Effect of MCI-186 on Ischemia-Induced Changes in Monoamine Metabolism in Rat Brain

Ryozo Oishi, PhD, Yoshinori Itoh, PhD, Masahiro Nishibori, MD, Toshiaki Watanabe, MS, Hiroyoshi Nishi, PhD, and Kiyomi Saeki, MD

We examined the effects of MCI-186 (3-methyl-1-phenyl-2-pyrazolin-5-one), a novel free radical scavenger and an inhibitor of ischemia-induced brain edema, on monoamine metabolism in the brains of both normal and ischemic rats. In normal rats, 3 mg/kg i.v. MCI-186, a dose that prevents ischemic brain edema, had no significant effect on brain concentrations of dopamine, norepinephrine, 5-hydroxytryptamine, or their metabolites. After the injection of 5 μl of 3% polyvinyl acetate into the left internal carotid artery, concentrations of 3,4-dihydroxyphenylacetic acid and homovanillic acid markedly increased, but that of norepinephrine decreased, in the left telencephalon of embolized rats compared with control rats injected with vehicle; the concentration of 5-hydroxyindoleacetic acid also increased slightly. These effects were maximal 2 hours after embolization. The turnover rate of dopamine between 6 and 8 hours after embolization was significantly higher but that of norepinephrine was slightly lower than that in vehicle-treated rats. When rats were treated with 3 mg/kg i.v. MCI-186 immediately after the injection of polyvinyl acetate, the embolization-induced changes in monoamine metabolism were less marked. Our results suggest that MCI-186 attenuates ischemia-induced changes in brain monoamine metabolism, probably due to its free radical scavenging action, although it has no marked effect in normal rats. (Stroke 1989;20:1557-1564)

Since changes in the concentrations of brain monoamines following cerebral ischemia were first reported by Zervas et al., many investigators have shown abnormalities in brain monoamine metabolism using various experimental models of brain ischemia. It has also been suggested that such abnormalities are associated with the pathophysiology of brain injuries, cerebral edema, or stroke. Polyunsaturated fatty acids are rapidly released following ischemia. In particular, arachidonic acid has been shown to induce brain edema, in which free radical reactions are involved. Recently, it has been reported that MCI-186 (3-methyl-1-phenyl-2-pyrazolin-5-one), a novel free radical scavenger, inhibits both nonenzymatic lipid peroxidation and lipoxygenase activity, although this compound is devoid of any marked inhibitory effect on cyclooxygenase activity in vitro. MCI-186 also shows strong suppressive activity in rats against brain edema resulting from occlusion of the middle cerebral artery and from cerebral embolization with polyvinyl acetate (PVA). However, there have been few studies to date on the effects of free radical scavengers on monoamine metabolism in normal and ischemic brain. Therefore, we examined the effects of MCI-186 on the metabolism of dopamine (DA), norepinephrine (NE), and 5-hydroxytryptamine (5-HT) in the brains of normal rats and of those subjected to cerebral ischemia.

In studies of neurotransmitter metabolism after experimental cerebral ischemia, models of global ischemia, such as occlusion of the common carotid artery in gerbils and occlusion of four vessels in rats, were mostly used. However, brain tissue damage and edema in general are more easily produced by models of partial rather than global cerebral ischemia. Considering this fact and the preventive effect of MCI-186 on ischemic brain edema resulting from embolization with PVA in rats, we employed a model of partial ischemia.

Materials and Methods

We used 202 male Wistar rats (Shizuoka Laboratory Animal Center, Hamamatsu, Japan) weighing...
300–350 g. The rats were housed in a room controlled at 22±2°C and maintained in an alternating 12-hour light/dark cycle (lights on at 6 AM). Food and water were given ad libitum. All experiments were performed between 9 AM and 4 PM.

Considering that a dose of 3 mg/kg MCI-186 inhibits brain edema induced by embolization with PVA13 or by occlusion of the middle cerebral artery,14 we administered 0, 3, or 30 mg/kg i.v. MCI-186 into 34 normal rats and killed them 1 or 2 hours later.

