J. Pharm. Pharmacol. 1979, 31: 619–621 Received December 5, 1978

The use of phospholipid liposomes for lithium administration. Polydipsic effect and tissue distribution of lithium

YAEL ZILBERMAN, DOV LICHTENBERG* AND YEHUDA GUTMAN

Department of Pharmacology, The Hebrew University-Hadassah Medical School, P.O. Box 1172, Jerusalem, Israel

Administration of lithium entrapped in phospholipid liposomes increased the lithium-induced polydipsia, but did not accelerate the onset of this effect. It also resulted in a larger accumulation of lithium in the liver, kidney and spleen, but not in the brain. The time course of polydipsia suggests that it depends on the intracellular lithium concentration. However, the rate of development of this effect depends on some additional factor.

Improvement of the acute manic state in manic-depressive disease by treatment with lithium salts is observed only after several days (Fieve 1975). Polydipsia, which is a common side effect of lithium therapy, resembles the psychiatric changes caused by lithium in that the development of both effects is gradual and requires several days to reach peak effects. The delayed development of both effects can be explained as being a result of the slow accumulation of lithium ions within the cell. An intracellular site of action for lithium ions has in fact been indicated by several findings (Mendels & Frazer 1973; Frazer et al 1973).

Transport into cells of drugs which penetrate cell membranes poorly has been previously achieved by the use of phospholipid liposomes (Tyrrel et al 1976; Gregoriadis 1976). Entrapment of drugs in liposomes is obtained by ultrasonic irradiation of lipids in aqueous solutions of the drugs. This leads to the formation of phospholipid vesicles (liposomes), with the drug entrapped in the internal volume of the liposomes. Incubation of liposomes with cells in culture (Huang & Pagano 1975; Papahadjopoulos et al 1974), or injection of liposomes into animals (Rahman et al 1974) result in the incorporation of the liposomal lipids into the bilayer structure of the biological membranes while the entrapped volume is transferred into cell cytoplasm. This process, which probably occurs mostly through a vesicle-cell fusion mechanism (Pagano & Huang 1975), can thus enable drugs which cannot penetrate cell membranes to exert intracellular activities.

Therefore, we found it interesting to explore the possibility of enhancing the introduction of lithium ions into cells, through the use of liposomes. In the present study, the effect of entrapment of lithium in liposomes on the intensity and on the rate of the onset of lithium effects was investigated. This paper presents the results of a study on the polydipsic effect of lithium and on lithium concentrations in various organs, following the administration of liposome-entrapped lithium chloride.

* Correspondence.

MATERIALS AND METHODS

Animals

Male rats of the Hebrew University strain (Sabra), weighing 150 g at the beginning of the experiments were used.

Water intake

The rats were placed in individual cages. Water intake was measured daily, starting 2 days before the first injection. The water intake of the day preceding the first injection is referred to as drinking on day 0.

Administration of lithium and sodium

The rats were divided into three groups and injected intraperitoneally twice daily (at 9 a.m. and 4 p.m.) with isotonic solutions of the following compositions: Group A—150 mM NaCl; Group B—150 mM LiCl; Group C—liposome-entrapped LiCl. This was prepared in the following way: a suspension of 175 mM egg yolk lecithin (EYL), and 50 mM cholesterol was sonicated in 150 mM LiCl until the suspension cleared up. In another experiment NaCl entrapped in liposomes was prepared and the effect on water intake of rats was studied. The daily electrolyte dosage was 2·6 mmol kg^{-1} throughout the experiment.

Collection of tissues

Groups of rats were killed 18 h after their last injection at different times over 10 days of lithium treatment. Samples of the liver, brain, spleen and kidney were weighed, dried and extracted with kidney were weighed, dried and extracted with 1 M HNO_3 (2 ml/150 mg tissue) for 48 h.

Lithium determination

Lithium concentrations were measured using a Perkin Elmer (Model 403) atomic absorption spectrophotometer at 670 nm, and compared with standard solutions of LiCl of various concentrations.

Results are expressed as means ± s.e. and were analysed by Student's *t*-test.

RESULTS

Water intake

Administration of liposome-entrapped NaCl did not affect the water intake of rats compared with the water consumption of rats given free NaCl. Fig. 1

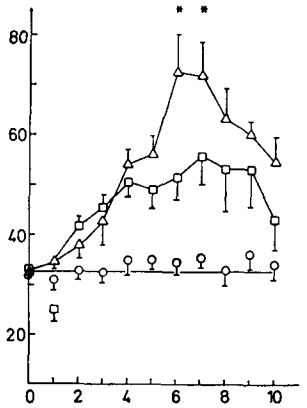

FIG. 1. The drinking volume (ordinate: water intake, ml rat^{-1}) of rats given LiCl (□—□), liposome-entrapped LiCl (△—△) and of rats given NaCl (○—○), as a function of time (abscissa: days). Daily electrolyte dose was 2·6 m mol kg^{-1}, given in two equal portions. At zero time, the water intake of the last day before beginning of injection. Days 0–6; n = 12 for LiCl, 12 for liposome-entrapped LiCl, 6 for NaCl; Days 7–13; n = 6 for all groups of rats. *, $P < 0{\cdot}05$.

