Middle Cerebral Artery Occlusion and Reperfusion in Primates Monitored by Microdialysis and Sequential Positron Emission Tomography

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Background and Purpose—In a previous investigation concerning the hemodynamic and metabolic changes over time displayed by sequential positron emission tomography (PET) in a middle cerebral artery (MCA) occlusion/reperfusion primate model, a metabolic threshold for irreversible ischemia could be identified (reduction of metabolic rate of oxygen [CMRO₂] to ≈60% of the contralateral hemisphere). To evaluate the potential of microdialysis (MD) as an instrument for chemical brain monitoring, the aim of this subsequent study was to relate the chemical changes in MD levels directly to the regional metabolic status (CMRO₂ above or below the metabolic threshold) and the occurrence of reperfusion, as assessed by PET.

Methods—Continuous MD (2 probes in each brain) and sequential PET measurements were performed during MCA occlusion (2 hours) and 18 hours (mean) of reperfusion in 8 monkeys (Macaca mulatta). Energy-related metabolites (lactate, pyruvate, and hypoxanthine) and glutamate were analyzed. The MD probe regions were divided into 3 categories on the basis of whether CMRO₂ was below or above 60% of the contralateral region (metabolic threshold level) during MCA occlusion and whether reperfusion was obtained: severe ischemia with reperfusion (n=4), severe ischemia without reperfusion (n=4), and penumbra with reperfusion (n=5).

Results—The lactate/pyruvate ratio, hypoxanthine, and glutamate showed similar patterns. MD probe regions with severe ischemia and reperfusion and probe regions with severe ischemia and no reperfusion displayed high and broad peaks, respectively, during MCA occlusion, and the levels almost never decreased to baseline. Penumbra MD probe regions displayed only slight transient increases during MCA occlusion and returned to baseline.

Conclusions—This experimental study of focal ischemia showed that the extracellular changes of energy-related metabolites and glutamate differed depending on the ischemic state of the brain during MCA occlusion and depending on whether reperfusion occurred. If MD proves to be beneficial in clinical practice, it appears important to observe relative changes over time. (Stroke. 2001;32:1574-1580.)

Key Words: microdialysis ■ middle cerebral artery occlusion ■ penumbra ■ reperfusion ■ tomography, emission computed ■ monkeys

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difference between the penumbra and infarcted regions was maintained from the time of MCAO throughout the entire reperfusion phase. A metabolic threshold for irreversible brain damage could be identified and appeared to be a reduction of CMRO2 to \( \approx 60\% \) compared with the contralateral hemisphere. The primates were also monitored with intracerebral MD. To further evaluate the potential of MD as an instrument for chemical monitoring of the brain, the specific aim of this subsequent study was to relate the chemical changes in MD levels of energy-related metabolites (lactate, pyruvate, and hypoxanthine) and the excitatory amino acid glutamate directly to the regional metabolic status (CMRO2 above or below the metabolic threshold) and the occurrence of reperfusion, as assessed by PET.

**Materials and Methods**

**Animals and Anesthesia**

The present study was composed of the same series of monkeys previously studied,8, 9 8 adult Macaca mulatta, weighing between 4.4 and 12.8 kg (mean 8.6 kg). The study protocol was approved by the local ethics committee for animal research (permissions c38/96 and c37/97). As described in detail earlier,9 anesthesia was maintained with a continuous infusion of a mixture of midazolam (0.1 mg/mL, Dormicum, Roche) and morphine hydrochloride (0.1 mg/mL) at 1 mL/kg per hour. Atracurium (1 mg/mL) was used for muscle relaxation at 0.5 mL/kg per hour. Basal glucose, electrolyte, and fluid requirements were maintained. A femoral artery was catheterized for blood pressure monitoring and blood sampling. Continuous arterial blood pressure, ECG, pulse oximetry, end-tidal CO2, intracranial pressure, and rectal temperature were monitored. A controlled heating mattress was used to maintain normothermia.

