The transfer of $^{35}$S-methionine sulphone across the blood-cerebrospinal fluid barrier

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The study of the transfer of amino-acids across the blood-brain and blood cerebrospinal fluid barriers is complicated by the rapid incorporation of amino-acids into the proteins and lipoproteins of the brain. The turnover of methionine in the brain has been demonstrated by the work of Gaitonde and Richter (1955, 1956), Niklas and Oehlert (1956), and Clouet and Richter (1959). In order to study the rate of transfer of amino-acids across the blood cerebrospinal fluid barrier it is necessary to use compounds similar to amino-acids but which do not enter into the metabolic processes of the brain. Koloušek and Babický (1961) investigated the metabolism of methionine sulfoximine and methionine sulphone in rat brain. They found that methionine sulphone was not incorporated in the acid insoluble fraction and concluded that methionine sulphone does not take part in protein synthesis in the brain. Methionine sulphone, therefore, appeared to be an inert amino-acid derivative which might be suitable for studies of blood-cerebrospinal fluid transport.

We report here the preliminary findings of an investigation into the blood-cerebrospinal fluid barrier to methionine sulphone in human subjects undertaken as part of an investigation of the blood-cerebrospinal fluid barrier in mental disorders. In previous work (Coppen, 1960) the rate of transfer of $^{24}$Na from blood to cerebrospinal fluid was measured: it was found to be normal in schizophrenic patients but very much slower in patients suffering from a depressive illness.

**Patients and Methods**

Three small groups of patients (13 in all) were selected for testing. The control group consisted of three psychiatically normal patients undergoing neurological investigations who were subsequently found to have no organic disease of the nervous system. Five schizophrenic patients and five patients suffering from

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from approximately the same volume of blood and cerebrospinal fluid no absorption correction was necessary.

The counting rates of the cerebrospinal fluid and blood samples were plotted against time (Fig. 1). The rate of entry was expressed as a transfer constant ($k_{in}$) in the equation:

$$\frac{d C_{C-SF}}{dt} = k_{in} C_b - C_{C-SF}$$

where $C_{C-SF}$ and $C_b$ is the concentration of methionine sulphone in cerebrospinal fluid and blood respectively. The transfer constant was estimated by graphical integration (Davson and Luck, 1959).

RESULTS AND DISCUSSION

The transfer rates of methionine sulphone from blood into cerebrospinal fluid are shown in Table I. The diagnosis, time of taking fluid after the injection of methionine sulphone, and the calculated values for $k_{in}$ have been given. The figures for $k_{in}$ show considerable scatter (range 0.00013 to 0.0031). The schizophrenic patients had slower entry rates than the other patients, but clearly no conclusion can be deduced from such small numbers. The case with spinal block is of interest since it shows that, similarly to Na$^{24}$ (Tubiana, Benda, and Constans 1951; Crow, 1955), methionine sulphone can pass from blood to cerebrospinal fluid independently of flow from the choroid plexus.

All the radioactivity of whole blood was found in compounds soluble in trichloracetic acid but it was also found that a considerable part of the radioactivity in these extracts was present in compounds other than methionine sulphone. $^{35}$S-Methionine sulphone was separated from other $^{35}$S-labelled compounds by adsorbing the sulphone on a cation exchange resin followed by elution with ammonia solution. Two-dimensional paper chromatography showed that about 95% of the radioactivity eluted from the resin was present as $^{35}$S-methionine sulphone. The washings of the resin contained other $^{35}$S-labelled compounds which accounted for 40 to 50% of the total radioactivity in the trichloracetic acid extracts of blood. In urine the uptake of $^{35}$S in these compounds reached 80 to 92% of the total radioactivity. A small amount of this radioactivity was precipitated as benzidine $^{35}$S-sulphate but the major fraction of $^{35}$S was present in other compounds which were not identified. It is therefore clear that methionine sulphone is not metabolically inert. The amounts of unchanged $^{35}$S-methionine sulphone remaining in the blood and cerebrospinal fluid were sufficient for transfer constants to be determined; but the possibility must be considered that the unidentified compounds might compete with methionine sulphone for transfer across the blood cerebrospinal fluid barrier.

**TABLE II**

<table>
<thead>
<tr>
<th>Substance</th>
<th>$k_{in}$min$^{-1}$</th>
<th>Animal</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl alcohol</td>
<td>0.225</td>
<td>Rabbit</td>
<td>Davson (1956)</td>
</tr>
<tr>
<td>Thiourea</td>
<td>0.0057</td>
<td>Dog</td>
<td>Davson (1956)</td>
</tr>
<tr>
<td>$^3$Cl</td>
<td>0.019</td>
<td>Dog</td>
<td>Davson (1956)</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.0087</td>
<td>Rabbit</td>
<td>Davson (1956)</td>
</tr>
<tr>
<td>$^4$Na</td>
<td>0.0062</td>
<td>Man (lumbar fluid)</td>
<td>Coppen (1960)</td>
</tr>
<tr>
<td>Tritiated water</td>
<td>0.025</td>
<td>N'An (lumbar fluid)</td>
<td>Coppen (1960)</td>
</tr>
<tr>
<td>Methionine sulphone</td>
<td>0.0020-0.0031</td>
<td>Man (lumbar fluid)</td>
<td>This paper</td>
</tr>
</tbody>
</table>

**TABLE I**

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Organic Group</th>
<th>Schizophrenic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>Sex</td>
<td>Time After Lumbar Puncture (hr.)</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>0.0019</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>0.0021</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>0.00074</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Means</td>
<td></td>
<td>0.0016</td>
</tr>
</tbody>
</table>
The estimates of the transfer constant for methionine sulphone are compared with values calculated for some other substances in Table II.

SUMMARY

The rate of transfer of methionine sulphone was measured from blood to lumbar cerebrospinal fluid in man. This substance was found to enter the cerebrospinal fluid relatively slowly at a rate comparable to that found for sodium ions.

REFERENCES

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