Evaluation of Masked Neurological Disorders in the Chronic Stage after Middle Cerebral Artery Occlusion in Rats

—Methamphetamine-induced Rotation and Regional Glucose Metabolism in Basal Ganglia—

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Abstract

Neurofunctional changes in rats in the chronic stage of focal cerebral ischemia induced by left middle cerebral artery (MCA) occlusion were examined. Neurological disorders and behavioral changes were observed with or without methamphetamine administration. Metabolic changes in the basal ganglia following methamphetamine intraperitoneal injection were evaluated by [¹⁴C]deoxyglucose autoradiography 30 days after occlusion. Neurological examination revealed persistent spontaneous rotation to the lesioned side in two of 18 rats, and forelimb flexion to the lesioned side in nine of 18 rats during a 28-day observation period after occlusion. Intraperitoneal administration of methamphetamine (4 mg/kg) induced full 360° rotation toward the lesion side in 14 of 17 rats. The number of rotations was inversely correlated with the size of the intact striatum on the lesion side, especially in rats with cerebral infarct located only in the striatum. Rats with extensive cortical lesion in addition to striatal lesion did not demonstrate this relationship. Deoxyglucose autoradiography in methamphetamine-untreated rats showed symmetrical local cerebral glucose utilization in the basal ganglia except for the subthalamic nucleus, striatum and sensorimotor cortex. Autoradiography in methamphetamine-treated and MCA-occluded rats showed a remarkable increase in glucose utilization in the anterior striatum, entopeduncular nucleus, substantia nigra pars reticulata, and sensorimotor cortex contralateral to the occlusion side, but not on the lesioned side. Rotational movements observed in methamphetamine-treated rats are related to lack of stimulation of the basal ganglia system on the ischemic side. The methamphetamine test may be useful for quantifying masked neuronal dysfunction in the chronic stage of experimental focal cerebral infarct in rats.

Key words: basal ganglia, focal ischemia, glucose metabolism, methamphetamine, middle cerebral artery occlusion

Introduction

Investigation of the pathophysiology of neuronal dysfunction in the chronic stage of focal cerebral ischemia requires examination of the neurological changes following ischemia. Neurological changes following focal cerebral ischemia in animals are

sometimes difficult to quantify.^{2,6,16)} In Wistar rats, occlusion of the middle cerebral artery (MCA) produces ischemic lesions, which vary in location and size, most frequently in the striatum and sensorimotor cortex.^{4,14)} Neurological deficits following MCA occlusion are mainly due to such cortical and subcortical striatal lesions. Behavioral changes associated

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with unilateral lesions in the nigrostriatal system have been widely investigated.^{1,7,9,10,12,15,17)} Rotational movement and abnormal posture toward the lesion side were observed following unilateral destruction of the striatum in rats.¹²⁾ Abnormal behavior was maximum in the first 2 days after injury, but disappeared by the 7th day postoperatively.⁹⁾ Intravenous administration of apomorphine, a dopaminergic agonist, also causes modification in motor behavior. The administration of amphetamine, which enhances the catecholaminergic neurotransmission in the central nervous system, evokes vigorous rotation toward the lesion side even after recovery from postural abnormalities and/or rotational movement following unilateral destruction of the nigrostriatal system in rats.^{15,17)}

These behavioral changes may be associated with metabolic changes in the basal ganglia and areas functionally related to the basal ganglia.^{1,7,9)} [¹⁴C]2-deoxyglucose (DG) autoradiography has demonstrated the approximate time course of functional changes in several cerebral structures following electrolytic unilateral striatal lesions.⁷⁾ A significant increase in glucose utilization was observed in the ipsilateral globus pallidus, entopeduncular nucleus and substantia nigra pars reticulata on the 7th day after the striatal lesion was formed electrolytically. However, no significant differences in local cerebral glucose utilization (LCGU) were found between the intact and lesioned sides of the basal ganglia on the 30th day after operation, when abnormal behavior was no longer apparent. Animals receiving apomorphine 7 days after the lesion formation demonstrated increased LCGU in the striatum, globus pallidus, entopeduncular nucleus, substantia nigra pars reticulata and subthalamic nucleus, and a decrease in the lateral habenula nucleus on the intact side. No such changes were on the lesioned side.