We estimated the effect of the free radical scavenger on the turnover of catecholamines by treating 25 normal rats with 250 mg/kg i.p. α-methyl-p-tyrosine (α-MT) in saline immediately before injecting them with one of five doses of MCI-186 in saline (0, 0.3, 1, 3, or 10 mg/kg i.v.); 2 hours later the rats were killed and the α-MT-induced depletions of NE and DA were determined.21 To investigate the effect of MCI-186 on the turnover of 5-HT, we treated 25 normal rats with 65 mg/kg i.p. pargyline in saline immediately before injecting them with one of the five doses of MCI-186; 90 minutes later we killed the rats and measured the pargyline-induced accumulation of 5-HT.21 For controls, 10 rats received two injections of saline (one intraperitoneally and one intravenously) and were killed 2 hours (n=5) or 90 minutes (n=5) later.

As described previously,15 33 rats were anesthetized with ether and the left internal carotid, external carotid, and pterygopalatine arteries were exposed following an incision along the anterior median line of the neck. Five microliters of 3% (wt/vol) PVA dissolved in 50% ethanol or vehicle was injected over 10 seconds into the internal carotid artery through a polyethylene tube inserted from the external carotid artery. During the injection of PVA, the pterygopalatine artery was temporarily closed with a clip. All PVA-treated rats showed marked paralysis of the contralateral limbs after surgery, but all survived until the end of the observation period (0, 1, 2, or 6 hours).

We estimated the turnover of catecholamines after cerebral embolism by treating six PVA-injected rats and six vehicle-injected rats with 250 mg/kg i.p. α-MT in saline 6 hours after injection. Two hours later we killed the rats and determined the α-MT-induced depletions of NE and DA compared with that of six PVA-injected and six vehicle-injected rats similarly treated with saline.

We estimated the effect of MCI-186 on the changes in monoamine metabolism after cerebral embolism by treating 46 rats with one of three doses of the free radical scavenger in saline (0, 1, or 3 mg/kg i.v.); 5 minutes later we injected the rats with PVA or vehicle. Two hours later we killed the rats for determination of the concentrations of DA, NE, 5-HT, and their metabolites.

To determine the concentrations of the monoamines and their metabolites, the rats were decapitated and the brains were rapidly removed and placed on ice. The brains were divided into the telencephalon and the brainstem (diencephalon-medulla oblongata); in 30 normal rats in which turnover was investigated, seven brain regions and the spinal cord (thoracic regions) were dissected as described previously.22 The tissue was homogenized with 0.4 M perchloric acid containing 0.1% L-cysteine and an appropriate amount of epine as an internal standard. After centrifugation, a 50-μl aliquot of the supernatant was injected into a high-performance liquid chromatograph (HPLC) with an electrochemical detector to determine the concentrations of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) according to the method of Magnussen et al.23 The amount of NE was detected simultaneously. To assay the total concentration of 3-methoxy-4-hydroxyphenyglycol (MHPG), 2 ml homogenate supernatant was transferred to a glass tube and heated at 100°C for 4 minutes to hydrolyze MHPG sulfate; the concentrations of HPLC were then determined by the method of Oishi et al.24

In brief, MHPG was extracted with 6 ml ethylacetate in the presence of 3 g K2HPO4 and 0.4 ml of 1 M borate buffer (pH 10.5). After evaporation of the ethylacetate layer, the residue was dissolved in 200 μl of 0.1 M HCl and a 100-μl aliquot was injected into an HPLC with an electrochemical detector. The HPLC system was composed of a pump (L-4000 S, Yanagimoto Manufacturing Co., Kyoto, Japan), a reverse-phase column (Yanapack ODS-H, 5 μm, 250×4 mm inside diameter), and a thin-layer voltammetric detector (VMD-101).

MCI-186 was synthesized at the Research Center, Mitsubishi Kasei Corp., Yokohama, Japan. α-MT methyl ester hydrochloride and pargyline hydrochloride were purchased from Sigma Chemical Co., St. Louis, Missouri, and PVA was purchased from Wako Pure Chemical Industries, Osaka, Japan. All drugs were dissolved in 0.9% saline, and the doses are expressed as the weights of the bases. All other chemicals used were of at least guaranteed reagent grade and were obtained from Nakarai Chemicals, Kyoto, Japan.

The significance of differences was evaluated by analysis of variance followed by Student’s two-tailed t test or Dunnett’s test.