**Surgery and MD**

The animal was fixed in a stereotaxic frame (model 1404, David Kopf Instruments). Two MD probes (CMA/10, membrane length 4 mm, shaft length 20 mm and 50 mm, respectively; CMA/ Microdialysis) were inserted stereotaxically into the right hemisphere within the deep and superficial regions of the MCA territory (expected infarction core and penumbra), according to coordinates defined by a stereotaxic atlas of the monkey brain.10 The deep MD probe was inserted into the basal ganglia (coordinates A 18, R 10, and H 7 ), and the superficial MD probe was inserted into the parietal cortex (coordinates A 10, R 20, and Z whole membrane inserted). The MD probes were fixed with dental cement (Sevriton, De Trey Dentsply Limited), which was placed around the probes and on the surrounding skull bone, where 3 anchor screws had been fastened (CMA/Microdialysis). A Camino device (Camino Laboratories) was inserted in the left hemisphere for monitoring of intracranial pressure. The monkey was placed in the supine position, fixed with ear plugs in a cradle, and transferred to the PET scanner for a baseline PET session.

After the baseline PET, the monkey was fixed in the stereotaxic frame again, and transorbital MCAO was performed under the microscope according to the method described by Hudgings and Garcia11 and O’Brien and Waltz.9 A Mayfield clip was used. After the wound had been closed, the monkey was placed in the cradle again, and a second PET session was performed during MCAO. After 2 hours of MCAO, the clip was removed, and sequential PET measurements were continued. The 2-hour MCAO was based on an earlier MCAO study in primates11 and on our pilot experiments.

MD monitoring was started immediately after probe implantation and was continued until the final PET session was completed. Artificial cerebrospinal fluid (mmol/L: Na+ 148, Ca2+ 1.2, Mg2+ 0.9, K+ 2.7, and Cl− 155) was delivered as perfusion medium by a microinjection pump at a rate of 2 μL/min. Samples were collected at 15-minute intervals until 4 hours after reperfusion in general and thereafter every hour. The samples were analyzed by high-performance liquid chromatography.14–16 Lactate, pyruvate, hypoxanthine, and glutamate were studied. The tentative MD reference levels are presented in Table 1. MD data were presented without correction for in vivo probe recovery, because no method for repeated determination of in vivo probe recovery was available.17–19 In the figures, it was not considered necessary to correct the MD time scale for dead space in the probe and outlet tubing, because of the long sampling intervals and the time resolution of sequential PET.

**Positron Emission Tomography**

The PET investigations were performed on a GEMS 2048-15B scanner (General Electric Medical Systems)20 as described in detail earlier.9 A computerized reorientation procedure was used to accurately align the consecutive PET studies to enable exact intraindividual comparisons.21 Each complete PET scanning procedure included measurements of CBF, cerebral blood volume (CBV), CMRO2, and OER with the use of the steady-state continuous 15O inhalation technique.22,23 Thus, a full PET session consisted of 3 examinations with different tracers: carbon [15O]monoxide (CBV), carbon [15O]dioxide (CBF), and [15O]oxygen (CMRO2 and OER) (correction for intravascular oxygen was based on the CBV scan).22,24

A complete PET session was performed at baseline after MD probe insertion, during MCAO, after 1 hour of reperfusion, and after 2 hours of reperfusion. The total number of additional complete PET sessions ranged from 1 to 5 (mean 4), depending on logistic circumstances. The final PET session was performed after 12 to 24 hours of reperfusion (mean 18 hours). In addition, incomplete PET sessions, including measurements of CBF only, were performed occasionally.

