated symptom scores. The one patient who scored highly on the self-rated Beck inventory had on the previous day taken his eldest daughter away to boarding school for the first time. He felt that his high score was directly related to that episode, and the self-reporting Beck scores measured at routine clinical assessment were normal both before and after this single high rating.

Although the plasma concentrations were lower at both one hour and five hours, and the increase in erythrocyte rubidium concentrations over the time of testing was greater in the patients, none of these differences achieved statistical significance (Table I). However, the differences were reflected in the pseudo-rate constant for rubidium uptake into the erythrocytes, which was significantly increased in the patients receiving lithium therapy when compared with the control group (Table I). There was no correlation between the pseudo-rate constant for rubidium uptake into erythrocytes and: the serum lithium concentration; the duration of lithium treatment; or the age of the patient.

The uptake of rubidium into the erythrocyte was linear over the period of the *in-vivo* test. The data for the three patients retested in this way are shown in Fig. 1.

The concentrations of potassium in both the plasma and the erythrocytes were similar in the two groups. Although there was a trend towards a higher intra-erythrocytic sodium concentration in the euthymic patients on lithium (mean 10.01 mmol/l in patients v. 8.01 mmol/l in controls) this difference did not achieve statistical significance. The plasma sodium concentration was similar in the two groups.

In order to assess further the changes in rubidium handling between untreated manic patients and euthymic patients taking lithium, each lithium-treated euthymic patient was paired with the manic patient matched most closely for age and weight, and the results of *in-vivo* rubidium loading were compared ($n=5$). It must be emphasised that these two groups were not originally selected to be matched populations. There was no significant difference in the mean age or weight of these two groups. The pseudo-rate constant for rubidium uptake into erythrocytes was significantly lower in the subgroup of the euthymic, lithium-treated patients (median 0.29, range 0.26–0.55) than in the matched, unmedicated, acutely manic group (median 0.48, range 0.35–0.65) ($P<0.05$) by signed-rank test). The individual data for the changes in the

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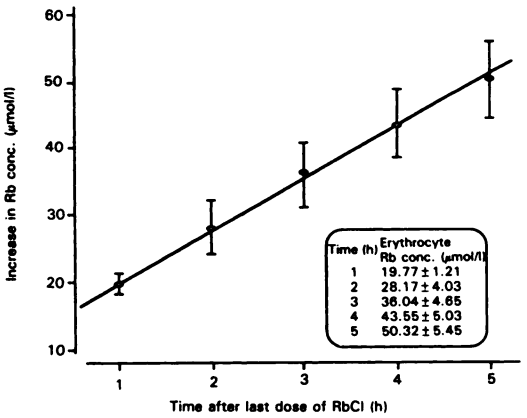


FIG. 1 The time course of the uptake of rubidium into erythrocytes in three euthymic patients taking lithium as prophylaxis for bipolar affective illness. Rubidium concentrations are shown as mean ±s.d.

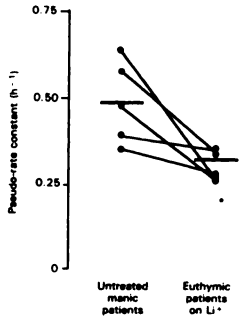


FIG. 2 A comparison of the pseudo-rate constant for rubidium uptake into erythrocytes between five unmedicated manic patients and five euthymic patients taking long-term lithium therapy for bipolar affective illness. The pseudo-rate constants ($h^{-1}$) are shown as the median values (horizontal bars) and the individual changes for each paired comparison. *$P<0.05$ by signed-rank.

pseudo-rate constant between the matched pairs, as well as the group medians, are shown in Fig. 2.

## Discussion

### Increased erythrocyte $Na^+,K^+$-ATPase in euthymic patients taking lithium

The results of this study show an increase in the rate of rubidium uptake into erythrocytes, as reflected in the pseudo-rate constant, in patients with a history of affective illness, currently well and taking long-term lithium, when compared with healthy controls. Our previous work using this *in-vivo* test shows that the increase in erythrocyte rubidium uptake reflects an increase in the *in-vivo* activity of $Na^+,K^+$-ATPase in the erythrocyte membrane (Boon, 1984; Wood *et al*, 1988*a*). Hence we conclude that there is an increase in the cation-transporting properties of $Na^+,K^+$-ATPase in euthymic patients taking lithium. This is consistent with the results of some of the earlier *in-vitro* studies of the effect of lithium on $Na^+,K^+$-ATPase in patients (Naylor *et al*, 1974; Hokin-Neaverson *et al*, 1976; Hesketh *et al*, 1978).

