Uncoupling of Oxygen and Glucose Metabolism in Persistent Crossed Cerebellar Diaschisis

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Background and Purpose—The pathophysiology of deafferentation-induced changes after stroke remains unclear. Some supratentorial strokes cause persistent decreases in blood flow and metabolism in the contralateral cerebellum (persistent crossed cerebellar diaschisis[CCD]). Our previous study showed uncoupling of oxygen consumption and blood flow in this condition, which may reflect a characteristic change in brain metabolism caused by deafferentation. This uncoupling might be related to oxidation of some substrates other than blood-borne glucose, which could also lead to the uncoupling of oxygen consumption and glucose utilization. The purpose of this study was to investigate whether oxygen consumption is uncoupled from glucose utilization in persistent CCD.

Methods—Using positron emission tomography in 10 unilateral supratentorial stroke patients, we evaluated regional blood flow, oxygen consumption, and glucose utilization in the cerebellar cortex in the chronic stage. Eight patients with a significant cerebellar blood flow asymmetry, defined as outside the 95% confidence limits predefined in 9 normal subjects, were selected as patients with persistent CCD.

Results—In patients with CCD, the cerebellar cortex contralateral to the stroke showed significant decreases in both oxygen consumption and glucose utilization compared with the ipsilateral cerebellar cortex. The decrease in oxygen consumption was less than the decrease in glucose utilization, resulting in a significant increase in the oxygen consumption/glucose utilization ratio.

Conclusions—Persistent CCD caused by stroke may induce uncoupling of oxygen consumption and glucose utilization, which may reflect a characteristic change in brain metabolism caused by deafferentation. (Stroke. 1999;30:1424-1428.)

Key Words: cerebellum ■ cerebral metabolism ■ diaschisis ■ tomography, emission computed
uncoupling of the CMRO₂ and the CBF in persistent CD may be related to the oxidation of some substrates other than blood-borne glucose which could also lead to the uncoupling of the CMRO₂ and the cerebral metabolic rate of glucose (CMR₂).

To investigate whether oxygen consumption is uncoupled from glucose utilization in persistent CD, we measured both the CMRO₂ and CMR₂ by using PET in patients with a unilateral supratentorial stroke and CCD in the chronic stage, and analyzed the changes in the calculated CMRO₂/CMR₂ ratio in the cerebellar cortex contralateral to the stroke.

**Subjects and Methods**

**Patients**

We studied 8 patients with a unilateral supratentorial stroke and persistent crossed cerebellar diaschisis. The subjects were selected from 10 consecutive patients with a unilateral supratentorial stroke in whom CBF, CMRO₂, OEF, cerebral blood volume (CBV), and CMR₂ were all measured using PET in the chronic stage. Criteria for selection were (1) satisfactory visualization of the cerebellum on the PET images; (2) significant CBF asymmetry in the cerebellum, which lay outside the 95% confidence limits as defined in 9 normal subjects, as described below (crossed cerebellar diaschisis); (3) absence of clinical symptoms of ischemia in the vertebrobasilar artery territory; (4) absence of gross morphological alterations in the cerebellum and brain stem on MR images; and (5) normal angiographic findings in the vertebrobasilar system, as determined by use of conventional angiography in patients with infarction and MR angiography in patients with hemorrhage. Two of 10 patients were excluded because they did not show significant CBF asymmetry in the cerebellum. The selected patients included 6 men and 2 women, aged 50 to 74 years (mean ±SD, 63 ±7 years). There were 2 patients with superficial middle cerebral artery (MCA) territory infarcts, 5 with deep MCA territory infarcts, and 1 with putaminal hemorrhage. Seven patients had hemiparesis, and 1 had sensory disturbance. The interval between the stroke event and the evaluations with PET ranged from 4 to 46 months (mean ±SD, 24 ±13 months). The size of the infarct, defined as a well-demarcated hypointense area on T₁-weighted MR images, ranged from 50 to 240 mm³ (mean ±SD, 153 ±69 mm³). No patient suffered from diabetes mellitus or starvation. They had no specific treatments that affected brain metabolism.

**Positron Emission Tomography**

The patient was allowed a light breakfast 6 hours before the PET study. Written informed consent was obtained from each patient under the guidance of the Ethics Committee of the Kyoto University Faculty of Medicine. The PCT-3600W system (Hitachi Medical Co) was used for PET scanning. This system acquires 15 slices with center-to-center distance of 7 mm and transaxial resolution of 6.5 mm full-width at half-maximum (FWHM) at the center. The slice thickness at the center was 6.9 mm FWHM and 5.9 mm FWHM, for in-plane and cross-plane slices, respectively.

The subject’s head was immobilized with a head-holder and positioned with light beams to obtain transaxial slices parallel to the interhemispheric line in the upper slice of the CBF image. We took care not to include the sinus in the regions of interest by comparison with the CBV image.

