Effects of RS-8359 on Reduced Local Cerebral Glucose Utilization in the Rat Subjected to Transient Forebrain Ischemia

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ABSTRACT—Changes in local cerebral glucose utilization (LCGU) of the postischemic rat brain were investigated using the rat four-vessel occlusion model. Following 20 or 30 min of ischemia, LCGUs of the cerebral cortices, striatum and hippocampus were decreased at 1 and 3 days postischemia, but were recovered at 7 days postischemia. Effects of repeated administration of RS-8359, (±)-4-(4-cyanoanilino)-7-hydroxycyclopenta(3,2-e)pyrimidine, (30 mg/kg x 2/day, p.o., 4 days) were examined at 3 days posts ischemia following 20 min of ischemia. Compared with the sham-operated group, the LCGUs of 22 out of 34 structures examined in the ischemic-control group were significantly reduced. In the RS-8359-treated group, however, significant reduction was observed in only 9 structures. Compared with the ischemic-control group, RS-8359 significantly ameliorated the reduction of LCGU in 12 structures. These results suggest that RS-8359 has beneficial effects on reduced glucose metabolism in the postischemic brain.

Keywords: RS-8359, Ischemia (rat brain), Local cerebral glucose utilization (LCGU)

The brain is an extraordinarily active organ in terms of glucose metabolism, and energy consumed in the brain is almost exclusively obtained from oxidation of glucose. Sokoloff et al. established an autoradiographic method using ¹⁴C-2-deoxyglucose to measure local cerebral glucose metabolism, the local cerebral glucose utilization (LCGU), of the rat (1). With this method, it has been shown that changes in LCGU mainly reflect changes in neuronal activity (2), implying that it is possible to evaluate local changes in neuronal function over the whole brain through examining changes in LCGU in the brain.

In 1979, Pulsinelli and Brierley developed a rat forebrain ischemia model, the four-vessel occlusion model (3), which is a representative model of cerebral ischemia that has been extensively used for studying stroke. Using this model, Pulsinelli et al. demonstrated that the LCGU values of forebrain regions where blood flow lowering during ischemia was severe remained reduced even at 2 days after 30 min of ischemia (4). In another study of histology, they observed severe neuronal damage in the area of the forebrain (5). On the contrary, in regions where lowering of the blood flow during ischemia was moderate or mild, both postischemic LCGU reduction and neuronal damage were slight or none (4). From a pharmacological point of view, the above results imply that postischemic LCGU reduction might be a target of pharmacological intervention.

In the present study, we first measured postischemic LCGU changes for a longer period than the previous study by Pulsinelli et al., examining whether the reduction of LCGU values in the forebrain continued for longer than 2 days, and we decided the proper time span to apply a drug. Then we evaluated the effects of RS-8359 (Fig. 1), which was repeatedly administered from just after ischemia, on reduced LCGU over the whole brain. RS-8359 is a reversible type A monoamine oxidase (MAO-A) inhibitor (6, 7), and it has also been known to ameliorate the increase in blood viscosity that occurs in rats subjected to cerebral ischemia (8, 9).

Fig. 1. Chemical structure of RS-8359.
MATERIALS AND METHODS

Animals

Male Wistar rats (Japan Slc., Inc., Hamamatsu) weighing 260 – 330 g were used. They were housed for at least 1 week under controlled conditions of light, temperature and humidity before the experiments.

Induction of ischemia

Cerebral ischemia was produced by the method of Pulcinelli and Brierley (3), with a slight modification. Under pentobarbital (50 mg/kg, i.p.) anesthesia, the bilateral vertebral arteries of the animals were electrocauterized. Then a pair of needle electrodes was inserted through the head skin covering the skull for recording the cortical electroencephalograph (EEG). Bilateral common carotid arteries were exposed, and a pair of threads was placed around both of these arteries for later clamping. Animals whose cortical EEG became flat by occlusion of the arteries for less than 30 sec were selected, and they were maintained with free access to water but were fasted overnight. On the next day, the animals were anesthetized with 1.5\% halothane, for exposure of the common carotid arteries. After the anesthesia was discontinued, the arteries were occluded with aneurysm clips for 20 or 30 min, and then reflowed by removing the clips. Only animals that lost their righting reflex during ischemia and for 5 min after reflow were used for later measurement of LCGU. The same procedure except for occlusion of the carotid arteries was given to animals in the sham-operated group. Carotid artery occlusion was performed in the morning.