The precise locations of the MD probes were identified by PET at the end of each experiment by using a 2-[15F]fluoro-2-deoxyglucose solution as the MD perfusion medium (Figure 1). This method was verified by histopathologic studies in which indium ink, injected into the MD probes after rupturing of the MD membrane, was localized in the histopathologic sections at the location identified by PET. A circular region of interest (ROI), 1 cm in diameter, was delineated around the identified probe region in the most basal slice showing activity. A corresponding ROI in the contralateral region was also delineated. The ROIs were duplicated for all PET scans. The PET results are presented as side-to-side ratios between the MD probe ROI and the corresponding contralateral ROI to overcome the influence of intraindividual and interindividual variations, such as variations in sedation, ventilation, and blood pressure.9 The state of the ischemic brain tissue in the MD regions during each PET session was classified during MCAO according to the metabolic threshold level of irreversible ischemia demonstrated earlier9: severe ischemia=CMRO2 <60% compared with the corresponding contralateral region; penumbra=decreased CMRO2 but ≥60% and OER >125% compared with the corresponding contralateral region. The occurrence of reperfusion was also assessed in MD probe regions.

**Statistical Methods**

Mean±SD values were used to describe changes over time and differences between groups. The Friedman test was used to test for changes over time in physiological variables. The sensitivity and specificity for severe ischemia were calculated for the MCAO period by use of the optimal cutoff level. The Spearman rank correlation coefficient was used to analyze the correlation between the MD substances during MCAO.

**TABLE 1. Tentative Pathological MD Levels of Lactate/Pyruvate Ratio, Hypoxanthine, and Glutamate in Studies Using Similar MD Systems**

<table>
<thead>
<tr>
<th>Pathological MD Level</th>
<th>Lactate/pyruvate ratio</th>
<th>Hypoxanthine</th>
<th>Glutamate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;20</td>
<td>&gt;6 μmol/L</td>
<td>&gt;2 μmol/L</td>
</tr>
</tbody>
</table>

Tentative pathological MD levels were obtained from the study of Persson et al.4

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Results

The MCAO reperfusion model displayed characteristic features of focal ischemia on PET, such as infarction core, penumbra, and reperfusion of various degrees (Figure 1). Three MD probes were excluded because of technical problems, leaving 13 MD probes for study. Although all MD probes were located in the focal ischemic regions, the 2 standardized MD locations selected stereotaxically did not consistently represent the infarction core and penumbra in each monkey as intended, because the regional distribution of focal ischemic changes showed some variation within the MCA territory.

The physiological variables during the experiments are presented in Table 2. There were significant changes (P<0.05) over time for hemoglobin, mean arterial blood pressure, temperature, and intracranial pressure. The absolute mean values of CBF, CMRO2, and OER in the MD probe regions from the sequential PET studies are presented in Table 3. To minimize the risk of influence from interindividual and intraindividual variations in physiological parameters, values relative to the corresponding contralateral regions were used throughout the study (Table 4; see Methods).

The MD probe regions studied were divided into the defined PET categories as follows: severe ischemia with reperfusion (n=4), severe ischemia without reperfusion (n=4), and penumbra (with reperfusion) (n=5). The penumbra regions exhibited a CMRO2 >75% of the contralateral regions, whereas the regions with severe ischemia showed significantly lower CMRO2 values (Table 4).

Each PET category displayed characteristic MD profiles that were similar for the LP ratio, hypoxanthine, and glutamate (Figure 2). Penumbra probe regions showed slight transient increases of the MD values during MCAO that returned to baseline levels during reperfusion. Probe regions with severe ischemia displayed higher and broader MD peaks during MCAO, and the values decreased only partially to a level above baseline in general. In probe regions with severe ischemia and no reperfusion, a second gradual increase was seen early after clip removal.

There was a consistent difference in the MD levels over time between probe regions assessed to have severe ischemia and penumbra probe regions (Figure 2). When the sensitivity and specificity for severe ischemia were calculated for the MCAO period (using the optimal cutoff level), all MD parameters showed relatively good sensitivity (LP ratio 7/8=0.88, hypoxanthine 8/8=1.0, and glutamate 6/8=0.75) and specificity (LP ratio 5/5=1.0, hypoxanthine 4/5=0.80, and glutamate 3/5=0.60), although glutamate appeared to be the least reliable substance reflecting the ischemic state. When the relationship between the MD parameters was
analyzed during MCAO, no statistically significant correlation was seen.