From the absolute CBF, CMRO₂, OEF, CBV, and CMR₂ values, we calculated the percentage difference between contralateral (CL) and ipsilateral (IL) cerebellar cortex (Δ%) as Δ% = (CL–IL)/IL ×100. We assumed that the values in the ipsilateral cerebellar cortex are not affected in CCD and that the resulting values reflected the percent differences caused by CCD. We also studied 9 normal subjects of similar age (mean age, 58 ±7 years) using the ¹⁵O-gas steady-state method, and calculated the asymmetry index (AI) between the right (R) and left (L) cerebellar cortex as AI = (R–L)/L ×100 and AI = (L–R)/(R×100). AI-L and AI-R for CBF in the normal subjects (mean ±SD) were –0.11 ±3.60% and 0.36 ±3.49%, respectively. The patients with significant cerebellar CBF asymmetry (ie, with an individual value of Δ% <−8.41% for a left supratentorial stroke or <−7.68% for a right supratentorial stroke, which is the lower 95% confidence limit as defined in normal subjects) were selected.

**Hemodynamic and Metabolic Parameters in Ipsilateral and Contralateral Cerebellar Cortices of 8 Patients With Stroke**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ipsilateral</th>
<th>Contralateral</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, ml/100 g/min</td>
<td>41.8±8.6</td>
<td>33.1±6.5*</td>
<td>−20.6±5.7</td>
</tr>
<tr>
<td>CMRO₂, μmol/100 g/min</td>
<td>109.4±18.8</td>
<td>95.3±16.9*</td>
<td>−12.8±4.5</td>
</tr>
<tr>
<td>OEF, %</td>
<td>47.1±6.7</td>
<td>51.6±5.9*</td>
<td>9.7±4.0</td>
</tr>
<tr>
<td>CBV, ml/100 g</td>
<td>3.61±0.68</td>
<td>3.11±0.45*</td>
<td>−13.0±7.0</td>
</tr>
<tr>
<td>CMR₂, μmol/100 g/min</td>
<td>25.5±4.3</td>
<td>20.3±3.4*</td>
<td>−20.0±6.6</td>
</tr>
<tr>
<td>CMRO₂/CMR₂ ratio</td>
<td>4.42±1.14</td>
<td>4.80±1.10*</td>
<td>9.4±7.5</td>
</tr>
</tbody>
</table>

Values are mean ±SD. *P < 0.05 vs corresponding value in the ipsilateral cortex by the Wilcoxon signed rank test (2-tailed).

18 times: just before, at 15, 30, 45, 60, 75, and 90 seconds after, and at 2, 3, 4, 6, 8, 10, 15, 20, 30, 45 and 60 minutes after FDG injection. The PET scan was started 40 minutes after FDG injection, and emission data were collected for 20 minutes. The CMR₂ was calculated by Phelp’s autodigraphic method, using fixed values of k₁ = 0.102, k₂ = 0.130, k₃ = 0.062, and k₄ = 0.0068 for the rate constants and 0.52 for the lumped constant. Functional images were reconstructed as 128×128 pixels, with each pixel representing an area 2.0×2.0 mm.

We analyzed images in the tomographic plane corresponding to the level of the cerebellum. We used the scan slice that most satisfactorily depicted the cerebellar hemisphere. First, in the CBF image, we placed 3 circular regions of interest, 16 mm in diameter, over the gray matter of the cerebellar hemisphere ipsilateral to the supratentorial lesion. These regions of interest were then copied over the contralateral side with respect to the anteroposterior axis, which was determined with respect to the interhemispheric line in the upper slice of the CBF image. We took care not to include the sinus in the regions of interest by comparison with the CBV image.

**Results**

The cerebellar cortex contralateral to the supratentorial lesion showed significant decreases in CBF, CMRO₂, and CMR₂ compared with the ipsilateral cerebellar cortex (Table). The decrease in CMRO₂ was less than the decrease in CMR₂, resulting in a significant increase in the CMRO₂/CMR₂ ratio. The increase in the CMRO₂/CMR₂ ratio was accompanied...
by a significant increase in the OEF and a significant decrease in CBV.

The percent difference of the CBF between the ipsilateral and contralateral cerebellar cortices was significantly correlated with the percent difference of the CMR_{glc} (r=0.76, P<0.05), with the percent difference of the CMRO_{2} (r=0.90, P<0.05) and with the percent difference of the CBV (r=0.81, P<0.05).

The increase in the CMRO_{2}/CMR_{glc} ratio was present in all individual patients, but the percent difference of the CMRO_{2}/CMR_{glc} ratio had a tendency to decrease with time elapsed since the insult (r=−0.69, P=0.067). The percent difference of the CMRO_{2}/CMR_{glc} ratio was not correlated with lesion size.

The Figure shows the images of the cerebellar blood flow and metabolism in a patient with a left putaminal hemorrhage. Among the 8 patients, this patient was studied at the earliest time since the stroke (4 months) and showed the most prominent hemispheric difference of the CMRO_{2}/CMR_{glc} ratio.