Drug administration

RS-8359 was suspended in 0.5\% sodium carboxymethyl cellulose (CMC). RS-8359 at the dose of 30 mg/kg or vehicle was orally administered in a constant volume of 1 ml/kg. Administration was performed twice a day for 4 days; at 5 min postischemia and in the evening on day 1, in the morning and in the evening on days 2 and 3, and in the morning and at 1 hr before LCGU determination on day 4.

Determination of LCGU

LCGU was determined according to the method of Sokoloff et al. (1). Surgery was done in the morning and the [\(^{14}\text{C}\)]-2-deoxyglucose experiment was performed in the afternoon. Animals were anesthetized with 1.5\% halothane in \(\text{N}_2\text{O}\) and \(\text{O}_2\) (2:1), and a femoral artery and a femoral vein were cannulated for monitoring of blood pressure and sampling of blood and for tracer administration, respectively. After the anesthesia was terminated, the animals were lightly restrained by loose-fitting plaster casts around the lower torso and then were allowed to recover for at least 3 hr. Before and during the LCGU experiments, blood pressure, rectal temperature, blood gases and blood pH were monitored. 2-Deoxy-D-[\(^{14}\text{C}\)]-glucose (0.3 ml, 30 \(\mu\)Ci; New England Nuclear, Boston, MA, USA) was infused intravenously over 30 sec; and 45 min later, the animals were decapitated. During that time, arterial blood was sampled 14 times to determine the radioactivity and glucose concentration in the plasma. After decapitation, the brain was rapidly taken out and frozen in isopentane chilled to \(-50^\circ\text{C}\). The brain was serially sectioned in 20-\(\mu\)m-thick slices at \(-20^\circ\text{C}\), placed on X-ray film together with a set of calibrated standards and exposed for 1 week. LCGU was evaluated with an MCID image analyzer (Imaging Research, Inc., St-Catharines, Canada).

Measurement of temporalis muscle temperature

In additional sets of animals, changes in temperature in the temporalis muscle were monitored. On the day of ischemia, the animals were anesthetized with 1.5\% halothane and a needle probe was inserted into the temporalis muscle and fastened by a ligature. After the common carotid arteries were exposed, anesthesia was discontinued and the arteries were occluded. The duration of anesthesia was around 10 min. The temperature in the temporalis muscle was monitored up to 2 hr postadministration.

Statistics

Statistical comparisons of LCGU values were performed with analysis of variance followed by Dunnett’s test and Duncan’s test.

RESULTS

Changes in LCGU at 1, 3 and 7 days after 30 or 20 min of ischemia

Changes in LCGU in the cerebral cortex, striatum and hippocampus after 30 min of ischemia are shown in Fig. 2. As will be shown in Tables 2 – 4, there were no significant differences in LCGU in any of the examined structures between the nontreated and the sham-operated groups. Accordingly, in Fig. 2, the normal values are regarded as the control values. In the parietal cortex, significant reductions of LCGU were present at 1 and 3 days postischemia; the percent reductions were 37.6\% and 26.1\%, respectively. LCGU at 7 days postischemia slightly exceeded the control level. In the other five cerebral cortices examined (frontal, sensorimotor, cingulate, auditory and visual), a similar pattern of LCGU reduction was observed at 1 and 3 days postischemia (data not presented). In the striatum, relatively large reductions of LCGU were present at 1 and 3 days postischemia; the percent reduc-
tions were 51.0% and 40.7%, respectively. At 7 days postischemia, LCGU returned to the control level. In the hippocampus as well, LCGU was significantly reduced at 1 and 3 days postischemia; the percent reductions were 39.6% and 14.9%, respectively. However, at 7 days postischemia, a fairly large increase in LCGU was observed, the percent increase being 69.7%. As shown in Fig. 2, the standard errors of LCGU values at 3 days postischemia were small at all three structures, indicating that variability among animals was little at this interval of postischemia.

In the case of 20-min ischemia, LCGU changes at 1 and 3 days postischemia were examined. In this case as well, LCGU values were significantly reduced at both 1 and 3 days postischemia (data not presented). Thus, 3 days postischemia is judged to be the most appropriate time to evaluate the effects of repeated administration of a drug.

Effects of RS-8359 on LCGU at 3 days after 20 min of ischemia

Physiological parameters just before LCGU measurements of the animals used in this experiment are shown in Table 1. There were no noticeable differences in these parameters among the four groups, except that blood pressure values of the three groups other than the nontreated group were slightly lower than that of the nontreated group. Thus, animals of all groups were physiologically in good condition.