Methamphetamine, an analog of amphetamine, is a potent central nervous system stimulant. Methamphetamine should thus induce rotational movement in rats with striatal infarct caused by MCA occlusion. This study investigated the changes in behavior and cerebral metabolism induced by administration of methamphetamine to rats in the chronic stage of ischemia caused by MCA occlusion.

Materials and Methods

Thirty-one mature female Wistar rats weighing approximately 300 g were anesthetized with ketamine hydrochloride (100–120 mg/kg intraperitoneally). A lidocaine solution (0.5%) was applied topically to the surgical wound. After enucleation of the left eye,

the left MCA was exposed *via* the transorbital approach and coagulated exactly at the olfactory tract in 21 rats.²⁾ In 10 sham-operated rats, the arachnoid surrounding MCA was dissected, but the artery was not coagulated. Surgical wounds were always cooled to avoid thermal cortical injury by bipolar cautery. Throughout the procedure, special care was taken to protect the vibrissae and trigeminal nerve. After the operation, the rats were returned to their cages.

Neurological scores were evaluated at various times after surgery in 18 MCA-occluded and four sham-operated rats according to the method of Bederson *et al.*²⁾ The effects of methamphetamine (4 mg/kg) on behavior were evaluated in 17 rats with occluded MCA and four sham-operated rats 28 days after operation. The number of full 360° rotations was determined at 10-minute intervals for 60 minutes after intraperitoneal injection of methamphetamine.

The rats were fasted for 1 day before [¹⁴C]DG autoradiography was conducted under the effect of methamphetamine 30 days after operation in eight MCA-occluded and three sham-operated rats. Seven occluded and six sham-operated rats untreated with methamphetamine were also studied. The rats were anesthetized with ketamine hydrochloride (100 mg/kg intraperitoneally) and lidocaine solution (0.5%) was applied topically to the surgical wound for additional anesthesia. Catheters were inserted into the left femoral artery and vein and the rats were restrained in a plaster cast on a board. After the animals had become fully alert, approximately 7–9 hours after anesthesia, a bolus injection of [¹⁴C]DG (100 μ Ci/kg) was given in the left femoral vein. Methamphetamine (4 mg/kg) was injected intraperitoneally 15 minutes before radioisotope administration. The arterial blood pressure and arterial blood gas levels were also measured before isotope injection. Timed arterial blood samples were taken to determine plasma glucose and [¹⁴C]DG concentration. The rats were sacrificed 45 minutes later with an intravenous overdose of sodium pentobarbital. The brains were immediately removed and frozen (–40°C). 20 μ m brain sections were made, placed on glass coverslips, dried on a hot plate (60°C) and layered with x-ray film (SB-5; Kodak, Rochester, N.Y., U.S.A.) for 5–7 days together with calibrated [¹⁴C]DG-embedded methylmethacrylate standards. The LCGU was assessed by the equation of Sokoloff *et al.*¹³⁾ Statistical evaluation of differences in LCGU between methamphetamine-treated and untreated rats used the nonparametric Mann-Whitney U-test. Interhemispheric differences were assessed by the Wilcoxon signed rank test.

The size of infarcted areas was measured in three

different coronal sections by a computer-assisted image analyzing system. The ratio of the total area of the intact striatum on the lesioned side to that on the contralateral side was determined.

Results

Twenty of 21 rats with occluded MCA demonstrated rotational movement and/or abnormal curved posture toward the lesion side several hours after surgery. Within 12 hours of the operation, these abnormalities decreased markedly.

Figure 1 shows the changes in neurological scores with time after MCA occlusion. Two of the 18 MCA-occluded rats demonstrated spontaneous circling (grade 3), throughout the 28-day observation period. On the first day after operation, five of 15 MCA-occluded rats are pushed toward the paretic side with reduced resistance (grade 2), six MCA-occluded rats flexed the forelimb on the other side of the lesion when held by the tail (grade 1), and two MCA-occluded and all four sham-operated rats extended both forelimbs toward the floor (grade 0). Forelimb flexion persisted during the 28-day observation period in nine of 18 MCA-occluded rats, but disappeared within 7 days in two rats.

Fourteen of 17 rats exhibited stereotypical rotational behavior after methamphetamine injection 28 days after MCA occlusion. Rats usually started to rotate toward the lesion side about 10 minutes after methamphetamine treatment and continued for 60 minutes. Three MCA-occluded and all four sham-operated animals were hyperactive, but did not rotate after methamphetamine administration.

