Biochemical Pharmacology, Vol. 27, pp. 813–814. Pergamon Press, 1978. Printed in Great Britain.

Lithium transport from cerebrospinal fluid

(*Received* 11 *July* 1977; *accepted* 10 *August* 1977)

The pharmacology of lithium salts has become a subject of much interest and importance since the advent of their use for the treatment of affective disorders [1]. Little is known concerning lithium transport between fluid compartments in the brain, although Prockop and Marcus [2] failed to find evidence for the active removal of lithium from CSF (cerebrospinal fluid) in the dog. An understanding of the transport of lithium between CSF and brain is of interest since it might allow an estimation of the lithium concentration in human brain if the CSF concentration was known. The present paper describes perfusion experiments to investigate the mechanism of transport of lithium from CSF. The results are also considered together with those of previous perfusion experiments in which the effects of lithium on sodium transport from blood to cerebrospinal fluid were studied [3].

Ventriculo-cisternal perfusion was carried out following the method of Pollay and Davson [4]. Male New Zealand White rabbits (wt 3–3.5 kg) were anaesthetised using intravenous sodium thiopentone (initially 40 mg/kg; subsequent doses as necessary). Bilateral perfusion was from the lateral ventricles to the cisterna magna at rates of between 27 and 37 μl/min into each ventricle. Perfusion was with an artificial CSF, pH 7.6, of composition (mM): Na^+ 152, K^+ 2.98, Mg^{2+} 1.0, Ca^{2+} 2.1, Cl^- 131, HCO_3^- 25.6, $H_2PO_4^-$ 0.76, Li^+ 1.0 together with 100 mg dextrose and 100 mg Dextran Blue per 100 ml. Perfusion was for 1 hr and 10 min samples of cisternal effluent were collected for analysis of lithium and Dextran Blue. During perfusion arterial blood samples were taken from the central ear artery for estimation of plasma lithium. After perfusion the animal was killed by thiopentone overdose and the brain excised. Lithium was extracted from the brain with 0.75 M nitric acid following the method of Bradbury *et al.* [5]. Recovery of lithium was 90 per cent. Dextran Blue concentrations were estimated by its extinction at 625 nm. A transport constant K_{out} and the clearance into brain were calculated for lithium following the methods of Bradbury and Davson [6]. Lithium was measured by atomic absorption spectroscopy at 670 nm. All chemicals were purchased from British Drug Houses Ltd., except for Tris (Sigma Ltd.) and Dextran Blue (Pharmacia).

During ventriculo-cisternal perfusion the effluent concentrations of Dextran Blue and lithium were found to be less than the respective concentrations in the inflowing fluid. The concentrations of both substances were initially low but increased and reached constant steady-state values after approximately 40 min. These steady-state effluent concentrations were lower than the concentrations in the inflowing fluid. Thus there is a dilution of both Dextran Blue and lithium during perfusion through the ventricles and cisterna magna. This dilution can be expressed as the ratio of outflowing (steady-state) to inflowing concentrations (C_0/C_i). As shown in Table 1 the steady-state value of C_0/C_i for lithium was found to be less than that for the non-diffusable marker Dextran Blue and this indicates a greater dilution of lithium than of Dextran Blue during passage through the ventricles and cisterns. Dextran Blue is thought not to diffuse out of the CSF containing spaces and its dilution is thought to represent the production of CSF [7]. Thus the additional dilution of lithium represents transport of lithium from the CSF containing spaces. This loss of lithium from the perfusion fluid can be expressed mathematically as a transport constant K_{out} [6]. The value of K_{out} for lithium together with the percentage clearance into brain are shown in Table 1. The calculation of these values was made assuming a plasma lithium concentration of zero during perfusion (measurement of plasma lithium showed concentrations of approximately 10^{-6} M). The value of K_{out} for lithium is less than the reported values for sugars which are removed by facilitated diffusion and similar to values for sodium, urea and creatinine which are thought to be lost by passive diffusion [6, 8].

The similarity of the values of K_{out} for lithium and for substances thought to diffuse from CSF to brain extracellular fluid suggests that lithium can diffuse from CSF across the ependyma into the brain. The results, in accord with those of Prockop and Marcus [2], show no evidence for an active transport system removing lithium from CSF. In contrast, both potassium and rubidium have been reported to be removed from CSF by an active transport system [9, 10]. The low clearance of lithium into brain similar to that found for sodium and calcium but lower than that for potassium [8, 11, 12] suggests lithium is slow to penetrate the intracellular space of brain. This, in turn, suggests that lithium enters nerve cells by a passive process rather than by an ion pump, at least in the case of the rabbit. Potassium, which is actively pumped into cells, has a clearance value into brain of 55 per cent [8, 12].

Perfusion of the rabbit ventricular system with an artifi-

Table 1. Parameters describing the transport of lithium from perfusion fluid during ventriculo-cisternal perfusion

Steady-state value of C_0/C_i for Dextran Blue	Steady-state value of C_0/C_i for Lithium	Transfer constant K_{out} for Lithium	Clearance of Lithium into brain as a % of total clearance
0.83 ± 0.048 (6)	0.71 ± 0.073 (7)	10.2 ± 4.2 (7)	15.8 ± 1.7 (4)

Figures given are mean values ± S.D. with the number of estimations in parentheses. C_i and C_0 represent inflowing and outflowing concentrations respectively.

cial-CSF containing 1 mM lithium chloride has been found previously to stimulate the transport of sodium from blood to CSF across the choroid plexus [3]. This effect was postulated to be due to lithium acting on the choroid plexus sodium pump which is thought to be responsible for sodium and potassium transport across that tissue [3, 7, 10]. In view of the proposed orientation of the ATPase in this system [3, 7, 13] it was proposed that the effect of lithium was at the K^+-sensitive side of the ATPase [3]. The present results, showing there to be no active transport of lithium from CSF in the rabbit, suggest that stimulation of sodium transport across the choroid plexus by lithium is not associated with any active transport of lithium by the sodium pump. Thus the effect of lithium on sodium transport may be an effect at an allosteric site on the sodium pump [14] rather than an effect at the transport site. It has been proposed previously that lithium may effect stimulation by acting at both sites [15].

In summary, lithium was found to be lost from the CSF-containing spaces during perfusion of the ventricles with an artificial-CSF containing 1 mM lithium chloride. This loss of lithium was characterised by a transport constant, the value of which suggested that lithium left the CSF by passive diffusion. The small amount (16 per cent) of lithium recovered in the brain showed that little lithium penetrated the intracellular space of brain. The lack of active removal of lithium by the choroid plexus under experimental conditions similar to those in which lithium stimulated choroid plexus sodium transport [3] suggests that active lithium transport is not necessary for lithium to stimulate the sodium pump.

Acknowledgements—The authors would like to thank Miss A. Oliver for technical assistance. J.H. thanks the Medical Research Council for a scholarship.

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