On the Intermediate Metabolism of Carbohydrates in the Brain of Healthy Persons

By
Satoshi Sato, Mitsuaki Tateyama, Chojiro Sasamori, Shigeru Kobayashi, Yaichiro Chiba and Yoshimasa Takeda

From the Department of Internal Medicine, Sendai National Hospital, Sendai; Director: Dr. T. Kato, Professor Emeritus of Tohoku University

(Received for publication, November 4, 1963)

On 19 healthy subjects distributed in almost all age ranges, the glucose, the pyruvic acid and the lactic acid contents were measured in the blood samples taken from the internal jugular vein and the femoral artery, simultaneously with the cerebral hemodynamics by N2O method, to determine the amount of metabolized carbohydrates in unit weight of brain tissue. The cerebral glucose consumption (CMRg1) was found in a close relationship with CMRO2, suggesting that the blood glucose is the most important source of energy for the brain. Cerebral arteriovenous differences of glucose and cerebral blood flow were in a negative correlation, indicating the constancy of glucose supply as energy source. Pyruvic acid and lactic acid were estimated to be carried out from the brain in almost all cases, but the correlation between the outflow of these acids and the cerebral oxygen consumption was obscure. The mean value of cerebral glucose consumption was almost equal to the sum of mean values of the cerebral oxidation of glucose and the amounts of acids transferred out of the brain. Hence, an equilibrium in carbohydrate metabolism of the brain of healthy persons was elucidated. In aged subjects, the derangement of carbohydrate metabolism is evident with a well balanced equilibrium on a lower level, presumably as a physiological senile phenomenon.

These findings and presumptions should be evaluated in future by more accurate methods, which enable us to analyze obtained values more exactly. From the present standpoint, we should be satisfied with the present summaries.

In the previous papers the present authors have discussed the cerebral hemodynamics in hypertensive and postapoplectic patients and in healthy persons, measuring them with Kety’s N2O method. In them, a tendency of decrease in cerebral blood flow and a marked diminution in cerebral oxygen consumption were demonstrated in hypertensive patients, especially in those with cerebral arteriosclerosis or over fifty years of age. These findings suggest that some abnormalities also in carbohydrate metabolism would be revealed in the brain of...
those patients, so far as the blood glucose is the main source of energy in the brain, as presumed by Himwich and others.

Hitherto, many points in the carbohydrate metabolism in the brain have been left obscure, because of the difficulties in the measurement of cerebral blood flow. Recently, the determination of carbohydrate metabolism per minute per unit weight of brain tissue was rendered possible, and Kety, Schienberg, Aizawa and others could reveal the important findings, the mean value of cerebral glucose consumption and cerebral respiratory quotient in healthy subjects were established. However, convincing results on the basic pattern of carbohydrate metabolism in the brain have not been reported yet, presumably because the evaluation of the small differences in the contents of sugar and other carbohydrates in different blood specimens implies many difficulties in the present situation.

In this report the carbohydrate metabolism in the brain of healthy subjects was studied with the method related below, and some interesting data could be obtained. They may contribute to the understanding of the mechanism of functional disturbances of the brain.

EXPERIMENTALS

METHOD

On 19 healthy persons, chosen equally from all age ranges between twenty and sixty years, the cerebral blood flow was measured by means of N₂O method, simultaneously the blood glucose by Folin-Wu’s method, the blood pyruvic acid by dinitrophenyl-hydrazine method, and the blood lactic acid by Dische and Laszlo’s method, on the specimens obtained from internal jugular vein and the femoral artery. The amounts of these substances transferred during the passage through the brain per 100 g of brain per minute were calculated by the formula as described below, and the cerebral oxidation rate of glucose was also calculated stoichiometrically from the cerebral oxygen consumption.

Abbreviations and formulae:
Cerebral blood flow (CBF)
Cerebral oxygen consumption (CMRO₂)
Agl, Apyr, Alac The amounts of glucose, pyruvic acid and lactic acid in arterial blood
Vgl, Vpyr, Vlac The amounts of glucose, pyruvic acid and lactic acid in venous blood
Cerebral glucose consumption (CMRG₁) A-Vgl × CBF/100
Rate of cerebral metabolism of pyruvic acid V-Apyr × CBF/100
Rate of cerebral metabolism of lactic acid V-Alac × CBF/100
Rate of cerebral oxidation of glucose 1.34 × CMRO₂
RESULTS AND DISCUSSION

As mentioned in the introduction, there are many difficulties in evaluating the small differences of these substances in arterial and venous blood that are not surmounted also in our investigation. Accordingly, the authors strove to obtain the approximate values and the general tendencies in the metabolism.

The mean values of $\text{CMRO}_2$ and $\text{CMRg}_1$ were given in Table I, showing some correlation with aging.

**Table I.** Cerebral Oxygen Consumption ($\text{CMRO}_2$) and Cerebral Glucose Consumption ($\text{CMRg}_1$) in Healthy Persons

<table>
<thead>
<tr>
<th>Mean Values of $\text{CMRO}_2$</th>
<th>Mean Value</th>
<th>Standard Deviation</th>
<th>Confidence Limit</th>
<th>Rejection Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young or middle aged 10 cases</td>
<td>3.47</td>
<td>0.26</td>
<td>±0.097</td>
<td>±0.28</td>
</tr>
<tr>
<td>Old aged 9 cases</td>
<td>2.87</td>
<td>0.61</td>
<td>±1.29</td>
<td>±0.41</td>
</tr>
<tr>
<td>Average in 19 cases</td>
<td>3.18</td>
<td>0.56</td>
<td>±1.15</td>
<td>±0.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Values of $\text{CMRg}_1$</th>
<th>Mean Value</th>
<th>Standard Deviation</th>
<th>Confidence Limit</th>
<th>Rejection Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young or middle aged 10 case</td>
<td>6.85</td>
<td>2.90</td>
<td>±6.80</td>
<td>±2.43</td>
</tr>
<tr>
<td>Old aged 9 cases</td>
<td>6.15</td>
<td>1.22</td>
<td>±4.47</td>
<td>±1.44</td>
</tr>
<tr>
<td>Average in 19 cases</td>
<td>6.50</td>
<td>2.47</td>
<td>±5.10</td>
<td>±1.19</td>
</tr>
</tbody>
</table>

Group of young or middle aged includes subjects younger than 50 years, while old aged older than 50 years.