No physiological variables except for PaCO_2 and HCO_3^- changed significantly during the autoradiography (Table 1). The autoradiographic study showed all 15 rats with MCA occlusion devel-

Fig. 1 Time course of neurological scores in 18 rats after MCA occlusion. Rats extend both forelimbs toward the floor (grade 0) or flex the forelimb on the other side of the injured hemisphere (grade 1) when held by the tail, are pushed toward the paretic side with reduced resistance (grade 2), or circle toward the paretic side consistently (grade 3). The closed circles linked with broken lines indicate the courses of individual rats.

oped cerebral infarct in the left striatum. Seven rats developed infarction of variable extents in the left cortex (Fig. 2). Some brain structures on the occluded side involved in the primary ischemic area showed decreased glucose utilization compared to that on the contralateral side in seven rats untreated with methamphetamine (Table 2). Likewise, the

Table 1 Physiological variables in autoradiographic study in 15 MCA-occluded rats

	Mean arterial blood pressure (mmHg)	Blood gas data					
		pH	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	HCO ₃ (mEq/l)	Base excess	Blood glucose (mg/dl)
Untreated (n = 7)	119 ± 4.2	7.48 ± 0.11	84.1 ± 2.4	24.1 ± 0.8	18.3 ± 1.2	-0.3 ± 2.9	88 ± 18
Treated (n = 8)							
before	121 ± 8.2	7.45 ± 0.01	90.3 ± 12.1	27.9 ± 4.0	19.1 ± 1.7	-2.2 ± 2.2	ND
after	126 ± 4.1	7.46 ± 0.03	89.9 ± 11.1	25.2 ± 4.4*	17.2 ± 2.2*	-2.8 ± 3.9	83 ± 11

Values are means ± SD. No variable before methamphetamine administration was significantly different from the methamphetamine-untreated rats by the Mann-Whitney U-test. *Significantly different ($p < 0.05$) from the values before methamphetamine administration by the Wilcoxon signed rank test. ND: not done.

Fig. 2 Representative autoradiographs at the levels of the caudate nucleus (*upper*) and globus pallidus (*lower*) 30 days after MCA occlusion. In the rat on the left, the infarcted area was restricted to the striatum. In contrast, the rat on the right developed extensive cerebral infarcts in both striatum and cortex.

Fig. 3 Autoradiographs with (*right*) and without methamphetamine treatment (*left*) in MCA-occluded rats. The entopeduncular nucleus, subthalamic nucleus and substantia nigra are indicated by arrows in upper, middle and lower, respectively. Note the remarkable increase in LCGU in the striatum, entopeduncular nucleus, subthalamic nucleus and substantia nigra on the intact side compared with the contralateral lesioned side in rats with methamphetamine treatment.

entopeduncular nucleus, subthalamic nucleus, substantia nigra pars reticulata, striatum and sensorimotor cortex on the occluded side demonstrated significantly different LCGU from that on the contralateral side in eight methamphetamine-treated rats (Table 2, Fig. 3).

Figure 4 shows the relationship between neurological score and rotational movement induced by methamphetamine. Ten MCA-occluded animals with neurological abnormalities (grade 1) and three of five MCA-occluded rats without detectable neurological abnormality (grade 0) also

showed methamphetamine-induced rotational movement. The autoradiograms showed the infarcts to be restricted to the striatum in these rats.