### Possible mechanisms for the stimulation of $Na^+,K^+$-ATPase by lithium

The mechanism of the stimulation of $Na^+,K^+$-ATPase *in vivo* by lithium is not clear. It is possible that the stimulation occurs as a consequence of an alteration in catecholamine function, which has been found in the brain after lithium treatment (see Wood & Goodwin, 1987). Such an effect of catecholamines on $Na^+,K^+$-ATPase via $\beta_2$-adrenoceptors has been demonstrated in patients following acute myocardial infarction, and is thought to underlie the hypokalaemia often seen in this group (Brown *et al*, 1983; Clausen & Flatman, 1980; Baron *et al*, 1985). However, in the periphery the major effect of lithium on adrenergic function is probably an uncoupling of receptor stimulation from the production of cyclic adenosine monophosphate by adenylate cyclase (Ebstein *et al*, 1976), and the predicted result of this uncoupling would be an inhibition of $Na^+,K^+$-ATPase activity. Furthermore, our own studies using the *in-vivo* rubidium load have shown no change in $Na^+,K^+$-ATPase activity in the erythrocyte after the administration of the $\beta_2$-adrenoceptor agonist drug salbutamol to healthy volunteers, and this suggests that an effect of catecholamines is not important in *in-vivo* changes in cation transport in erythrocytes measured in this way (Wood *et al*, 1988*a*).

It has also been suggested that lithium stimulates $Na^+,K^+$-ATPase by protecting the enzyme from inhibition by the vanadate ion. Such a protective effect of lithium salts has been shown in the erythrocyte *in vitro* (Naylor *et al*, 1981) and has subsequently also been demonstrated for the anticonvulsant carbamazepine, which is increasingly being used in the prophylactic management of affective illness (Naylor, 1985).

Naylor *et al* (1977) observed that the intraerythrocytic concentration of sodium is significantly increased in subjects taking lithium, and a raised intracellular sodium concentration is known to be stimulus to $Na^+,K^+$-ATPase activity. It may be, therefore, that lithium acts in some

unknown way to raise intracellular sodium concentrations, and that the stimulation of $Na^+,K^+$-ATPase is a secondary adaptive response. In contrast, a direct stimulation of $Na^+,K^+$-ATPase by intracellular lithium would be expected to lead to a decrease in the intracellular sodium concentration. There was an increase in the intra-erythrocytic sodium concentration in patients taking lithium in the present study, but it did not reach statistical significance (Table I). However, this may reflect the relatively small number of subjects tested as well as the relatively large variance in the intra-erythrocytic sodium concentrations measured in the patient group.

The similarity in the potassium concentrations in the plasma and cells from the patients and controls suggests that changes in the potassium:rubidium concentration ratio, and hence the relative substrate competition of the two ions for transport via $Na^+,K^+$-ATPase, is not likely to explain the difference in rubidium uptake between the two tested groups.

### The kinetics of rubidium uptake

Our measurement of the rate of rubidium uptake *in vivo* and the derivation of the pseudo-rate constant is likely to be a true reflection of the rate constant for uptake, but this can only be assumed because the extracellular rubidium concentrations remain relatively low throughout the test. Even under these conditions, the rate constant for the uptake process is a function of the ratio between the two parameters of the transport system, $V_{max}$ (the maximal rate of uptake under conditions of substrate saturation) and $K_m$ (a measure of the affinity of the enzyme for rubidium ions) (Aronson, 1989). It is possible that the observed change in the pseudo-rate constant for rubidium uptake is the net result of a combination of changes in $V_{max}$ and $K_m$. The direction of the changes in the individual parameters cannot be deduced from our data. Individual measurement of these two parameters would be possible in an *in-vitro* assay, but such studies have not previously been undertaken.

