CHANGES OF IONIC CONCENTRATIONS IN SERUM AND BLOOD CELLS OF RATS AFTER LITHIUM ADMINISTRATION

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Lithium concentration in serum was higher than that in blood cells 3 hours after single lithium chloride administration (200 mg/kg). The ratio of extra- to intracellular lithium concentration was, however, reversed 12 hours after single administration, indicating that excretion of intracellular lithium was much slower than that of extracellular one. Intracellular accumulation of lithium increased by repeated administrations of lithium, and consequently intracellular lithium concentration became nearly equal to extracellular one even 3 hours after a last administration. When blood cells accumulated lithium ions, the intracellular potassium decreased and the intracellular sodium also tended to decrease. It was suggested that therapeutic doses of lithium should be controlled by measuring the intracellular lithium concentration, since the pharmacological or toxic actions of lithium would be directly associated with this concentration.

It has been well known that lithium is a useful therapeutic agent for the treatment of manic-depressive psychoses in the field of psychiatry. The pharmacological actions of lithium to these psychoses, however, have not been clarified yet. There seems to be two possible ways by which lithium would act to central nervous system. First, lithium may change the neural function by interfering with metabolic processes in neural tissues, particularly those of synaptic transmitters. Second, it may modify the neural function by interfering with the ionic processes of membrane excitation in neural tissues. The present experiments were carried out in connection with the second possibility of lithium actions.

Effects of lithium on the ionic processes of membrane excitation, viz., the nerve conduction and synaptic transmission, were studied in a recent experiment, and it was suggested that the
mode of actions of lithium was directly associated with the changes in intracellular potassium and sodium concentrations which were altered by intracellular accumulation of lithium ions. The fundamental mechanism underlying the ionic distributions in intra- and extracellular spaces in neural tissues should be the same as those in other tissues. Thus, the changes in ionic concentrations in neural tissues, which are caused by lithium administration, would be essentially similar to these changes observed in intra- and extracellular spaces in blood. The present experiment was designed on the basis of this assumption, in order to speculate the changes in the ionic distributions in central nervous system, which were caused by lithium administrations.

METHODS

The experiments were carried out with male Wistar rats weighing 180 to 210 g. Lithium chloride was administered by i. p. injections (2 ml/kg), and blood was collected by decapitation at a certain period after lithium administration. The estimations of concentrations of lithium, potassium and sodium ions were made by use of an atomic absorption spectrophotometer (Hitachi 208), and the extra- and intracellular (serum and blood cells) concentrations of these ions were calculated according to the values of hematocrit.

RESULTS

1) Lithium concentrations in serum and blood cells

The time course of changes in lithium concentrations in serum and blood cells was studied after single administration of lithium chloride (200 mg/kg) : each experimental group contained ten rats. The lithium concentration in serum was significantly higher than that in blood cells 3 hours after lithium administration: these lithium concentrations in serum and blood cells were 2.73 ± 0.23 meq/l and 1.99 ± 0.21 meq/l, respectively. Excretion of the intracellular lithium ions was observed to be much slower than that of the extracellular lithium concentration. Thus, the intracellular lithium concentration became nearly equal to the extracellular lithium concentration 6 hours after lithium administration, and the former became significantly higher than the latter 12 hours after administration. The lithium concentrations in serum 6 and 12 hours after administration were 1.90 ± 0.01 meq/l and 1.26 ± 0.14 meq/l, respectively, while those in blood cells were 1.79 ± 0.14 meq/l and 1.73 ± 0.12 meq/l, respectively. These results are summarized in Figure 1.

Changes in the lithium concentrations in serum and blood cells were also studied after repeated administrations of lithium chloride (200 mg/kg/12 hr for
3 or 4 times) ; each experimental group contained ten rats. Both extra- and intracellular lithium concentrations in blood were increased by repeated administrations, but the differences between these two concentrations became small. Indeed, no significant differences were observed between these two values estimated 3 hours after a last administration of lithium in these experiments. These results are shown in Figure 2.

![Figure 2](image)

**Fig. 2** Changes in the lithium concentrations in serum and blood cells after single (200 mg/kg) and repeated (200 mg/kg/12 hr for 3 or 4 times) administrations of lithium chloride.

2) Potassium and sodium concentrations in serum and blood cells

Potassium and sodium concentrations in serum and blood cells were estimated 3 hours after a last administration of repeated lithium chloride applications (200 mg/kg/12 hr for 4 times). Both experimental and untreated control groups contained ten rats. Both extra- and intracellular sodium concentrations in the test group were significantly smaller than those in the control group; the sodium concentration in serum was 128.2 ± 1.1 meq/l in the test group and 139.0 ± 1.0 meq/l in the control group, while that in blood cells was 14.5 ± 0.27 meq/l in the test group and 22.98 ± 3.75 meq/l in the control group. No significant difference in the potassium concentration in serum was observed between the test and control groups. The intracellular potassium concentration in the test group, however, was significantly smaller than that in the control group: the potassium concentration in the control and test groups was 122.0 ± 0.29 meq/l and 94.5 ± 1.62 meq/l, respectively. These results are summarized in Figure 3.

![Figure 3](image)

**Fig. 3** Changes in the potassium and sodium concentrations in serum and blood cells after repeated administrations of lithium chloride (200 mg/kg/12 hr for 4 times). Open and dotted squares are control and test values, respectively.

**DISCUSSION**

The fundamental mechanism underlying the extra- and intracellular distributions of sodium and potassium ions must be the same in all different kinds.
of tissues. It has been shown that the transport mechanism of lithium ions across the muscle cell membrane is essentially similar to that across the erythrocyte membrane\(^4\)\(^5\). Presumably, the mechanism underlying the extracellular and intracellular ionic distributions, which was established after lithium administration, may also be the same in different tissues. Thus, the present experimental results seem to suggest the extra- and intracellular distributions of lithium, potassium and sodium ions in the central nervous system.

Since the membrane permeability to lithium ions may be comparable to that to sodium ions\(^4\), lithium and sodium ions would move into cells at an almost same rate. Unlike sodium ions, however, the intracellular lithium ions can not be easily extruded by a pump mechanism\(^4\)\(^5\)\(^11\). Thus, lithium ions would be gradually accumulated inside of cells. It would be expected that nerve cells accumulate more lithium ions, comparing with blood cells, since nerve cells produce action potentials during which a large amount of lithium ions, together with sodium ions, would move into the intracellular space.

The grade of pharmacological or toxic actions of lithium would be directly related to the intracellular lithium concentration. In other word, the therapeutic or toxic effect of lithium would be directly associated with the intracellular concentration rather than the extracellular concentration of lithium. According to the present experiment, the excretion of intracellular lithium was much slower than that of extracellular lithium, showing that the intracellular lithium concentration was often higher than the extracellular one. Thus, it seems to be more preferable to estimate the lithium concentration in blood cells rather than that in serum, in order to determine the therapeutic or toxic doses of lithium.

It has been suggested that the effects of lithium on the ionic processes of membrane excitations can be explained by changes in the intracellular potassium and sodium concentrations, which was caused by an intracellular lithium accumulation\(^11\)\(^3\)\(^10\). According to the present experiment, the intracellular potassium concentration was markedly reduced when lithium ions were accumulated inside of cells. Furthermore, the intracellular sodium concentration appeared to be reduced simultaneously. The nerve cell membrane would be depolarized when the intracellular potassium concentration decreased, and the sodium pump would be depressed when the intracellular sodium concentration decreased. These changes in the intracellular potassium and sodium concentrations appear to be directly associated with the actions of lithium to nerve cells.

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REFERENCES

5) Maizels, E.: Active cation transport in


