The potential use of lithium as a marker for the assessment of the sources of dietary salt: cooking studies and physiological experiments in men

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Summary

1. Lithium was investigated for its possible use as a marker for identifying the various sources of NaCl in the diet. Micromolar concentrations of lithium can be detected in various vegetables, tap water and also in urine specimens of adult volunteers. The lithium content of vegetables varied from 6.1 to 24.5 μmol of lithium/kg dry weight, with the exception of spinach and aubergines which had much higher concentrations. The excretion of the element in 24 h urine specimens ranged from 2 to 4 μmol of lithium/day.

2. Experiments were performed to assess whether both lithium and sodium would penetrate foods at the same rate during cooking. The rates of penetration into food for both elements were proportional to their concentration in the cooking water despite a sodium/lithium ratio of 50:1.

3. Physiological experiments were conducted to investigate the handling of small doses of lithium by the body. A dose of 250 μmol of lithium was chosen as optimal and given orally to healthy volunteers in either single or continuous aqueous doses of lithium carbonate. The recoveries of oral lithium in urine were 92 ± 5% (SD) and 97 ± 4 (SD) (n = 5) for single and continuous doses respectively.

4. The daily addition of 100 mmol of oral NaCl to the diet of volunteers receiving a standard dose of lithium did not affect urinary lithium excretion rates nor the final recovery of the administered lithium.

5. These studies suggest that lithium carbonate may be a useful marker for the uptake of NaCl into cooked food; after eating lithium-enriched food the monitoring of urinary lithium output may then be used to quantify the amount of sodium derived from the specific foods.

Key words: lithium, marker substance, salt.

Introduction

The interest in the role of dietary salt (NaCl) in the development of essential hypertension and the advice to reduce salt intake as a preventive measure have highlighted the need to know the sources of dietary salt [1-7]. Estimates of the amounts of table and cooking salt, i.e. the discretionary sources, are often based on measures such as the household purchases of salt, with no allowance being made for losses during cooking or at the table [8, 9]. Salt present in manufactured food may not all be ingested if the item is cooked in water; variable amounts of these cooked foods are taken by individuals so that the assessment of the different routes for salt entry into the diet is complex.

There is therefore a need to develop a new approach. A marker substance which could trace the quantity of sodium from table and cooking salt through the cooking and eating processes would be advantageous. Ideally a marker which was excreted in the urine in proportion to the sodium excreted by this route would allow the non-discretionary sources of salt to be calculated once specific sources of salts were labelled appropriately with the marker.

Fig. 1 indicates an approach which may overcome this problem. Lithium was chosen as the possible marker for salt because in the periodic table it has a position analogous to that of sodium; it is also frequently used as a substitute for sodium in biochemical studies [10] and the amount of natural lithium in food was expected to be low [11].
The present paper describes the analytical procedures used for detecting lithium in micromolar concentrations and assessing the amounts of sodium and lithium taken up by foods during cooking. Studies were also undertaken to see whether lithium was excreted rapidly in the urine and whether the urinary lithium output was affected by concomitant changes in salt intake.

**Materials and methods**

Lithium was measured in aqueous solution as lithium carbonate with a Pye Unicam SP9 Atomic Emission spectrophotometer and with nitrous oxide rather than air/acetylene as the gas in order to reduce interference from the common anions such as phosphate and sulphate, which are known to depress the instrumental response to the alkaline earth metals [12]. Lithium-free KCl was added to lithium standards to increase the signal by minimizing the ionization of lithium. A solution with a KCl concentration of 0.15% was found to be satisfactory and was used when specimens were diluted before measuring lithium. When urine specimens were measured for their normal lithium content the undiluted specimens were used and contained more than the required KCl concentration. Urinary specimens containing additional lithium excreted after oral doses of lithium were routinely diluted with 0.15% KCl. Adding sodium to lithium standards did not affect the signal providing allowance was made for the minute amount of lithium contaminating the AnalaR preparation of NaCl. The accuracy of the lithium measurement was checked in urine and other specimens by the method of standard addition.

The effect of nitric acid on lithium measurement was also tested since urine was preserved with a maximum final concentration of 0.1 mol/l nitric acid; food samples were digested in concentrated nitric acid and had a concentration in the final analysed solution of 2.5 mol/l. Nitric acid up to 0.1 mol/l had a negligible effect on the lithium measurement and at 2.5 mol/l the small suppressive effect amounted to less than 1% of the response from the unacidified standard. The preservation of urine specimens and storage before analyses produced oxalates and other precipitates but the precipitate was shown to contain no lithium. Thus the lithium concentration of six freshly voided urines remained unchanged after both acidification and storage at -20°C for 26 days. For routine measurements of urine specimens therefore, any precipitate was allowed to sediment so that the nebulizer inlet of the spectrophotometer was not blocked. All specimens were analysed in duplicate.