For the three patients who agreed to take a second rubidium load it was possible to confirm that the uptake of rubidium into erythrocytes was linear in the presence of therapeutic concentrations of lithium (Fig. 1). This is clearly an important precondition for the calculation of the pseudo-rate constant for rubidium uptake as described above. Furthermore, it excludes the possibility of any complex time- or rubidium-concentration-dependent action of lithium on the regulation of rubidium uptake via $Na^+,K^+$-ATPase during the period of the *in-vivo* test.

Despite the observed increase in the rate of rubidium uptake into the erythrocyte, we were not able to demonstrate any significant increase in actual intra-erythrocytic rubidium concentrations in patients. One explanation for this apparent discrepancy is that the plasma rubidium concentrations are lower at both one hour and five hours after the oral load, and that the fall in mean plasma concentration between one hour and five hours is greater in the patients (4.89 μmol/l) than in the control group (3.83 μmol/l). This increase in the clearance of rubidium from the plasma suggests that the rate of uptake of rubidium from the plasma into all tissues may have been greater in the lithium-treated patients. As a consequence of the increased clearance of plasma rubidium the erythrocytes might have been exposed to lower rubidium concentrations throughout the time of the uptake experiment, and a true increase in the *rate* of rubidium uptake into the erythrocyte might not therefore have been reflected in an actual increase in intra-erythrocytic rubidium concentrations.

### The effect of lithium in manic illness: a synthesis of the *in-vivo* studies

The comparison of the pseudo-rate constant for erythrocyte rubidium uptake in acute manic illness and in euthymic lithium-treated patients suggests that there is actually a *fall* in cation transport activity *in vivo* during the symptomatic recovery of manic patients to a euthymic state. It is arguable that the untreated manic patients constitute a more appropriate control group for studying the dynamic change in cation transport after the treatment of affectively ill patients with lithium in order to make inferences about the mechanism of action of the drug in mania. The fall in rubidium uptake *in vivo* demonstrated here after the treatment of affectively ill patients with lithium does not support the hypothesis based on earlier studies, that the activity of $Na^+,K^+$-ATPase falls in mania and depression and increases as the illness remits or is successfully treated. In a separate investigation we have studied the effect of lithium upon $Na^+,K^+$-ATPase *in vivo* in healthy volunteers (Wood *et al*, 1986), and have demonstrated a stimulation of the enzyme in the group following 21 days of lithium treatment.

In an attempt to form an hypothesis to explain the effect of lithium in manic illness, we have combined the results of the above study with our present data and conclude that the successful treatment of mania with lithium is associated with a fall in cation transport *in vivo* to normal levels, but that lithium independently causes a direct stimulation of

rubidium uptake via $Na^+,K^+$-ATPase (as this has been demonstrated in both patients and healthy volunteers). This explanation would imply that the crucial action of lithium in mania is not upon $Na^+,K^+$-ATPase. However, these results are equally well explained by the hypothesis that the $Na^+,K^+$-ATPase enzyme in the erythrocyte membrane of individuals predisposed to develop affective illness is functionally different from that of healthy volunteers, and that as one consequence of the difference it is inhibited after the administration of lithium, whereas the activity of 'normal' $Na^+$, $K^+$-ATPase found in healthy volunteers is increased by lithium ions.

## Conclusions

We have shown stimulation of cation transport *in vivo* in euthymic patients taking lithium for the prophylactic management of bipolar affective illness, when compared with healthy controls, but a significant fall when compared with untreated manic patients.

There are two explanations compatible with these results. Firstly, that lithium has a direct stimulatory effect on erythrocyte $Na^+,K^+$-ATPase, but that this effect is independent of the antimanic action of the drug. Thus the demonstrated intermediate $Na^+,K^+$-ATPase activity in euthymic lithium-treated patients is the net result of a reduction in activity on return to a normal mental state and a direct stimulatory effect of lithium upon enzyme activity. Secondly, it is also possible that the $Na^+,K^+$-ATPase of patients at risk of developing affective illness is structurally and functionally different from the enzyme of healthy individuals, and that this abnormality causes it to respond differently to the presence of therapeutic concentrations of lithium. According to this model the intermediate enzyme activity in treated patients reflects a fundamentally different effect of lithium upon $Na^+,K^+$-ATPase in patients with manic–depressive illness.

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