(1) Cerebral glucose consumption ($\text{CMRg}_1$) and rate of cerebral oxidation of glucose

As shown in Fig. 1, the distribution of $\text{CMRg}_1$ was of considerable wider range, and as related above, the cases with decreased $\text{CMRg}_1$ appeared a little more frequent in the group of advanced age. A close parallelism would be found between $\text{CMRg}_1$ and $\text{CMRO}_2$, while a negative correlation between $A-\text{Vg}_1$ and CBF was demonstrated, suggesting the existence of a mechanism to maintain the balance between glucose consumption and its supply, presumably because the blood glucose is the most important source of energy for the brain function. The correlations between $A\text{g}_1$ and $A-\text{Vg}_1$ or between $A\text{g}_1$ and $\text{CMRg}_1$ were obscure (Fig. 2).
Intermediate metabolism of pyruvic acid in the brain

The distribution of arterio-venous differences of pyruvic acid was markedly wide, and its content in venous blood was larger than that in arterial blood in all cases. This finding is leading to the concept that the pyruvic acid is carried out of the brain of normal subjects as a rule.

The amount of expelled pyruvic acid seemingly decreased in accordance with aging (Fig. 3). No close relation between CMRO2 and the arterio-venous difference of pyruvic acid content could be demonstrated.

Intermediate metabolism of lactic acid in the brain
Intermediate Metabolism of Carbohydrates in Brain

The cerebral arterio-venous differences of lactic acid show a marked dispersion of their values. But in all cases, just as in pyruvic acid metabolism mentioned above, the concentration in venous blood was higher than that in the arterial blood; thus exportation of lactic acid from the brain also could be presumed as a proper process in carbohydrate metabolism in the brain. No quantitative relationship could be demonstrated between the outflow of lactic acid and either CMRO$_2$ or CMRg1.

(4) Mutual relationships among carbohydrates metabolized in the brain

Table II shows that the sum of cerebral oxidation rate of glucose calculated from CMRO$_2$ and the outflow of pyruvic acid and lactic acid, all in the mean,

<table>
<thead>
<tr>
<th>Cerebral glucose consumption (CMRg1)</th>
<th>Cerebral glucose oxidation (CMRO$_2 \times 1.34$)</th>
<th>Lactic acid output (V–A lac × 100/CBF)</th>
<th>Pyruvic acid output (V–A pyr × 100/CBF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.50</td>
<td>4.23</td>
<td>2.00</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 6.31</td>
</tr>
<tr>
<td>mg/100g of brain, per minute</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
being equivalent to 6.31 mg of glucose per 100 g brain per minute, is nearly equal
to the mean value of CMRg1, that is 6.50 mg per 100 g brain per minute.

From this result, it is also suggested that an equilibrium is maintained in the
brain of healthy persons in respect of carbohydrate metabolism, as it is partially
estimated by Gibbs and Scheinberg.

In addition, we must point out the question on the differences of the actual
values of cerebral exportation of pyruvic acid and lactic acid in our results from
those of other investigators. It may depend upon the difference in each methods
employed by the different investigators. Further investigation is needed in this
field.

As mentioned above, with advance of aging, CMRO2 together with CMRg1
decreases to some extent and the amount of pyruvic acid and lactic acid outflows
is also decreased in general. From these data, the following mechanism may be
deduced.

With advance of aging, senile atrophy and derangement in the metabolism of
the brain will gradually develop, resulting even in the decrease of energy demand.
In this condition, a relatively small amount of glucose and/or oxygen will meet
the decreased demand. Accordingly, it is clear that the intermediate metabolic
products would not be increased in the brain tissue, and consequently the outflow
of them was left unchanged or rather decreased. An equilibrium on a lowered
level may be maintained in these cases.

There are many disputes on the cause of diminished metabolism in the
brain in senile subjects, being attributed to senile vascular change by some investiga-
tors or to primary senile hypofunction of the brain tissue by others.

From our results, however, we are inclined to explain the mechanism of the
diminution chiefly as a result of lowered metabolism primarily owing to senile
hypofunction of the brain tissue which gradually develops, though some vascular
change may also be considered unquestionably as exaggerating the progress of
tissue damages, because it is rationally presumed that the decrease of these acids
in venous blood will be expected only when the oxygen supply is sufficient to meet
the demand of the tissues, and the combined decrease of these acids and CMRg1
suggests the lowered metabolic level without concomitant lack of oxygen. On the
other hand, if the brain activity is not lowered and the vascular change develops
by aging, the latter should restrict the oxygen supply at first, causing acid forma-
tion in the brain, which results in the increase of acids issue from the brain with
aging; but it was not the case as revealed by our investigation.

If these assumptions are reliable, they will contribute to the explanation of
cerebral carbohydrate metabolism also in hypertension and cerebral arteriosclero-
is, where the circulatory insufficiency is believed to precede the lowered brain
function, in other words, to precede the lowered carbohydrate metabolism of the
brain.
References