Effect of ornithine alpha oxoglutarate on brain metabolism in patients with chronic liver disease

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SYNOPSIS Patients with chronic liver disease, yet without severe encephalopathy, were found to show evidence of increased brain utilization of glucose. The changes were abolished after an intravenous infusion of 15 g ornithine alpha oxoglutarate, given over a period of 15 minutes. The possible implications of these observations are discussed.

When ammonium salts were given intravenously to freely ventilating dogs to raise the blood ammonia to those levels found in hepatic encephalopathy, the glucose utilization of the brain was increased without similar increase in oxygen consumption. This rise in glucose utilization resulted in lactic acidosis and hyperventilation (James et al., 1974).

The earliest disturbance of brain metabolism in patients with liver disease was an increase in the cerebral utilization of glucose at a time when oxygen consumption was little changed. Cerebral blood flow initially was elevated (Porro et al., 1969). However, as the encephalopathy became more severe, oxygen and glucose consumption of the brain, together with cerebral blood flow, decreased. These changes have been interpreted as showing evidence of anaerobic glycolysis (Alexander et al., 1965).

Despite the fact that Fazekas et al. (1956) were unable to detect any correlation between the changes in cerebral oxygen consumption and the elevation of blood ammonia in their patients, of all possible aetiological factors concerned in the genesis of encephalopathy, ammonia still remains one of the most favoured (Zieve, 1966).

In the dog experiments referred to above administration of ornithine alpha oxoglutarate not only alleviated the rise in blood ammonia that occurred but also favourably affected the changes in brain metabolism (James et al., 1972).

The purpose of the present study was to determine in patients with hepatic disease whether ornithine alpha oxoglutarate infusion affected brain metabolism in any similar way, particular attention being paid to cerebral glucose utilization. Patients with chronic liver disease who exhibited only minimal neurological signs (grade 1 electroencephalogram (EEG) at most) were chosen, as it was felt that these were the most likely of all to have high cerebral glucose consumption rates. Brain oxygen and glucose consumption were studied in six such patients before and after the intravenous infusion of ornithine alpha oxoglutarate (OAKG) over a period of 15 minutes.

A further patient admitted in deep coma (grade 4 EEG) was also studied before and after four hours' infusion with 60 g ornithine alpha oxoglutarate.

METHODS

CEREBRAL BLOOD FLOW AND METABOLISM Cerebral blood flow was measured using radioactive krypton gas by a modification of the McHenry desaturation technique (McHenry, 1964). Under 2% procaine local anaesthesia, small needles (21 gauge) with catheters attached were inserted in the jugular bulb as described by Gibbs et al. (1945), and into the femoral artery. Once the needles and attached catheters were in position the patient breathed from a spirometer containing radioactive 85Krypton in air for 10 minutes. Then the patient breathed room air and timed samples were taken from both femoral artery and jugular bulb during the next 10 minutes.

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TABLE 1

EFFECT OF 15 g ORNITHINE ALPHA OXOGLUTARATE GIVEN INTRAVENOUSLY OVER 15 MINUTES ON CEREBRAL BLOOD FLOW, CEREBRAL OXYGEN AND GLUCOSE CONSUMPTION OF PATIENTS WITH CHRONIC LIVER DISEASE BUT WITH MINIMAL ENCEPHALOPATHY; ARTERIAL AND JUGULAR VEIN LACTATE LEVELS ARE ALSO SHOWN

<table>
<thead>
<tr>
<th>Patient and sex</th>
<th>Diagnosis</th>
<th>Age (a)</th>
<th>Cerebral blood flow (ml/100 g/min)</th>
<th>Cerebral oxygen consumption (ml/100 g/min)</th>
<th>Cerebral glucose consumption (mg/100 g/min)</th>
<th>Arterial lactate (mmol/l)</th>
<th>Jugular vein lactate (mmol/l)</th>
<th>PaCO₂ mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>Portacaval shunt, portal vein thrombosis</td>
<td>24</td>
<td>3.3</td>
<td>51</td>
<td>3.4</td>
<td>8.0</td>
<td>5.6</td>
<td>1.065</td>
</tr>
<tr>
<td>2 M</td>
<td>Alcoholic cirrhosis</td>
<td>70</td>
<td>65</td>
<td>52</td>
<td>6.2</td>
<td>10.0</td>
<td>2.210</td>
<td>1.530</td>
</tr>
<tr>
<td>3 F</td>
<td>Alcoholic cirrhosis</td>
<td>30</td>
<td>67</td>
<td>70</td>
<td>2.3</td>
<td>4.0</td>
<td>11.0</td>
<td>7.0</td>
</tr>
<tr>
<td>4 F</td>
<td>Cryptogenic cirrhosis, portacaval shunt</td>
<td>29</td>
<td>47</td>
<td>62</td>
<td>1.7</td>
<td>3.4</td>
<td>4.2</td>
<td>2.0</td>
</tr>
<tr>
<td>5 F</td>
<td>Primary biliary cirrhosis</td>
<td>46</td>
<td>38</td>
<td>38</td>
<td>2.4</td>
<td>2.4</td>
<td>8.3</td>
<td>5.3</td>
</tr>
<tr>
<td>6 F</td>
<td>Cryptogenic cirrhosis</td>
<td>26</td>
<td>79</td>
<td>85</td>
<td>2.1</td>
<td>4.4</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Mean SEM</td>
<td></td>
<td></td>
<td>63</td>
<td>60</td>
<td>2.4</td>
<td>3.4*</td>
<td>7.6</td>
<td>5.0*</td>
</tr>
</tbody>
</table>

* Significantly different from control value of 5% level by Wilcoxon's sum of ranks method.
for subsequent \(^{85}\)Krypton analysis. The conventional height over area formula was used to derive cerebral blood flow.