Table 2 shows the LCGU values of the cerebral cortices, striatum and hippocampus. Between the nontreated and the sham-operated groups, there were no significant differences in LCGU in any of these structures. With regard to the ischemic-control group, all the LCGU values, except those of the hippocampal CA1 and the dentate gyrus, were significantly lower than those of the sham-operated group. On the other hand, in the RS-8359-treated group, LCGU values of only four cerebral cortices and hippocampal CA3 were significantly lower than the corresponding values of the sham-operated group. Comparing the RS-8359-treated and the ischemic-control groups, LCGU values of all the cortical structures and striatum of the RS-8359-treated group were significantly higher than those of the ischemic-control group. With regard to the hippocampal CA1 and the dentate gyrus, there were no significant differences in LCGU among all the four groups.

Table 3 demonstrates the LCGU values in structures in the forebrain (except the cerebral cortices, striatum and hippocampus), diencephalon and midbrain. Between the nontreated and the sham-operated groups, there were no significant differences in LCGU in any of these structures. With regard to the ischemic-control group, all the LCGU values, except those of the substantia nigra pars reticulata and the inferior colliculus, were significantly lower than those of the sham-operated group. On the contrary, in the RS-8359-treated group LCGU values of only four structures, the amygdala, thalamus, lateral geniculate body and medial geniculate body, were significantly lower than the corresponding values of the sham-operated group. Comparing the RS-8359-treated and the ischemic-control groups, LCGU values of the amygdala, lateral habenula, medial geniculate body, superior colliculus and substan-
tia nigra pars compacta were significantly higher than those of the ischemic-control group.

Table 4 shows the LCGU values in structures in the pons and medulla oblongata, cerebellum and white matter. Regarding these structures, reduction of LCGU was observed only in the reticular formation, internal capsule and cerebellar white in the ischemic-control group, compared with the sham-operated group. With other combinations of comparison, there were no significant differences in LCGU.

The results can be summarized as follows: Compared with the sham-operated group, in the ischemic-control group, LCGU was reduced significantly in as many as 23 of 34 structures examined, whereas in the RS-8359-treated group, LCGU reduction was observed only in 9 structures. Comparing the ischemic-control and the RS-8359-treated groups, LCGU values of 12 structures of the RS-8359-treated group were significantly higher than those of the ischemic-control group. Thus, using the rat forebrain ischemia model, it was clearly shown that RS-8359 ameliorated the postischemic reduction of LCGU.

Changes in temperature in the temporalis muscle before and after administration of RS-8359 are shown in Table 5. In the ischemic-control group, temperature in the temporalis muscle dropped to as low as 32.7°C at the end of ischemia, and it rapidly elevated to 35.2°C at 5 min postischemia, when administration was performed, and then gradually increased. No significant differences were found between the ischemic-control and the RS-8359-treated groups for 2 hr after administration.
Table 3. Local cerebral glucose utilization (µmol/100 g/min) in forebrain (other than cerebral cortices, striatum and hippocampus), diencephalon and midbrain in nontreated, sham-operated, ischemic-control and RS-8359-treated rat brain

|                | Nontreated (n=6) | Sham-operated (n=5) | Ischemia Control (n=5) | RS-8359 (n=5) |
|----------------|------------------|---------------------|-----------------------|---------------|
| Forebrain      |                  |                     |                       |               |
| lateral septum | 51.3±1.7         | 48.4±2.3            | 39.5±1.6+             | 43.0±2.2      |
| globus pallidus| 42.4±1.7         | 44.5±2.4            | 34.8±0.9+             | 40.0±2.2      |
| amygdala       | 52.5±2.1         | 56.8±1.3            | 42.3±1.1++            | 47.5±1.8+++   |
| Diencephalon   |                  |                     |                       |               |
| thalamus       | 75.9±2.4         | 79.3±2.1            | 58.5±2.7++            | 65.6±3.1+++   |
| lateral habenula| 91.0±2.3        | 92.6±3.1            | 78.6±2.8+             | 88.7±3.7+     |
| lateral geniculate| 75.3±2.4    | 77.2±2.4            | 51.3±2.4++            | 57.8±2.3+++   |
| medial geniculate| 85.2±2.4      | 88.6±1.7            | 61.8±3.7++            | 70.5±2.4+++   |
| hypothalamus   | 45.1±1.6         | 48.1±2.6            | 40.0±1.2−             | 45.2±2.4      |
| Midbrain       |                  |                     |                       |               |
| superior colliculus | 63.2±2.1    | 66.0±1.7            | 54.9±2.3++            | 62.3±2.7+     |
| red nucleus    | 56.6±1.8         | 59.6±2.0            | 49.7±2.4+             | 54.1±2.6      |
| S.N.C.         | 52.1±1.2         | 50.6±2.0            | 43.9±1.8+             | 49.7±2.0+     |
| S.N.R.         | 44.1±1.7         | 45.1±2.6            | 41.9±1.8              | 47.7±2.0      |
| inferior colliculus | 116.7±2.8  | 116.7±3.7           | 115.1±6.7             | 119.0±5.5     |

Values are means±S.E.M. S.N.C.: substantia nigra pars compacta, S.N.R.: substantia nigra pars reticulata. *P<0.05 vs. sham-operated by Dunnnett’s test. **P<0.01 vs. sham-operated by Dunnnett’s test. *P<0.05 vs. ischemic-control by Duncan’s test.