Results

In normal rats, 3 mg/kg MCI-186 had no significant effect on the levels of DA, NE, 5-HT, or their metabolites in the telencephalon and brainstem 1 or 2 hours after treatment compared with i.v. saline (Table 1). However, 30 mg/kg MCI-186 significantly increased the 5-HIAA level but significantly decreased the NE level in the telencephalon 1 hour after treatment.

As shown in Table 2, α-MT decreased NE levels in the brain regions examined by 39–54% compared with i.p. saline. When injected immediately after α-MT, 1 mg/kg MCI-186 slightly but significantly inhibited the α-MT-induced NE depletion in the
TABLE 1. Effect of MCI-186 on Levels of Monoamines and Their Metabolites in Rat Brain

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3,4-Dihydroxyphenylacetic acid (ng/g)</th>
<th>Homovanillic acid (ng/g)</th>
<th>Norepinephrine (ng/g)</th>
<th>3-Methoxy-4-hydroxyphenylglycol (ng/g)</th>
<th>5-Hydroxytryptamine (ng/g)</th>
<th>5-Hydroxyindoleacetic acid (ng/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour after treatment</td>
<td>Telencephalon</td>
<td>Vehicle</td>
<td>1,477.2±17.9</td>
<td>205.1±9.5</td>
<td>196.3±1.6</td>
<td>386.1±4.9</td>
</tr>
<tr>
<td></td>
<td>MCI-186</td>
<td>3 mg/kg</td>
<td>1,437.4±20.7</td>
<td>206.8±7.2</td>
<td>212.6±10.8</td>
<td>366.5±7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg</td>
<td>1,476.5±14.8</td>
<td>225.5±6.2</td>
<td>212.5±18.1</td>
<td>358.3±9.0*</td>
</tr>
<tr>
<td></td>
<td>Brainstem</td>
<td>Vehicle</td>
<td>141.2±3.7</td>
<td>51.8±6.4</td>
<td>53.2±3.1</td>
<td>628.4±10.4</td>
</tr>
<tr>
<td></td>
<td>MCI-186</td>
<td>3 mg/kg</td>
<td>158.1±11.4</td>
<td>59.6±8.6</td>
<td>53.9±3.1</td>
<td>635.5±5.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg</td>
<td>153.0±7.3</td>
<td>63.5±5.7</td>
<td>62.3±9.4</td>
<td>604.7±21.2</td>
</tr>
<tr>
<td>2 hours after treatment</td>
<td>Telencephalon</td>
<td>Vehicle</td>
<td>1,504.7±27.9</td>
<td>199.8±5.0</td>
<td>186.0±10.5</td>
<td>370.8±13.4</td>
</tr>
<tr>
<td></td>
<td>MCI-186</td>
<td>3 mg/kg</td>
<td>1,471.4±24.4</td>
<td>190.7±2.3</td>
<td>174.4±6.7</td>
<td>351.3±7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg</td>
<td>1,478.8±8.8</td>
<td>194.3±9.6</td>
<td>182.8±10.8</td>
<td>341.5±3.9</td>
</tr>
<tr>
<td></td>
<td>Brainstem</td>
<td>Vehicle</td>
<td>134.9±3.0</td>
<td>43.5±3.6</td>
<td>46.1±5.3</td>
<td>595.3±6.3</td>
</tr>
<tr>
<td></td>
<td>MCI-186</td>
<td>3 mg/kg</td>
<td>130.2±3.5</td>
<td>45.7±1.3</td>
<td>47.4±2.6</td>
<td>589.7±15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg</td>
<td>139.0±12.3</td>
<td>46.5±4.0</td>
<td>52.0±6.5</td>
<td>617.4±25.7</td>
</tr>
</tbody>
</table>

Data are mean±SEM ng/g of 6 (vehicle) or 5 (MCI-186) rats.

midbrain. Slight inhibitory effects of 1–10 mg/kg MCI-186 on the α-MT–induced NE depletion observed in some other brain regions was not significant. The α-MT–induced depletion of DA in the striatum was not affected by MCI-186 (Table 2). As shown in Table 3, pargyline increased 5-HT levels in the brain regions examined by 200–330% compared with i.p. saline. MCI-186 had no effect on pargyline-induced 5-HT accumulation at any dose examined.