An illustrative example of the category with penumbra features is shown in Figure 3. Penumbra conditions with high OER and slightly affected CMRO$_2$ are seen during MCAO, followed by normoperfusion in the reperfusion phase. In parallel, small transient elevations of the LP ratio, hypoxanthine, and glutamate can be observed during MCAO.

An example of the category with severe ischemia and reperfusion is given in Figure 4. CMRO$_2$ was severely impaired during MCAO and did not recover substantially despite reperfusion. An immediate marked increase of the LP ratio and hypoxanthine was seen in the beginning of the MCAO. After 2 hours of reperfusion, hypoxanthine reached baseline, and the LP ratio was decreased to a level twice as high as baseline, where it remained. Glutamate showed relatively high baseline values but increased rapidly during MCAO and decreased thereafter, but not to a normal level. Later, glutamate also showed a second slow gradual increase toward the baseline level.

Figure 5 shows the MD and PET graphs in an illustrative case with severe ischemia without reperfusion. CMRO$_2$ was severely depressed during MCAO and did not recover. Biphasic curves were seen for the LP ratio, hypoxanthine, and glutamate. During MCAO, the LP ratio was increased 3-fold, hypoxanthine was increased 6-fold, and glutamate was increased 3-fold.

Discussion

MD probe regions assessed to have severe ischemia (CMRO$_2$ <60% compared with the corresponding contralateral region) and penumbra probe regions showed different MD profiles when the whole experimental period was studied (Figure 2). Despite that finding, it is apparent that one problem in the application of MD as a monitoring instrument in neurosurgical intensive care is to judge whether a moderately increased level of the LP ratio, for example, represents an ongoing situation with light and potentially reversible ischemia or is merely a late reflection of an earlier episode of severe and irreversible ischemia. This problem is, to some extent, overcome when continuous monitoring is used and when relative changes over time are studied. In clinical practice, a sudden elevation of the LP ratio, for example, might serve as a warning. According to the results of the present study, it is likely that a complete infarction has developed if the peak is high and is perhaps also followed by a secondary increase. If the peak is low and the level returns to baseline, it is likely that there was a transient penumbra situation and that the brain tissue survived.
and sensitivity, 1 and in the present study, it showed the acute situation. The LP ratio appears to be the most robust provide information of the ischemic state of the brain in an cases. However, it was obvious that all MD parameters evaluated with caution because of the limited number of hypoxanthine, and glutamate as markers of ischemia must be expectation (work in progress).

Evaluation of a combination of MD substances with different features is another possible strategy to gain more information. Zero levels of MD glucose and a concomitant increase of the LP ratio probably reflect an acute situation of severe ischemia, and persistent elevation of MD glycerol levels probably reflects the development of an infarction.4,19,25 Detailed analysis of the glycerol data in relation to the PET results may substantiate this expectation (work in progress).

The estimations of the predictive values of the LP ratio, hypoxanthine, and glutamate as markers of ischemia must be evaluated with caution because of the limited number of cases. However, it was obvious that all MD parameters provide information of the ischemic state of the brain in an acute situation. The LP ratio appears to be the most robust marker of acute ischemia. In the previous MD and PET study of SAH patients, the LP ratio had both the highest specificity and sensitivity,1 and in the present study, it showed the highest specificity and the second best sensitivity.

