Magnesium exchange between blood and cerebrospinal fluid

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OPPELT, W. W., I. MACINTYRE, AND D. P. RALL. Magnesium exchange between blood and cerebrospinal fluid. Am. J. Physiol. 205(s): 959-962. 1963.—Magnesium exchange between plasma and cerebrospinal fluid (CSF) was studied in dogs using Mg²⁺Cl⁻ and MgCl₂. Normal CSF/plasma magnesium ratio in this animal is 1.34. In face of a plasma magnesium concentration 300-400% of normal, the CSF magnesium only rose to a maximum of 21% above control at the end of 5.5 hr. Intravenously injected Mg²⁺Cl⁻ enters the CSF rapidly, reaching equilibrium within 2-3 hr. The exit rate of magnesium from the CSF has a half time of about 70 min when CSF magnesium levels are close to normal or they are greatly elevated. This rate is not affected by increasing plasma magnesium concentrations. It is concluded that an active transport mechanism is involved in transporting magnesium from blood to CSF, and that diffusion and bulk filtration are responsible for the removal from the CSF.

METHODS

Mongrel dogs, weighing from 8 to 13 kg, were lightly anesthetized with pentobarbital. One group of four dogs received an intravenous infusion of MgCl₂ or MgSO₄, maintaining a constant elevated plasma magnesium concentration for 5.5 hr. Plasma and CSF samples were obtained frequently and magnesium concentrations determined. Another group of five dogs received one intravenous injection each of Mg²⁺Cl⁻ (half-life 22 hr), and plasma and CSF radioactivity were closely followed. A third group of dogs received one injection each of Mg²⁺Cl⁻ into the cisterna magna, and the disappearance of radioactivity in the CSF was followed. Six of these dogs had normal plasma magnesium concentrations, while six received simultaneous intravenous infusions of MgCl₂, raising to and maintaining their plasma magnesium at 300-400% of normal. In the fourth group of eight dogs, MgCl₂ was injected into the cisterna magna, raising CSF magnesium concentration 15- to 30-fold, and the disappearance of this additional magnesium was measured. CSF samples were obtained by withdrawing 0.2 ml from a needle fixed in the cisterna magna. Experiments in which the CSF became blood-tinged were discarded. Plasma samples were obtained by venipuncture with a heparinized syringe.

All chemical determinations of magnesium were carried out in duplicate by the flame spectrophotometry method of Alcock et al. (1). The isotopic magnesium was counted in a Packard Auto Gamma spectrometer, and all results were corrected for decay.

RESULTS

Normal magnesium concentrations. In 14 dogs, the average normal plasma magnesium concentration was 1.61 mEq/liter, with a range of 1.33-2.0 mEq/liter. In 19

however, not been investigated. This report concerns studies carried out in the dog, in which the exchange of radioactive and nonradioactive magnesium was measured between blood and CSF.

Cohen in 1927 first observed that magnesium concentration in cerebrospinal fluid (CSF) was significantly greater than in plasma (2). He also noted that CSF magnesium levels tended to remain stable in face of changing plasma concentrations, but that these CSF values approached those of plasma in tuberculous meningitis when the blood-CSF barrier is presumably impaired (10). Other workers confirmed these findings (3, 7, 9, 15, 16), and McCance and Watchorn in 1932 (8) concluded that CSF magnesium concentration was normally fixed at a definite level by an active cellular process. More recently, Kemeny et al. (4-6) infused magnesium intravenously and found that, in spite of significant elevation of plasma magnesium, CSF magnesium tended to remain stable. The mode of entry of magnesium into the CSF and its exit from that fluid has,

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1 A preliminary report of these experiments was presented to the Federation of American Societies for Experimental Biology. (Federation Proc. 21: 300, 1962).
dogs, average CSF magnesium concentration was 2.16 mEq/liter, with a range of 1.93-2.90 mEq/liter. Thus the normal CSF/plasma magnesium ratio was 1.34. Since normally about 40% of plasma magnesium is protein bound (12) and presumably not available for exchange across the blood-CSF barrier and little, if any, CSF magnesium is thus bound, the CSF/plasma ratio of exchangeable magnesium was about 2.2.

Intravenous magnesium infusions. A continuous intravenous infusion of MgCl₂ was administered to three dogs, and one dog received a similar infusion of MgSO₄. Sufficient magnesium was given to maintain plasma magnesium at 275-360% of control values for 5.5 hr (Fig. 1). During the total experiment, CSF magnesium only rose to 91% above control levels. A gradual increase in CSF magnesium seemed evident during the infusion, the CSF values during the 1st hr being 5% above control, during the 2nd hr 12%, during the 3rd hr 14%, and during the 4th and 5th hr 18% above control.

Intravenous injection of tracer doses of Mg²⁺, Mg²⁺Cl₂, 40-90 μc, representing 2.3-4 mg magnesium, was rapidly injected intravenously into five dogs. It was noted that after mixing had taken place, plasma radioactivity disappeared with a half time of 2-3 hr (Fig. 2). CSF radioactivity appeared rapidly, steadily increased, reached its peak at an average of 150 min after injection, and then fell off with a half time similar to that in plasma. CSF radioactivity, however, remained constantly at a higher level than plasma activity, the ratio of the two values was close to the normal CSF/plasma ratio for magnesium. Chemical determinations of magnesium in plasma and CSF after isotope injection did not show any significant change as compared to control values.