shows the water intake of rats injected with LiCl and liposome-entrapped LiCl as well as the water intake of rats given NaCl. NaCl treatment did not affect water intake, whereas both LiCl and liposome-entrapped LiCl caused a significant increase of the drinking volume of the rats, from the third day of treatment onwards. Until the 4th day of the lithium treatment there was a gradual slow increase of the water consumption by both groups, reaching 150% of the water intake by the control group. On the 6th and 7th day of the treatment, the daily water intake of the rats which were given entrapped LiCl exceeded significantly that of rats which were given free LiCl. From the 8th day of the treatment onwards, there was a decline in the water consumption by rats of both groups, the decrease in rats of Group C being larger than in those of Group B.

Accumulation of lithium in tissues

The lithium contents of several tissues of the rats are given in Fig. 2. The main observations were: (1) No differences were found between the lithium content of the brain of rats given free LiCl and liposome-entrapped LiCl, (at 3, 6 or 10 days of treatment).

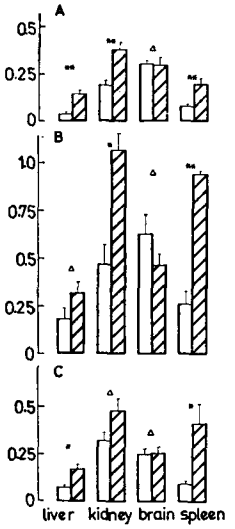

FIG. 2. Lithium content of liver, kidney, brain, and spleen of rats treated with either LiCl (open bars) or partially entrapped LiCl (crossed bars) for 3 days (A), 6 days (B) and 10 days (C). The results presented in B and C are taken from the same experiment presented in Figure 1. (n = 6 for all groups.) * $P<0{\cdot}01$; ** $P< 0{\cdot}001$. Ordinate: Li (μmol g^{-1}).

(2) Lithium concentrations in the liver, spleen and kidney of the rats given entrapped LiCl were higher than those found in the respective tissues of rats given free LiCl. (3) Comparison of panels B and C of Fig. 2, which refer to the same experiment as the results of water intake, shows that there was a decrease in the lithium content of several tissues, from the 6th to the 10th day of treatment.

DISCUSSION

The polydipsic effect of lithium probably originates in the kidney and is secondary to the polyuric effect

of lithium (Gutman et al 1971). The present results show that entrapment of LiCl in phospholipid liposomes brings about an increase in the polydipsic effect of lithium, accompanied by an increased accumulation of Li^+ in several tissues. An increase of the accumulation of Li^+ in the tissues could be expected to result in acceleration of the development of polydipsia; and/or an augmentation of the effect. It is obvious from our data that although there was increased accumulation of lithium in the kidney, the polydipsic response was not accelerated but was significantly augmented. The extent of the polydipsic effect seems therefore to be related to the intracellular lithium concentration, but the rate of development of the effects depends on some additional factor.

No enchancement of lithium accumulation in the brain was observed in the rats given liposome-entrapped LiCl at any of the periods tested. This can be an indication that liposomes of the composition used in our experiments do not penetrate the blood-brain barrier, and therefore only free lithium ions reach the brain. It also supports the suggestion that lithium-induced polydipsia is of peripheral, most likely renal, origin. In any event, the liposomes in these experiments would not be suitable for use to accelerate the onset of the psychiatric effect of lithium nor for the increase of its effect. Moreover, an increased incidence of peripheral side effects may be expected.

Acknowledgement

The authors wish to thank the Charles E. Smith Family Foundation, Israel Centre of Psychobiology for financial support.

REFERENCES

Fieve, R. R. (1975) in: Freedman, A. M., Kaplan, H. I., Sadock, B. J. (eds) Comprehensive Textbook of Psychiatry II, Williams and Wilkins Co., 428 E. Preston Street, Baltimore, Md. 21202, USA

Frazer, A., Mendels, J., Secunda, S. K., Cochrane, C. M., Bianchi, C. P. (1973) J. Psychiatr. Res. 10: 1–7

Gregoriadis, G. (1976) New Engl. J. Med. 295: 704–710

Gutman, Y., Ben Zakein, F., Livneh, P. (1971) Eur. J. Pharmacol. 16: 380–384

Huang, L., Pagano, R. E. (1975) J. Cell Biol. 67: 38–48

Mendels, J., Frazer, A. (1973) J. Psychiatr. Res. 10: 9–18

Pagano, R. E., Huang, L. (1975) J. Cell Biol. 67: 49–60

Papahadjopoulos, D., Mayhew, E., Poste, G., Smith, S., Vail, W. J. (1974) Nature (London) 252: 163–166

Rahman, Y. E., Rosenthal, M. W., Cerny, E. A., Moretti, E. S. (1974) J. Lab. Clin. Med. 83: 640–647

Tyrrel, D. A., Heath, T. D., Colley, C. M., Ryman, B. E. (1976) Biochim. Biophys. Acta 457: 259–302