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 CCD 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 (CMRglc).

To investigate whether oxygen consumption is uncoupled from glucose utilization in persistent CCD, we measured both the CMRO₂ and CMRglc by using PET in patients with a unilateral supratentorial stroke and CCD in the chronic stage, and analyzed the changes in the calculated CMRO₂/CMRglc 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 CMRglc 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 ± 6 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 mm² (mean ± SD, 153 ± 69 mm²). 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 orbitomeatal line. As part of the scanning procedure but before the PET study, germanium-68–galium-68 transmission scanning was performed for 20 minutes for attenuation correction. For the ¹⁵O-gas study, C⁰O₂ and O² were inhaled continuously at 300 MBq and 500 MBq per minute, respectively. The scan time was 5 minutes, and arterial blood was sampled 3 times during each scan. We calculated CBF, CMRO₂, and OEF based on the steady-state method. Inflation of 1.20 GBq of C¹⁵O was used to measure CBV, and CMRO₂ and OEF were corrected with respect to the CBV. After the completion of the ¹⁵O-gas study, the subject was intravenously infused with 166 to 281 MBq (4.5 to 7.6 mCi) of ¹⁵F-labeled 2-deoxyglucose (FDG). Arterial blood samples were withdrawn at 18 times: just before, at 15, 30, 45, 60, 75, and 90 seconds after FDG injection. The PET scan was started 40 minutes after FDG injection, and emission data were collected for 20 minutes. The CMRglc was calculated by Phelps’s autodigraphic method, using fixed values of K¹⁵ = 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.

From the absolute CBF, CMRO₂, OEF, CBV, and CMRglc 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 = (R-L)/R × 100. AI 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 (i.e., 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>CMRglc, 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/CMRglc 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).

We compared the results in each cerebellar cortex using Wilcoxon’s signed rank test (2-tailed).

Results

The cerebellar cortex contralateral to the supratentorial lesion showed significant decreases in CBF, CMRO₂, and CMRglc compared with the ipsilateral cerebellar cortex (Table). The decrease in CMRO₂ was less than the decrease in CMRglc, resulting in a significant increase in the CMRO₂/CMRglc ratio. The increase in the CMRO₂/CMRglc 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 CMRglc (\( r = 0.76, P < 0.05 \)), with the percent difference of the CMRO2 (\( r = 0.90, P < 0.05 \)) and with the percent difference of the CBV (\( r = 0.81, P < 0.05 \)).

The increase in the CMRO2/CMRglc ratio was present in all individual patients, but the percent difference of the CMRO2/CMRglc ratio had a tendency to decrease with time elapsed since the insult (\( r = -0.69, P = 0.067 \)). The percent difference of the CMRO2/CMRglc 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 CMRO2/CMRglc 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 CMRO2 and CMRglc compared with the ipsilateral cerebellar cortex. The CMRO2 decreased less markedly than did CMRglc, which resulted in an increase in the CMRO2/CMRglc ratio. The increase in the CMRO2/CMRglc 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 CMRO2 from the CMRglc and CBF may reflect a characteristic change in brain metabolism caused by deafferentation.

The increase in the CMRO2/CMRglc 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 CMRO2 and CMRglc in
patients with CCD due to acute stroke showed no difference between the decrease in the CMRO$_2$ and CMR$_{glc}$. 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.$^{16}$ 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 CMR$_{o}$ 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 CMR$_{glc}$/CMRO$_2$ 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.$^{17,18}$

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 mioieties other than glucose (e.g., 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 disturbed in persistent CCD and the energy production via oxidative metabolism of glucose may be matched to demand. In addition, oxygen metabolism for energy production may not induce the uncoupling of CMRO$_2$ and CBF. Another possibility is that oxygen is being used to oxidize some substrates for purposes other than energy production. One possible candidate of the substrate may be arachidonic acid. In the infarcted human brain, delayed induction of COX-2 (the inducible form of cyclooxygenase) in remote brain areas has been demonstrated.$^{10}$ COX-2 is the rate-limiting enzyme in prostanoid synthesis, and it mediates the formation of prostaglandin G$_2$ from 1 molecule of arachidonic acid and 2 molecules of oxygen.$^{19}$ Its expression is regulated by physiological synaptic activity or growth factors, suggesting a role for COX-2 and its prostanoid products in suggesting a role for COX-2 and its prostanoid products inasso-synaptic plasticity or survival.$^{19,20}$ Therefore, activation of arachidonic acid metabolic pathways, including an induction of COX-2, may increase the oxygen consumption uncoupled from glucose use in relation to transneuronal degeneration of postsynaptic neurons or remodeling of the surviving neural networks.

The major problems of the $^{15}$O steady-state method are the underestimation of CBF and CMRO$_2$,$^{21}$ which might lead to a low CMRO$_2$ and a low CMRO$_2$/CMR$_{glc}$ ratio in our patients, as previously discussed.$^{22}$ 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.$^{23}$ In our preliminary analysis of the rate constants$^{24}$ 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 CMR$_{o}$ 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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