Table 4. Local cerebral glucose utilization (µmol/100 g/min) in pons and medulla oblongata, cerebellum and white matter in nontreated, sham-operated, ischemic-control and RS-8359-treated rat brain

|                  | Nontreated (n=6) | Sham-operated (n=5) | Ischemia Control (n=5) | RS-8359 (n=5) |
|------------------|------------------|---------------------|-----------------------|---------------|
| Pons, Medulla oblongata |                  |                     |                       |               |
| dorsal raphe     | 53.2±2.2         | 57.4±3.1            | 46.4±1.8              | 54.7±4.6      |
| reticular formation| 42.8±1.1       | 44.7±2.8            | 35.2±2.3+             | 40.6±2.8      |
| superior olive   | 112.9±5.0        | 112.8±2.7           | 110.7±7.6             | 125.6±5.5     |
| vestibular nucleus| 85.3±2.3        | 85.9±4.0            | 77.7±4.5              | 89.1±5.7      |
| cochlear nucleus | 110.6±4.0        | 108.4±3.1           | 99.8±3.9              | 116.6±6.8     |
| Cerebellum       |                  |                     |                       |               |
| cortex           | 41.2±1.7         | 44.5±2.1            | 37.1±2.2              | 43.6±2.4      |
| nuclei           | 70.9±2.4         | 72.5±1.5            | 65.3±3.1              | 77.1±4.2      |
| White matter    |                  |                     |                       |               |
| corpus callosum  | 29.2±2.0         | 32.6±3.2            | 25.3±0.9              | 27.6±1.3      |
| internal capsule | 23.5±1.3         | 25.4±2.2            | 17.4±1.1++            | 20.4±1.2      |
| cerebellar white | 24.9±1.2         | 24.6±2.3            | 17.7±1.2+             | 22.2±2.4      |

Values are means±S.E.M. Cerebellar nuclei: interpositus nucleus and dentate nucleus. *P<0.05 vs. sham-operated by Dunnnett’s test. **P<0.01 vs. sham-operated by Dunnnett’s test.
DISCUSSION

In a previous study, Pulsinelli et al. demonstrated that postischemic LCGU values of forebrain regions remained severely reduced for up to 2 days, whereas those of other regions, where ischemia was moderate or mild, were only slightly reduced or not changed (4). In other studies, they examined postischemic changes in ATP level, cerebral blood flow and activity of protein synthesis (4, 10). All these latter parameters returned to the control level by 1 day or 2 days postischemia. Therefore, changes in LCGU do not correspond to changes in the latter parameters. Since changes in LCGU are thought to reflect changes in neuronal activity (2), LCGU might have more significant relevance to the final outcome of an ischemic insult than the other parameters.

The results of the present study clearly demonstrated that LCGU values of numerous structures remained reduced at 3 days after either 30 or 20 min of ischemia, although LCGU values (at least apparently) had returned to the normal level at 7 days after 30 min of ischemia. From a therapeutic point of view, the therapeutic time window is an important factor in the study of cerebral ischemia. Taking this into consideration, the interval of 1 day after ischemia is too short and the longer interval of 3 days is better. Furthermore, the variability of LCGU values at 3 days postischemia in the present study was small. Accordingly, it is concluded that LCGU at 3 days after either 20 or 30 min of ischemia using the four-vessel occlusion model is the most appropriate index to evaluate the effects of drugs on postischemic reduction of glucose metabolism.

In a histological study of the four-vessel occlusion model, Pulsinelli et al. observed extensive neuronal damage over the cerebral cortex, striatum and hippocampus at 3 days after 30 min of ischemia (4). Therefore, since the experimental conditions in the present study were essentially the same as those in the study of Pulsinelli et al., in our experiments also, neuronal damage must have progressed considerably by 7 days postischemia. If that is the case, the apparent recovery of LCGU found at 7 days postischemia in the present study might not be a real recovery of normal glucose metabolism. A detailed histological study is warranted to elucidate more clearly the properties of postischemic LCGU changes.