Samples were also taken from the artery and the jugular bulb for oxygen and glucose content so that consumption of oxygen and glucose by the brain could be calculated.

Arterial and venous samples for lactate levels were obtained from the six patients with mild encephalopathy.

Oxygen content was measured by the method of Linden et al. (1965) and glucose by a glucose oxidase method (Trinder, 1969).

The pH and PCO\(_2\) were measured with appropriate radiometer electrodes. Lactic acid levels were measured by the method of Hohorst (1963).

The aerobic index has been calculated as an index of the aerobic metabolism of glucose as suggested by Alexander et al. (1965).

\[
\frac{A-V O_2 (\text{mmol})}{6 \times A-V \text{ glucose (mmol)}} \times 100\%
\]

Normal values are above 80%.

RESULTS

No attempt was made to evaluate any clinical difference in the patients with minimal encephalopathy.

CEREBRAL BLOOD FLOW  A wide scatter in values from 38 ml/100 g/min to 79 ml/100 g/min was found. There was no overall change in cerebral blood flow as a result of OAKG therapy but individually some changes were fairly substantial (patient 1 and patient 4). Changes in PaCO\(_2\) do not appear to have been the reason for these flow changes (Table 1).

CEREBRAL METABOLISM  In most patients there was an increase in cerebral oxygen consumption.

In one (patient 1) of the two patients where there was no change (patients 1 and 5), cerebral oxygen consumption was already within the normal range. There was a fall in the glucose consumption in five of the six patients and in all patients an apparent improvement in the aerobic index. Before therapy the mean aerobic index was 40% and after therapy, 93%.

Both arterial and venous lactate levels were initially raised (upper limit of normal 1.5 mmol/l) but no consistent changes occurred after the administration of OAKG. It should also be noted (Table 1) that some of the arteriovenous differences of lactate are reversed.

PATIENT WITH COMA  After OAKG infusion cerebral blood flow and oxygen consumption increased and glucose consumption fell. There was no obvious change in the patient’s clinical state despite some marginal improvement in the EEG. The patient died of fulminant hepatitis several days later.

DISCUSSION

The finding of cerebral anaerobic glycolysis in patients with hepatic encephalopathy has again been confirmed.

The six patients with chronic liver disease were found to have an elevated brain blood flow and increased brain glucose utilization together with a depression in the cerebral aerobic index. These values are very similar to those reported by us previously and further confirm the findings of Polli et al. (1969).

As expected, the values for brain oxygen consumption were higher than those for patients with severe neurological abnormality (Lunzer et al., 1974).

The validity of calculating brain oxygen, glucose consumption, and lactic acid production depends on whether the venous blood concentration draining the organ is in equilibrium with the tissue concentration and that the arterial concentration is constant (Zierler, 1961).

Alexander et al. (1965) felt that so far as the brain was concerned equilibrium was quickly attained for both oxygen and glucose but not for lactate.

Oxygen and glucose consumption levels have been calculated (Table 2); separate values for arterial lactate and venous lactate are tabulated.
Unfortunately, it is unclear what happens to the excess glucose consumed by the brain. The arterial lactate levels are increased (normal up to 1.5 mmol/l) but there is no clear evidence as to whether or not increased brain lactate production is occurring.

The increase in glucose utilization and ultimate failure of the tricarboxylic acid cycle was attributed by Bessman and Bessman (1955) to the depletion of intracellular alpha oxoglutarate by excess ammonia. They postulated that glutamate and eventually glutamine would be formed; the rise in lactic acid could be explained as being secondary to the failure of the cycle.

On the other hand, it has been argued by McKhann and Tower (1961) that lactic acidosis in liver disease could result from the inhibition of decarboxylation of pyruvate to acetyl CoA by ammonia. Some further evidence to support this contention was cited by Klassen et al. (1969) who found increased muscle lactic acid production in patients and that this was related to blood ammonia elevation. Since fatty acid utilization was normal, these workers felt that the citric acid cycle was functioning normally from acetyl CoA onwards.

Ornithine alpha oxoglutarate administration causes a fall in the cerebral glucose utilization and an increase in oxygen consumption. It is known that ammonia can, in laboratory animals, provoke cerebral anaerobic glycolysis (James et al., 1974) and that OAKG is able to lower blood ammonia in patients with liver failure (Michel et al., 1971). Thus, ornithine alpha oxoglutarate could act as suggested by Michel et al. (1971) by lowering blood ammonia levels. Alternatively, it could accelerate the citric acid cycle by replenishing the intermediaries or by bypassing the pyruvate decarboxylase stage.

The fall in cerebral glucose utilization could then be explained by some form of negative feedback mechanism from the cycle.

We have previously suggested that CO₂ production could be the important factor. It is known that elevated CO₂ levels decrease (Xanalatos and James, 1972) and lowered CO₂ levels increase glucose utilization by the brain (Alexander et al., 1965).

It must be remembered also that ammonia is only one of many factors that can cause cerebral anaerobic glycolysis. Thus, the finding of anaerobic glycolysis in patients with hepatic encephalopathy together with its reversal by OAKG does not necessarily imply that ammonia is involved.

In patients with hepatic encephalopathy, the biochemical disturbance of anaerobic glycolysis can be at least partially reversed with alpha oxoglutarate administration but the mechanism by which these changes are effected remains in doubt.

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