Figures 1–3 show concentrations of the monoamines and their metabolites in the left (injected) telencephalon at various times after the injection of

TABLE 2. Effect of MCI-186 on α-Methyl-p-Tyrosine–Induced Depletion of Norepinephrine and Dopamine in Rat Brain 2 Hours After Treatment

<table>
<thead>
<tr>
<th>Region</th>
<th>α-Methyl-p-Tyrosine (mg/kg i.p.)</th>
<th>0</th>
<th>250</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCI-186 (mg/kg i.v.)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Norepinephrine (ng/g)</td>
<td>Cerebral cortex</td>
<td>261.2±8.6</td>
<td>121.3±4.4</td>
</tr>
<tr>
<td></td>
<td>Hippocampus</td>
<td>287.9±9.4</td>
<td>175.2±8.6</td>
</tr>
<tr>
<td></td>
<td>Thalamus</td>
<td>371.4±14.1</td>
<td>208.4±7.4</td>
</tr>
<tr>
<td></td>
<td>Hypothalamus</td>
<td>1,241.1±52.5</td>
<td>642.8±13.1</td>
</tr>
<tr>
<td></td>
<td>Midbrain</td>
<td>373.3±5.2</td>
<td>201.7±4.3</td>
</tr>
<tr>
<td></td>
<td>Pons-medulla</td>
<td>344.2±9.1</td>
<td>175.2±3.2</td>
</tr>
<tr>
<td></td>
<td>Spinal cord</td>
<td>189.9±8.1</td>
<td>115.1±6.0</td>
</tr>
<tr>
<td>Dopamine (μg/g)</td>
<td>Striatum</td>
<td>10.25±0.26</td>
<td>5.15±0.07</td>
</tr>
</tbody>
</table>

Data are mean±SEM ng/g of 5 rats.

*p<0.05 different from corresponding α-methyl-p-tyrosine + saline-treated group.
Table 3. Effect of MCI-186 on Pargyline-Induced Accumulation of 5-Hydroxytryptamine in Rat Brain 90 Minutes After Treatment

<table>
<thead>
<tr>
<th>Region</th>
<th>Pargyline (mg/kg i.p.)</th>
<th>MCI-186 (mg/kg i.v.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0 0.3 1 3 10</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>397.4±50.5</td>
<td>819.2±46.2 835.9±27.5 785.2±33.2 828.8±28.6 856.1±7.7</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>175.9±9.2</td>
<td>568.8±20.0 590.9±40.0 570.3±38.7 585.2±20.3 578.8±47.8</td>
</tr>
<tr>
<td>Thalamus</td>
<td>457.4±29.6</td>
<td>1,328.0±75.1 1,371.3±113.7 1,411.5±75.4 1,321.3±105.8 1,348.8±60.7</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>437.2±20.5</td>
<td>1,321.0±28.3 1,283.8±90.4 1,369.8±21.6 1,396.6±82.8 1,408.1±41.4</td>
</tr>
<tr>
<td>Midbrain</td>
<td>583.0±44.5</td>
<td>1,926.6±106.7 1,904.4±120.4 2,105.3±68.8 2,007.9±94.3 2,108.3±107.1</td>
</tr>
<tr>
<td>Pons-medulla</td>
<td>359.1±27.8</td>
<td>1,028.7±92.3 1,068.9±64.4 1,082.9±48.3 1,058.8±64.5 1,053.4±34.1</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>283.3±14.9</td>
<td>626.2±14.7 617.8±35.2 653.0±26.0 642.5±14.5 645.1±13.3</td>
</tr>
<tr>
<td>Striatum</td>
<td>257.7±11.0</td>
<td>589.5±11.4 568.6±40.9 626.1±13.9 610.8±38.1 653.9±43.8</td>
</tr>
</tbody>
</table>

Data are mean±SEM ng/g of 5 rats.