**Cooking experiments**

Preliminary analyses on a variety of raw vegetables were performed to assess their natural lithium content and to ensure that vegetables with a high lithium content were excluded from subsequent metabolic studies on lithium absorption and excretion. Duplicate samples of some of these vegetables, i.e. potatoes, runner beans and cabbage, were cooked under conditions which simulated normal culinary practices. This was designed to assess the rates of sodium and lithium penetration into foods. Cooking water containing NaCl and lithium carbonate at concentrations providing a sodium/lithium ratio of approximately 50:1 was used, since this ratio was calculated as probably appropriate for later epidemiological studies. A check on the total recovery of lithium and sodium in the cooking experiments was also made. Additional experiments were conducted to assess the effect of different cooking times on elemental penetration.

For elemental analyses the cooked and uncooked foods had to be digested with concentrated nitric acid. Preliminary digestion studies with dilute nitric acid (0.5 mol/l) for 1 h showed that there was inadequate release of lithium from foods. Total digestion with concentrated nitric acid proved necessary since there was as much as a fivefold increase in the lithium released by the concentrated acid. Foods, analysed for their natural lithium content, were prepared by being quickly washed in de-
ionized water, freeze-dried, weighed, chopped and then ground. A 2 g aliquot of the powder was then digested with concentrated nitric acid in Pyrex crystal tubes [13] and then diluted to 100 ml with deionized water having a final KCl concentration of 0.15%. After filtering through ashless Whatman paper no. 541 the solution was ready for analysis.

Optimization of lithium dose in relation to physiological and toxic effects

The normal rates of urinary lithium excretion were assessed in ten healthy normal adults living in Cambridgeshire who collected urine for seven sequential 24 h periods. The urinary lithium output for all specimens was found to be $3.2 \pm 0.8 \mu\text{mol}/\text{day}$ (mean $\pm$ sd) with an average output for the individuals ranging from 1.9 to 4.4 $\mu\text{mol}$/day. These results compared with values of 5.9 $\mu\text{mol}$ of lithium/day in a group of Cambridge nutritionists who were known to be on a different diet with a higher vegetable intake.

These very low rates of lithium excretion were on average about 0.01% of the daily dose of lithium used for therapeutic purposes in psychiatric patients [14]. A lithium dose of 250 $\mu\text{mol}$ was therefore identified as a suitable intake since even this hundredfold increase above baseline lithium excretion represented only about 1% of the therapeutic dose. Thus from the toxicological point of view the plasma concentrations to be expected from this dose would be far below that considered hazardous.

Physiological experiments

Single dose studies. One male and eight non-pregnant female members of the unit staff or Cambridge student population collected urine specimens for eight continuous 24 h periods. Baseline lithium output was assessed in the first 2 days and on day 3 a single aqueous test dose of 250 $\mu\text{mol}$ of lithium carbonate was ingested and the rate of excretion in urine monitored.

Continuous dose studies. The effects of sodium loads on the excretion of lithium during the course of 14 days of daily aqueous doses of lithium were tested in two non-pregnant women and four men who collected continuous 24 h urines for a period of 26 days. On days 1 and 2 urinary baseline lithium was assessed before the daily lithium dose being started on day 3. From day 3 to day 17 the daily dose of lithium was given with meals to simulate a continuous feeding study. From day 11 to day 17 an additional daily dose of 100 mmol of sodium was taken as NaCl in the form of ‘slow sodium’ tablets. The final period from day 17 to day 26 was used to check on lithium recovery. During this study the subjects continued with their normal diet and activity patterns. The studies were approved by the MRC Dunn Nutrition Laboratory Ethical Committee.

Results

A variety of vegetables including raw and processed beans, peas, cauliflower, brussels sprouts, root vegetables, mushrooms, leeks, potatoes, carrots and courgettes were analysed for their lithium content. All had very low lithium concentrations ranging from 6.1 to 24.5 $\mu\text{mol}$ of lithium/kg dry weight of vegetables. Spinach and aubergines, however, proved to have 168 and 794 $\mu\text{mol}$ of lithium/kg dry weight, respectively. These two vegetables were therefore excluded from further studies and not included in later metabolic balance studies. The lithium content of tap water proved to be less than 0.3 $\mu\text{mol}$/l.

Cooking experiments

Table 1 shows the proportion of both sodium and lithium which penetrated foods on cooking, cooking times being shown for each vegetable. No difference in the sodium/lithium ratio of the cooked vegetables was found when the cooking time for potatoes was increased to 40 min (data not shown). Two different molar ratios of lithium and sodium were also used to check on any interactions between the elements during their uptake into foods but there was again no appreciable difference between the two conditions. The sodium/lithium ratio in the cooked vegetables attained a slightly higher value than the labelled salt added to the cooking water because of pre-existing sodium and lithium in the raw vegetables: when the amount of the elements penetrating the vegetables was calculated then there was a remarkable equivalence of uptake of sodium and lithium despite the very different elemental concentrations in the cooking water. Recoveries for the experiments ranged from 87 to 107%.