Table 2 LCGU following MCA-occlusion and methamphetamine treatment

	Sham-operated (left/right)		MCA-occluded (lesioned/intact side)	
	Untreated (n = 6)	Treated (n = 3)	Untreated (n = 7)	Treated (n = 8)
Sensorimotor cortex	66 ± 4/65 ± 1	151 ± 21/158 ± 21	41 ± 27*/75 ± 23	73 ± 55*/134 ± 34 [#]
Anterior striatum	57 ± 4/58 ± 4	96 ± 11/ 93 ± 15	42 ± 20*/68 ± 8	59 ± 38*/ 88 ± 14 [#]
Posterior striatum	50 ± 5/49 ± 4	79 ± 10/ 87 ± 9	31 ± 17*/65 ± 17	50 ± 27*/ 88 ± 14
Globus pallidus	29 ± 2/29 ± 3	50 ± 5/ 48 ± 8	34 ± 9 /36 ± 11	42 ± 9 / 46 ± 14
Entopeduncular nucleus	30 ± 4/28 ± 3	57 ± 12/ 56 ± 9	39 ± 8 /41 ± 8	46 ± 9*/ 64 ± 15 [#]
Subthalamic nucleus	46 ± 2/44 ± 2	106 ± 13/104 ± 16	54 ± 4*/62 ± 7	78 ± 29*/ 92 ± 23
Substantia nigra pars reticulata	36 ± 5/35 ± 6	68 ± 11/ 65 ± 8	41 ± 9 /39 ± 9	57 ± 12*/ 63 ± 15 [#]
Red nucleus	42 ± 2/42 ± 2	84 ± 16/ 83 ± 15	53 ± 10 /41 ± 9	71 ± 12 / 69 ± 11
Lateral habenula	71 ± 6/68 ± 15	48 ± 6/ 49 ± 8	75 ± 16 /77 ± 16	44 ± 6 / 45 ± 9 [#]

Values are means ± SD. *Significantly different ($p < 0.05$) from the values of the contralateral side by the Wilcoxon signed rank test. [#]Significantly different ($p < 0.05$) from the values in methamphetamine-untreated rats by the Mann-Whitney U-test.

Fig. 4 Correlation between neurological score and methamphetamine-induced rotation counts in 19 rats with or without cortical lesions 28 days after MCA occlusion.

Figure 5 shows the correlation between relative size of the intact striatum and methamphetamine-induced rotations. In six rats without cortical lesions, the number of rotations was inversely correlated with relative size of the intact striatum, but there was no correlation in eight rats with cortical

infarctions.

The correlation between methamphetamine-induced rotations and interhemispheric differences in LCGU in the basal ganglia are shown in Fig. 6. The number of methamphetamine-induced rotations was inversely correlated to the ratio of LCGU on the lesioned side to that on the contralateral side in the entopeduncular nucleus, but was not statistically significant.

Discussion

The changes in behavior observed in this study, disappearance of abnormal posture and hemiplegia, following MCA occlusion suggest that adaptive compensatory changes occur within the bilateral neuronal pathways which regulate symmetrical motor activity. Methamphetamine-induced rotation in animals with predominantly subcortical striatal lesions was inversely correlated with the size of the intact striatum, and only occurred in rats with intact striatum on the infarcted side less than 40% of the size of the contralateral striatum. The observation that two of 18 rats with MCA occlusion showed spontaneous circling toward the lesion side persisting for the 28-day observation period is important for understanding the mechanism underlying neurofunctional recovery after focal ischemia in MCA-occluded rats (Fig. 1). The striatum on the occluded side in these rats was nearly completely destroyed. The intact striatum is therefore essential for estab-

Fig. 5 Correlation between relative size of intact striatum and frequency of methamphetamine-induced rotations in 14 rats with (○) and without cortical lesions (●). Relative size of intact striatum is expressed by the ratio of the total area of the intact striatum on the lesioned side to that on the contralateral side. In rats without cortical lesions, the number of rotations appeared inversely correlated with relative size of intact striatum ($r = 0.766$), but this was not seen in rats with cortical infarcts.

Fig. 6 Correlation between methamphetamine-induced rotation counts and interhemispheric differences in LCGU in the globus pallidus (A), entopeduncular nucleus (B), substantia nigra pars reticulata (C) and subthalamic nucleus (D) of 14 rats treated (●) and untreated (○) with methamphetamine. Interhemispheric differences are expressed by the ratio of LCGU on the lesioned side to that on the non-lesioned side. Methamphetamine-induced rotation counts appeared inversely correlated to the ratio of LCGU in the entopeduncular nucleus ($r = 0.735$).

lishing symmetrical posture following MCA occlusion in rats.