**Discussion**

This study demonstrates that oxygen consumption is uncoupled from glucose utilization in persistent CCD. We found that the cerebellar cortex contralateral to the supratentorial stroke showed a significant decrease in both the CMRO_{2} and CMR_{glc} compared with the ipsilateral cerebellar cortex. The CMRO_{2} decreased less markedly than did CMR_{glc}, which resulted in an increase in the CMRO_{2}/CMR_{glc} ratio. The increase in the CMRO_{2}/CMR_{glc} ratio was accompanied by an increase in the OEF and a decrease in the CBV. Because the increase in OEF is not accompanied by the increase in CBV (as observed in ischemia), persistent CCD may result in increased OEF via a mechanism distinct from that in ischemia. The uncoupling of the CMRO_{2} from the CMR_{glc} and CBF may reflect a characteristic change in brain metabolism caused by deafferentation.

The increase in the CMRO_{2}/CMR_{glc} ratio in persistent CCD may be a time-dependent process that occurs in the subacute or chronic stage after stroke. We have no acute versus chronic longitudinal data from the same patients. However, an earlier study of the relationship between the CMRO_{2} and CMR_{glc} in
patients with CCD due to acute stroke showed no difference between the decrease in the CMRO$_2$ and CMR$_{glc}$.	extsuperscript{7} Thus, the increase in the CMRO$_2$/CMR$_{glc}$ ratio in persistent CCD may not be explained by the simple decrease in physiological neural input that may occur in CCD in the acute stage, although an increase in physiological neural activity in the normal brain may be associated with an increase in the CMR$_{glc}$/CMRO$_2$ ratio.	extsuperscript{16} The decrease in the CBF was correlated with that in the CMR$_{glc}$, suggesting that the decrease in CBF may result from the decrease in glucose demand. Thus, the CMRO$_2$ may have been increased on the top of the normal metabolic loss after a decrease in physiological neural input. The increase in the CMRO$_2$/CMR$_{glc}$ ratio had a tendency to decrease with time elapsed since the insult, suggesting that the CMRO$_2$/CMR$_{glc}$ ratio increases in the relatively early phase after deafferentation and then returns to normal gradually. Therefore, the increase in the CMRO$_2$/CMR$_{glc}$ ratio might be related to certain processes occurring after deafferentation, which may include transneuronal degeneration of postsynaptic neurons or some adaptive responses for neuronal survival and synaptic reorganization.	extsuperscript{17,18}

At present, we have no convincing explanation of the mechanism of the increase in the CMRO$_2$/CMR$_{glc}$ ratio in persistent CCD. One possibility is that oxygen is being used to metabolize energy-producing moieties other than glucose (eg, glycogen stores, ketone bodies, amino acids, and lipids). However, supplemental energy production from other substrates may not be needed, because the blood supply of glucose is not primarily required. Therefore, supplemental energy production from other substrates may not be explained by the simple decrease in physiological neural input.

The major problems of the $^{15}$O steady-state method are the underestimation of CBF and CMRO$_2$,	extsuperscript{21} which might lead to a low CMRO$_2$ and a low CMRO$_2$/CMR$_{glc}$ ratio in our patients, as previously discussed.	extsuperscript{22} The ipsilateral cerebellar CMRO$_2$ and CMRO$_2$/CMR$_{glc}$ ratio were 109.4 $\mu$mol/100 g/min and 4.42, whereas the expected value from the literature would be in the region of 150 $\mu$mol/100 g/min and 5 to 6, respectively. Although this method may also underestimate the hemispheric differences of both the CBF and CMRO$_2$, the degree of the effect is the same for both the CBF and CMRO$_2$, with no effect on the hemispheric difference of OEF. In addition, the degree of the hemispheric difference of the CBF was similar to that of the CMR$_{glc}$ in this study. Thus, the increases in the OEF and in the CMRO$_2$/CMR$_{glc}$ ratio may not result from measurement errors of CBF and CMRO$_2$. The measurement of the CMR$_{glc}$ by Phelps' autoradiographic method is affected if changes in the rate constants and lumped constant values occur in persistent CCD.	extsuperscript{23} In our preliminary analysis of the rate constants,	extsuperscript{24} in persistent CCD in some patients included in this study, the cerebellar CMR$_{glc}$ values obtained by the kinetic method had a tendency to be lower than those obtained by the autoradiographic method, which might lead to a further increase in the CMRO$_2$/CMR$_{glc}$ ratio (data not shown).

In conclusion, persistent CCD induces uncoupling of oxygen consumption and glucose utilization. The CMRO$_2$ is decreased less than the CMR$_{glc}$, which results in the increased CMRO$_2$/CMR$_{glc}$ ratio. The increase in the CMRO$_2$/CMR$_{glc}$ ratio may indicate the occurrence of some qualitative changes in brain metabolism in response to deafferentation. Further investigation is needed to clarify the cellular mechanisms underlying the effects of deafferentation and their relationship to neuronal death and anatomic reorganization.

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References


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