Physiological studies

Fig. 2 shows the pattern of urinary excretion of lithium in one of the subjects given a single test dose of 250 $\mu\text{mol}$ of lithium. Nine subjects had, on average, a baseline lithium excretion of $6.2 \pm 2.2 \mu\text{mol}/\text{day}$ with a total recovery of 91.6 $\pm 4.8\%$ of the ingested lithium. Five of these subjects received lithium for the first time in this study, whereas the other four had been tested several weeks previously with a capsule of powdered lithium carbonate designed to contain 250 $\mu\text{mol}$ of lithium, but which proved too variable in lithium content. The four previously exposed individuals showed a higher
rate of urinary lithium excretion in the first day after the lithium dose (Table 2) with only 34% of the dose being retained after 24 h compared with a value of 43% in those exposed for the first time. This difference was highly significant \( P < 0.001 \) on day 1 and continued being significant on day 2 \( P < 0.05 \). This suggested that the previous exposure to lithium had altered the body's handling of the element. In both groups, however, there was an approximately exponential decline in excretion compatible with a single pool of body lithium and a constant fractional rate of lithium turnover. The recovery rate in both groups was high, varying from 84.5 to 98.1%, the lowest value being found in a competitive sportsman.

When a further group of five men and women were given daily doses of lithium carbonate for 14 days the total recovery in the urine amounted to 96 ± 3.7% (mean ± sd) of the dose ingested. This suggested that faecal or sweat losses of lithium must be surprisingly small. There was no evidence that 100 mmol of NaCl daily induced enhanced losses of lithium by other routes or selective sequestration of lithium in the body. The usual intakes of sodium of the five volunteers during the days of lithium ingestion ranged from 105 ± 44 to 255 ± 64 mmol/day and varied from 212 ± 37 to 299 ± 48 mmol of sodium when 100 mmol of sodium as 'slow sodium' was added. Three of the individuals were on intakes exceeding 300 mmol, one individual reaching a maximum level of intake of 371 mmol of sodium.
TABLE 2. Daily excretion of lithium by subjects given 250 μmol of lithium carbonate with or without previous exposure to lithium

Daily urinary lithium output significantly different: *P < 0.05; **P < 0.01; ***P < 0.001 (†P < 0.10).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Recovery in urine (%)</th>
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<td>41.7</td>
<td>31.4</td>
<td>28.1</td>
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<td>Mean ± sd</td>
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<td>67.0 ± 9.5</td>
<td>44.8 ± 8.8</td>
<td>34.7 ± 7.6</td>
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Discussion

The present study showed that it is possible to measure accurately micromolar concentrations of lithium in food and urine by the use of an atomic emission spectrophotometer with a nitrous oxide/acetylene gas mixture. It was also allowed for tap water to contain very high lithium concentrations and to be very high. The two elements into vegetables of very different composition and macromolecular structure. This suggested that lithium could indeed be used to track Na entry to food and thus suggested the possibility of monitoring sodium intake as shown in Fig. 1.

Despite these very high sodium intakes lithium recoveries were very high. Inspection of the daily urinary lithium output in these five subjects (Fig. 3) also revealed a rise in lithium to a plateau value which was unaffected by the sudden increase in sodium intake.
The next step was to assess the body's handling of standard doses of lithium. After unsatisfactory preliminary trials with powdered lithium carbonate more accurate doses were obtained by using lithium in liquid form. Surprisingly high recoveries of lithium were obtained in the urine, suggesting that faecal and sweat losses of lithium were small.

The chance finding of a more rapid excretion rate of lithium to these small doses of lithium in those previously exposed had not been described before. Goodnick et al. [17] with pharmacological doses of lithium fed to patients for many months suggested the opposite, i.e. that the excretion of lithium carbonate in urine was slower and blood lithium concentrations higher in those receiving long term lithium therapy. Studies by Groth et al. [18] with single pharmacological doses of lithium carbonate of 10.8 and 40.6 mmol gave half-life values of urinary lithium which approximated to those found in this study, but the mechanisms for renal lithium excretion may well be different with those much higher doses.

The surprisingly high recovery of lithium in the urine despite the substantial sodium load and the more rapid early excretion of lithium by the kidney in volunteers previously exposed (Table 2) suggests that there may be preferential excretion of lithium by the kidney. If so then the monitoring of both lithium and sodium excretion as a means of documenting discretionary and total salt intakes could lead to a misleading picture if there were preferential renal excretion of lithium since this would lead to a spuriously high proportion of salt being considered as derived from discretionary sources. It was this concern which led us to undertake a full metabolic balanced study to compare the routes of excretion of lithium and sodium.

The use of the lithium itself did not produce any special problems; the taste was unnoticeable and there were no symptoms. The doses used were 1% of those considered toxic and its use in cooking did not seem to alter the quality of the food in any way. These encouraging results suggested that a more detailed metabolic study could be justified providing a satisfactory mixture of lithium and sodium to simulate ordinary salt could be obtained.

The preparation of a suitable mixture and its testing under metabolic conditions form the basis of the next paper.

Acknowledgments

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References