A possible explanation for the rotational behavior in rats with unilateral lesions of the nigrostriatal system may be imbalanced striatal activity. The symmetrical LCGU in the bilateral entopeduncular nucleus and substantia nigra observed in rats on the 30th day after MCA occlusion suggests that recovery of neuronal function is associated with balanced glucose metabolism in the bilateral basal ganglia. Our autoradiographic study showed that increased metabolic imbalance induced by methamphetamine treatment in the entopeduncular nucleus was correlated with rotational movement (Fig. 6). Striatal lesions may abolish the LCGU modification caused by apomorphine in the globus pallidus, substantia nigra pars reticulata and lateral habenula on the lesioned

side.^{7,9} Most LCGU changes caused by intravenously administered apomorphine in these structures are ascribed to activation of striatal dopamine receptors. The entopeduncular nucleus and substantia nigra receive large inhibitory synaptic input from striatum and this may possibly be related to postural behavior. Our autoradiographic results were compatible with those in the previous study using a nigrostriatal lesion model.^{7,9} Methamphetamine may possibly stimulate only the nuclei of the basal ganglia system on the non-occluded side, causing an imbalance in glucose metabolism and neuronal activity.

The results of our DG study require careful analysis. First, since some areas of interest, *e.g.* the striatum and lumped sensorimotor cortex, may be infarcted, rate and lumped constants obtained from normal animals may not be valid. In our study,

analysis of DG data, particularly to evaluate the relationship between LCGU and rotational movement following methamphetamine treatment, was mainly focused on the area not directly involved in the primary ischemic zone. Secondly, the ischemic striatal lesion promotes histological changes and glial proliferation in the ipsilateral basal ganglia such as the substantia nigra in the chronic stage after MCA occlusion. Isacson *et al.*⁸⁾ suggested that glial proliferation is the cause of high glucose uptake in the substantia nigra 7–14 days after formation of a striatal lesion. However, our study found no such abnormally high uptake of DG in the structures of the basal ganglia. We examined changes in LCGU by comparing data with and without methamphetamine. The increased LCGU in these structures after methamphetamine administration was considered due to neurofunctional activation.

When ischemic lesions were not restricted to the striatum after MCA occlusion, no correlation between the relative size of the intact striatum and methamphetamine-induced rotations was observed (Fig. 5). In rats with extensive cortical lesions, the mechanism leading to rotation after methamphetamine treatment may be more complicated. The corticostriatal pathway may possibly modulate dopaminergic striatal functions and contribute to postural behavior.^{3,5,11)} Amphetamine induced rotational behavior toward the lesion side 3–7 days after unilateral cortical ablation in rats.³⁾ The rotations decreased with time and were followed by amphetamine-induced rotation in the contralateral directions.⁵⁾ The hypersensitivity of the ipsilateral striatum to remaining nigral input is assumed to cause the change in direction of induced rotation with time. Lesions of corticostriatal pathways also affect rotation induced by amphetamine or apomorphine in rats with unilateral 6-hydroxydopamine-induced lesions of the dopaminergic pathway. Several mechanisms for functional recovery after injury to the central nervous system have been proposed, including structural reorganization, reversal of remote functional depression (diaschisis), receptor hypersensitivity and the establishment of substitute brain circuits. Since ischemic lesions vary in location and size in an experimental focal cerebral ischemia model, the mechanism causing the disappearance of neuronal deficits may be very complicated.

In this study, the chronic cortical infarct appeared to prevent methamphetamine-induced rotations caused by the striatal infarct although small cortical lesions apparently enhance methamphetamine-induced rotational behavior even in rats with small striatal lesions. The variability of the data may be

due to variations in the extent of ischemic lesions in the sensorimotor cortex. For large ischemic cortical lesions, a different mechanism may apply. The sensitivity of the intact striatum to input from the motor cortex may change chronologically following MCA occlusion. Also, animal to animal variation in chronological changes may occur. Different neural networks which regulate the corticostriatal system may be involved in animals with extensive cortical and subcortical lesions, as noted in this study. The corticostriatal pathway stimulates the basal ganglia. If inhibitory pathways to the corticostriatal system are impaired anatomically and functionally (cortical deactivation by white matter ischemic lesion), the corticostriatal pathway will be functionally stimulated resulting in canceling of rotational movement following methamphetamine treatment. Another possible mechanism is drug delivery to structures in this system. The distribution of methamphetamine in these structures may vary in animals with different extents of ischemic lesions.

In conclusion, methamphetamine-induced rotational behavior is closely related to ischemic striatal lesions, and cortical lesions may modify the induced rotational movement, possibly depending on the cortical lesion sites and/or cortical afferent pathways in the subcortical white matter. The methamphetamine test should prove useful for evaluating masked neuronal dysfunction following MCA occlusion in rats.

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