The relatively large increase in LCGU found at 7 days postischemia in the hippocampal formation was largely based on a remarkable increase in LCGU in the CA1 subfield in the hippocampus. Our preliminary immunohistochemical study showed a remarkable proliferation of GFAP-reactive astrocytes only in the CA1 subfield at 7 days postischemia (unpublished data). Therefore, the large increase in LCGU at 7 days postischemia in the hippocampal formation can be ascribed to glial proliferation in the CA1 subfield. Presumably this glial proliferation has already started at 3 days postischemia in the CA1 subfield, causing the apparent normalization of LCGU in this area (Table 2). A similar phenomenon has been reported in a study using another type of rat model of cerebral ischemia (11). Because the remarkable proliferation of GFAP-reactive astrocytes was observed only in the CA1 subfield, we assume that in other brain regions, changes in LCGU reflect changes in neuronal activity.

Using the rat two-vessel occlusion model (bilateral carotid artery occlusion + lowering blood pressure by bleeding) (12, 13), Kozuka et al. examined the effects of preischemic hyperglycemia on postischemic changes of LCGU (14). In their study, although the reduction of cerebral blood flow during ischemia was of the same degree in both hyperglycemic and normoglycemic groups, the postischemic reductions of LCGU over the whole brain in the hyperglycemic group were more profound than those in the normoglycemic group. Under the same experimental conditions, hyperglycemic animals died around 24 hr postischemia with seizures, whereas normoglycemic animals survived. In both the four-vessel occlusion model and the two-vessel occlusion model, it generally holds true that the more pronounced the postischemic reduction of LCGU at a given site in the brain is, the more severe the postischemic tissue damage.

Table 5. Temperature in the temporalis muscle before and after administration of RS-8359 in rats subjected to forebrain ischemia

| Treatment | (n) | Ischemia | Postadministration |
|-----------|-----|----------|--------------------|
| Control   | (8) | 35.8 ± 0.1 | 35.2 ± 0.2 | 35.4 ± 0.2 | 35.7 ± 0.2 | 36.4 ± 0.2 |
| RS-8359   | (5) | 35.9 ± 0.3 | 35.0 ± 0.2 | 35.5 ± 0.2 | 35.6 ± 0.2 | 35.9 ± 0.2 |

Rats were subjected to 20 min of ischemia and then were administered RS-8359 (30 mg/kg, p.o.) or vehicle at 5 min postischemia. Rats were anesthetized with 1.5% halothane for around 10 min before ischemia. Values are means ± S.E.M.
is. These results directly demonstrate that the postischemic reduction of LCGU in these ischemic models is harmful to animals.

It has been known that RS-8359 is a reversible inhibitor of MAO-A (6, 7). Furthermore, it has been also known that RS-8359 has properties to ameliorate blood rheology in ischemic animals; RS-8359 ameliorated the lowered erythrocyte deformability and the increased blood viscosity induced by bilateral carotid artery occlusion in rats (8, 9). The dose of 30 mg/kg, p.o. used in the present study was chosen as a sufficient dose to exert beneficial effects on blood rheology. The relationship between the MAO-A inhibition and the rheological effects is not clear. A study concerning this relationship is now in progress in our laboratory using other MAO-A inhibitors. As represented by delayed hypoperfusion (4, 15–19), which lasts for several hours after global ischemia, postischemic abnormalities of the cerebral circulation do exist. Therefore, agents that affect blood rheology might exert some effects on cerebral glucose metabolism through actions on the cerebral circulation. It is conceivable that the mitigation of postischemic reduction of LCGU by RS-8359, which was demonstrated in the present study, might be based on the improvement of aggravated blood rheology by RS-8359. Although administration was performed preischemically, another study of ischemia has demonstrated protective effects of RS-8359 against neuronal necrosis (20). Further study will be necessary to elucidate the detailed mechanism of the action of RS-8359.

Cerebroprotection by lowering of the brain temperature during and after, especially immediately after, ischemia has been clearly demonstrated (21, 22). Since it has also been indicated that the temporalis muscle temperature closely reflects the brain temperature (21), in the present study, changes in temperature in the temporalis muscle before and after administration of the agent were monitored up to 2 hr postadministration. The control and the RS-8359-treated groups show similar time courses of temperature, indicating that amelioration of LCGU reduction by RS-8359 was not caused by hypothermia.

In conclusion, we attempted to utilize postischemic reduction of LCGU as a target of pharmacological intervention. RS-8359 ameliorated reduction of glucose metabolism in the brain, suggesting beneficial effects of this agent in the treatment of cerebrovascular disorders.

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