PVA or vehicle. DA levels in PVA-injected rats were not significantly different from those in vehicle-injected control rats at any time (Figure 1). However, DOPAC levels were markedly raised to 191%, 291%, and 195% of control 1, 2, and 6 hours, respectively, after PVA injection. HVA levels were also significantly elevated to 153%, 274%, and 177%, respectively, of control. NE levels significantly decreased to 66%, 70%, and 84% of control 1, 2, and 6 hours, respectively, after PVA injection (Figure 2). However, MHPG levels in PVA-injected rats were not significantly different from control at any time. The 5-HT and 5-HIAA levels changed fairly markedly even after injection of vehicle (Figure 3). Compared with control, 5-HT levels were not affected by PVA injection. However, the 5-HIAA level in PVA-injected rats was significantly higher than that in vehicle-injected rats 2 hours after injection.

Figure 4 shows concentrations of the monoamines and their metabolites in brain regions other than the left telencephalon 2 hours after the injection of PVA or vehicle. In the right telencephalon, only HVA levels increased significantly in PVA-injected rats compared with vehicle-injected control rats. However, this increase was far less marked (22%) than that in the ipsilateral side (174%). In the left brainstem of PVA-injected rats, DOPAC and HVA levels were significantly higher than control, by 50% and 60%, respectively. However, no significant changes in concentrations of the monoamines and their metabolites were observed in the right brainstem.

Table 4 shows the turnover rates of NE and DA in the left telencephalon determined between 6 and 8 hours after injection of PVA or vehicle. The turnover rate of NE in PVA-treated rats was approximately 80% of that in vehicle-treated control rats, but the difference was not significant. The turnover rate of DA in PVA-treated rats was significantly greater than in control.

Table 5 shows the effect of MCI-186 on cerebral embolism-induced changes in concentrations of the monoamines and their metabolites in the left telencephalon 2 hours after injection of PVA or vehicle. Concentrations of DOPAC and HVA, as well as the DOPAC:DA and HVA:DA ratios, were significantly elevated in PVA-injected rats compared with vehicle-injected control rats. However, this increase was far less marked (22%) than that in the ipsilateral side (174%). In the left brainstem of PVA-injected rats, DOPAC and HVA levels were significantly higher than control, by 50% and 60%, respectively. However, no significant changes in concentrations of the monoamines and their metabolites were observed in the right brainstem.
MCI-186 and Monoamine Metabolism

FIGURE 2. Plot of changes in concentrations of norepinephrine (NE) and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in left telencephalon of rats injected with polyvinyl acetate (PVA) (●, n=6) or vehicle (○, n=5) into left internal carotid artery and killed at times shown. Results are mean±SEM. *p<0.01, **p<0.001 different from vehicle-treated group.

Vehicle-injected control rats. NE levels were significantly lower and the MHPG:NE ratio was significantly greater than control. Although no significant changes were observed in either 5-HT or 5-HIAA levels, the 5-HIAA:5-HT ratio was significantly elevated compared with control. MCI-186 at 1 mg/kg i.v. did not inhibit the changes in concentrations of DOPAC, HVA, or NE, or in the DOPAC:DA and HVA:DA ratios induced by PVA injection; however, the MHPG:NE and 5-HIAA:5-HT ratios were not different from those in vehicle-injected rats. In rats treated with 3 mg/kg MCI-186, no significant changes in any parameter except NE level was produced by PVA injection; the slight attenuation of the embolization-induced NE decrease was not significant. In rats treated with 3 mg/kg MCI-186, the ischemia-induced change in the 5-HIAA:5-HT ratio was significantly inhibited. The concentration of 5-HT was significantly greater than that in embolized but i.v. saline-treated rats but not significantly different from that in unembolized rats.

Discussion

MCI-186 has been reported to be more effective than glycerol in attenuating ischemic brain edema induced by occlusion of the middle cerebral artery. In our previous study, the mean±SEM water content of the ipsilateral hemisphere determined 24 hours after embolization with PVA was 81.9±0.4% in the control rats without drug treatment compared...
with 81.4±0.5% and 80.3±0.1% (p<0.01) in rats receiving 1 and 3 mg/kg i.v. MCI-186, respectively, 5 minutes before embolization. The mechanism of MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13 MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13 MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13 MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13 MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13 MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13 MCI-186's preventive action on ischemic brain edema may be attributed to free radical scavenging and to the inhibition of both nonenzymatic lipid peroxidation and lipoxygenase activity.12>13
Thus, we sampled mainly the entire telencephalon ipsilateral to the PVA injection.