Glutamate has been proposed to be an excellent marker of ischemia in an in vivo MD study during cranial base and cerebrovascular surgery,26 and glutamate release was correlated with CBF in patients with head injury.27 In the present study, glutamate showed both the lowest sensitivity and lowest specificity, but in the previous study of SAH patients, it showed high sensitivity.1 The conflicting results may have several explanations. The excitatory amino acids (EAAs) may have multiple sources, because several mechanisms are probably involved alone or together, depending on the degree of ischemia. Possible sources of increased EAAs are release of the transmitter pool due to depolarization, reversal of the cellular reuptake systems, nonspecific leakage from injured cells, and leakage via a disrupted blood-brain barrier. The quantitative contribution from the different sources probably varies. The transmitter release may change the extracellular concentrations abruptly, as demonstrated in the epileptic focus with sampling performed at 2-minute fractions.28 However, the total amount released might be small and may be beyond the level of detection with the use of sampling fractions of 15 minutes, as in the present study. Another

### Table 4. Relative Side-to-Side Ratios of CMRO2, CBF, and OER in MD Probe Regions From Sequential PET Studies

<table>
<thead>
<tr>
<th></th>
<th>SI-Rep</th>
<th>SI-No Rep</th>
<th>Penumbra</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.04±0.08 (n=4)</td>
<td>0.99±0.07 (n=4)</td>
<td>0.95±0.08 (n=5)</td>
</tr>
<tr>
<td>MCAO</td>
<td>0.32±0.09 (n=4)</td>
<td>0.12±0.09 (n=4)</td>
<td>0.75±0.09 (n=5)</td>
</tr>
<tr>
<td>R1</td>
<td>0.55±0.19 (n=4)</td>
<td>0.24±0.12 (n=4)</td>
<td>0.90±0.10 (n=5)</td>
</tr>
<tr>
<td>R2</td>
<td>0.56±0.16 (n=4)</td>
<td>0.15±0.08 (n=4)</td>
<td>0.87±0.19 (n=5)</td>
</tr>
<tr>
<td>R4</td>
<td>0.46 (n=1)</td>
<td>0.15±0.17 (n=2)</td>
<td>0.85±0.15 (n=5)</td>
</tr>
<tr>
<td>R8</td>
<td>0.37 (n=1)</td>
<td>0.05±0.06 (n=2)</td>
<td>0.76±0.34 (n=5)</td>
</tr>
<tr>
<td>F</td>
<td>0.44±0.24 (n=4)</td>
<td>0.36±0.15 (n=2)</td>
<td>0.81±0.16 (n=5)</td>
</tr>
<tr>
<td>CBF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.12±0.11 (n=4)</td>
<td>1.03±0.07 (n=4)</td>
<td>1.02±0.10 (n=5)</td>
</tr>
<tr>
<td>MCAO</td>
<td>0.31±0.11 (n=4)</td>
<td>0.17±0.08 (n=4)</td>
<td>0.48±0.16 (n=5)</td>
</tr>
<tr>
<td>R1</td>
<td>1.28±0.34 (n=4)</td>
<td>0.25±0.08 (n=4)</td>
<td>1.16±0.16 (n=5)</td>
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<tr>
<td>R2</td>
<td>1.07±0.29 (n=4)</td>
<td>0.17±0.04 (n=4)</td>
<td>1.13±0.13 (n=5)</td>
</tr>
<tr>
<td>R4</td>
<td>1.00±0.23 (n=4)</td>
<td>0.20±0.10 (n=2)</td>
<td>1.15±0.11 (n=5)</td>
</tr>
<tr>
<td>R8</td>
<td>0.90±0.16 (n=3)</td>
<td>0.09±0.01 (n=2)</td>
<td>1.01±0.27 (n=5)</td>
</tr>
<tr>
<td>F</td>
<td>0.68±0.28 (n=4)</td>
<td>0.20±0.01 (n=2)</td>
<td>1.10±0.27 (n=5)</td>
</tr>
<tr>
<td>OER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.92±0.10 (n=4)</td>
<td>0.96±0.03 (n=4)</td>
<td>0.93±0.05 (n=5)</td>
</tr>
<tr>
<td>MCAO</td>
<td>1.14±0.35 (n=4)</td>
<td>0.48±0.35 (n=4)</td>
<td>1.72±0.39 (n=5)</td>
</tr>
<tr>
<td>R1</td>
<td>0.44±0.15 (n=4)</td>
<td>0.86±0.38 (n=4)</td>
<td>0.79±0.12 (n=5)</td>
</tr>
<tr>
<td>R2</td>
<td>0.53±0.06 (n=4)</td>
<td>0.72±0.44 (n=4)</td>
<td>0.77±0.10 (n=5)</td>
</tr>
<tr>
<td>R4</td>
<td>0.56 (n=1)</td>
<td>0.51±0.54 (n=2)</td>
<td>0.75±0.11 (n=5)</td>
</tr>
<tr>
<td>R8</td>
<td>0.52 (n=1)</td>
<td>0.18±0.25 (n=2)</td>
<td>0.72±0.14 (n=5)</td>
</tr>
<tr>
<td>F</td>
<td>0.62±0.20 (n=4)</td>
<td>1.83±0.63 (n=2)</td>
<td>0.77±0.16 (n=5)</td>
</tr>
</tbody>
</table>