Removal of magnesium from the CSF. Mg²⁺Cl₂, 0.8 ± 0.2 μc, representing 0.04-0.8 mg magnesium, was injected into the cisterna magna of six dogs, followed by vigorous barbotage. This amount of isotope caused a rise of 5-50% in CSF magnesium concentration. After an initial mixing phase of 30-60 min, CSF radioactivity disappeared with an average half time of 70 min (Table 1, Fig. 3). There was no noticeable difference in disappearance rate in those dogs where CSF magnesium was raised 50% as compared to those where only a 5-10% increase occurred. Similar intracisternal injections of Mg²⁺Cl₂ were done in six dogs whose plasma magnesium was elevated about 300% by means of a simultaneous continuous intravenous infusion of MgCl₂. Under these conditions, decrease of CSF radioactivity occurred at the same rate as in the dogs with normal plasma magnesium concentrations (Table 1, Fig. 3).

MgCl₂, 0.5-1.0 mEq, was injected into the cisterna magna of eight dogs, followed by vigorous barbotage. This caused a 15- to 30-fold increase in CSF magnesium concentration, with 5-min postinjection values of 30-60 mEq/liter. No change in plasma magnesium concentration was detected. The disappearance rate of this excess magnesium was followed over 6 hr, and was found to have a half time of about 75 min (Table 1, Fig. 3). This is very similar to the rate observed in the isotope experiments where CSF magnesium concent-
CSF MAGNESIUM EXCHANGE

Table 1. Exit of magnesium from CSF

<table>
<thead>
<tr>
<th>Time, min, After Injection</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Dogs receiving 0.8-1.2 μc Mg³⁺Cl₂ intracisternally</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>19.0±0.5</td>
<td>7.6±1.1</td>
<td>3.4±0.7</td>
<td>2.0±0.4</td>
<td>1.2±0.6</td>
</tr>
<tr>
<td>B</td>
<td>13.0±2.4</td>
<td>6.4±1.6</td>
<td>3.7±1.0</td>
<td>1.7±0.4</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>C</td>
<td>45.0±5.8</td>
<td>34.0±6.7</td>
<td>20.4±5.7</td>
<td>9.0±2.3</td>
<td>5.2±2.0</td>
</tr>
</tbody>
</table>

Values are the per cent of the 5-min CSF magnesium radioactivity, (for groups A and B) or 10-min excess CSF magnesium concentration (group C), ± standard error of the mean remaining at the indicated times.

Discussion

This study demonstrated that CSF magnesium concentrations do not respond quickly to an elevated plasma magnesium level. After 3-4 hr of maintenance of an elevated plasma magnesium concentration, a small but significant elevation of CSF magnesium occurred. This suggests that plasma and CSF magnesium might reach a new steady-state ratio if the abnormally elevated plasma magnesium were maintained long enough. The mechanism that maintains the normal CSF/plasma magnesium ratio and prevents rapid equilibration with plasma probably involves active transport of this ion from the plasma into the CSF. This concept is supported by the fact that normally a significantly higher concentration of magnesium is maintained in CSF as compared to plasma and that there is a tendency to maintain a fixed CSF concentration in face of changing plasma levels. That this mechanism is not just one of relative impermeability to magnesium of the blood-CSF barrier (when plasma magnesium is elevated) is indicated by our finding that isotopically labeled magnesium enters the CSF rapidly and is equilibrated within 2-3 hr. This also suggests that the mode of exit of magnesium from the CSF is involved in the maintenance of a stable CSF magnesium concentration.

In general, there are three major ways by which a compound may leave the CSF. These are removal by bulk flow, by nonspecific diffusion, and by active transport. Bulk flow refers to the filtration of CSF from the subarachnoid space through the one-way valve system of the arachnoid villi into the venous system. It is thus a nonspecific way of removing CSF with its total contents, and in the steady state its rate is dependent on the rate of production of new CSF. Data of Rothman et al. (14) on the rate of removal of inulin from the CSF and of Oppelt et al. (11) on the rate of CSF production show that the rate of removal by bulk flow has a half time in excess of 2 hr. From our findings of a half-time removal rate of about 70 min when close-to-normal CSF magnesium concentrations were maintained, it seems likely that bulk flow alone cannot account for the removal of magnesium from the CSF. An additional mechanism, at least in part diffusion, appears to be present. If a compound or ion is removed from the CSF by simple diffusion only, the relative rate of its removal should be independent of its concentration in the CSF. Our data shows that the rate of removal of bulk flow has a half time in excess of 2 hr. From our findings of a half-time removal rate of about 70 min when close-to-normal CSF magnesium concentrations were maintained, it seems likely that bulk flow alone cannot account for the removal of magnesium from the CSF. An additional mechanism, at least in part diffusion, appears to be present. If a compound or ion is removed from the CSF by simple diffusion only, the relative rate of its removal should be independent of its concentration in the CSF. Our data shows that the rate of removal half time was about 70 min with normal CSF magnesium and 75 min when CSF magnesium concentration greatly increased. This is consistent with the postulation that diffusion and bulk flow are important in the removal of magnesium from the CSF.

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REFERENCES