MCI-186 had an optimal inhibitory effect on ischemic brain edema at a dose of 3 mg/kg i.v. without showing any adverse effects.14 This dose of MCI-186 caused no significant change in the levels of DA, NE, 5-HT, or their metabolites in the nonischemic brain, although at a higher dose (30 mg/kg) we observed slight but significant changes in the telencephalic levels of NE and 5-HIAA. The results of α-MT–induced NE depletion suggest a slight inhibition by MCI-186 of NE turnover in some brain regions. However, 5-HT turnover was not changed by MCI-186. From these results, we conclude that MCI-186 may only slightly affect the metabolism of some monoamines in nonischemic rat brain at doses that are effective against ischemic brain edema.

There is much evidence of changes in monoamine metabolism produced by cerebral ischemia. However, markedly different results have been obtained from different models, different species, and different experimental conditions. There may be many factors that affect the brain levels of monoamines and their metabolites after the induction of cerebral ischemia. The reduced activities of energy-dependent Na+ and Ca2+ pumps subsequent to cerebral ischemia may lead to depolarization and an increased intracellular Ca2+ concentration in the nerve terminals. These changes may in turn result in an increased release of monoamine neurotransmitters and the enhancement of monoamine turnover. The increased monoamine turnover may be detected by increases in concentration of the metabolites, and in some cases by changes in concentrations of the monoamines themselves. Cerebral ischemia also inhibits monoamine synthesis, which requires oxygen and energy-dependent reuptake mechanisms,26,27 thereby leading to decreases in concentrations of the monoamines and their metabolites. Furthermore, the transport of monoamine metabolites out of ischemic brain is reduced.17 In the case of cerebral ischemia induced by occlusion of the carotid artery and followed by reperfusion, the factors affecting monoamine metabolism may be more complicated.

We observed marked changes in monoamine metabolism in the left telencephalon, ipsilateral to the PVA injection, after embolization. Although the DA level remained unchanged, the DOPAC and HVA levels increased markedly. This may reflect enhanced DA turnover, that is, increases in release, reuptake, and degradation associated with an increased DA synthesis. This view is supported by the fact that the turnover rate for DA remained high until 6–8 hours after embolization. Tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis, has a high affinity for oxygen.28 Therefore, it is likely that the activity of this enzyme was maintained at almost normal levels in this model of cerebral ischemia. Severe cerebral ischemia may lead to a decrease in the DA level.1,4,29,30 On the other hand, the NE level markedly decreased, while the MHPG level remained unchanged. These results may be due to an initial increase in the release of NE after embolization and a subsequent inhibition of NE synthesis and reuptake. In contrast to tyrosine hydroxylase, dopamine-β-hydroxylase has a low affinity for oxygen.31 A reduction in the uptake of [3H]NE has been observed in synaptosomes obtained from ischemic gerbil brains.26

We did not consistently observe an increase in the 5-HIAA level 2 hours after embolization; the increase was significant in the first experiment (Figure 3) but not in the second (Table 5). However, in both experiments, the 5-HIAA:5-HT ratio was significantly increased by brain ischemia. This may be due to a slight enhancement of 5-HT turnover. Weinberger and Cohen27 reported that the sensitivity of cerebral nerve terminals to ischemic damage is higher in DA and NE neurons than in 5-HT neurons. Taken together, it seems probable that a marked increase in DA turnover, an increase in the release of NE combined with the inhibition of its synthesis and reuptake, and a slight increase in 5-HT turnover are produced in the brain ischemia model we used.

MCI-186, especially at 3 mg/kg i.v., inhibited the changes in monoamine metabolism occurring during brain ischemia, suggesting that free radical reactions are involved in the ischemia-induced changes in monoamine metabolism. Wurtman and Zervas2 postulated that distorted neurotransmitter function may be involved in the pathogenesis of progressive cerebral ischemia. It has been reported that p-chlorophenylalanine decreases the incidence of stroke caused by cerebral ischemia4 and that α-MT inhibits ischemic damage to nerve endings in the cerebrum.32 The preventive effect of MCI-186 on ischemia-induced changes in brain monoamine metabolism may contribute to its suppressive activity on ischemic cerebral edema in addition to its free radical–scavenging action.

References


KEY WORDS • MCI-186 • metabolism • rats
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