Values are mean±SD.
possibility to consider is the different ischemia-induced extracellular accumulation of EAAs demonstrated between the cerebral cortex and white matter. There is a possibility that the deep MD probes that were intended to be inserted in the basal ganglia were placed instead in the internal capsule. However, this appeared not to be the case when the probe locations on the PET images were analyzed, and the deep probes did not show inconsistent glutamate patterns more often than did the cortical probes (data not presented). Again, the best way to improve the diagnostic accuracy of MD monitoring is probably to look at relative changes over time and to use several markers in combination, eg, the LP ratio, glucose, glutamate, and glycerol together, because no one marker will probably ever be completely reliable.

In the probe regions assessed to have severe irreversible ischemia during MCAO, the MD patterns differed after removal of the clip, depending on whether reperfusion occurred or not. It is obvious that the second increase of the MD substances in probe regions without reperfusion represents infarction and cell necrosis with nonspecific leakage of various biochemical substances, as also demonstrated in a human case of occlusive stroke. In probe regions with severe ischemia and reperfusion, there was usually no second increase seen after the MCAO peak, but the LP ratio and glutamate were sustained at clearly increased levels in general and did not reach baseline, as in the case of MD regions with penumbra conditions. It is likely that manifest infarction and cell necrosis do not emerge as early when reperfusion occurs. Under such circumstances, the chemical substances are released more slowly over a longer period of time, and when cell necrosis occurs, a large amount already has been released. Under all circumstances, regions with CMRO₂ <60% of the opposite side during MCAO proved not to recover and to develop infarction irrespective of reperfusion, when the PET scans were studied earlier for the whole brains and compared with histopathology (Figure 1). An interesting preliminary observation is that glycerol, which is an end product of phospholipid breakdown from the cell membranes, showed a marked sustained elevation after MCAO that did not differ whether reperfusion occurred or not in cases judged to have severe irreversible ischemia during MCAO, but this was in strong contrast to penumbra regions, in which glycerol returned to baseline levels (authors’ unpublished data, 2001).

In conclusion, the present experimental study of focal ischemia showed that the extracellular changes of energy-related metabolites and glutamate differed depending on the ischemic state of the brain during MCAO and depending on whether reperfusion occurred. If MD proves to be beneficial for chemical monitoring of the brain in clinical practice, it appears important to look at relative changes over time.
Figure 5. MD and PET graphs from an illustrative case of severe ischemia without reperfusion. CMRO₂ was severely depressed during MCAO and did not recover. Biphasic curves were seen for the LP ratio, hypoxanthine, and glutamate. During MCAO, the LP ratio was increased 3-fold, hypoxanthine was increased 6-fold, and glutamate was increased 3-fold.

Acknowledgments

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References


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