Sustained Increase in Adrenergic Activity in Gerbil Striatum Following Transient Ischemia

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ABSTRACT—We investigated the changes in striatal monoaminergic functions, focusing on the release and metabolism, in a cerebral ischemic model induced by a 5-min bilateral occlusion of the carotid arteries (BOCA) and reperfusion in anesthetized gerbils. In the microdialysis study, the striatal extracellular level of dopamine (DA) markedly increased (144-fold) immediately after BOCA. Although norepinephrine (NE) and 5-hydroxytryptamine (5-HT) could not be detected in the dialysates throughout the baseline period, they increased to detectable levels after BOCA. On the contrary, the tissue contents of NE and 5-HT decreased or tended to decrease up to 4 hr following reperfusion. Striatal DA contents did not show any changes in the early period after ischemia-reperfusion and slightly increased at 4 hr or later. Tissue contents of 3-methoxytyramine (3-MT), a metabolite of DA by catechol-O-methyltransferase (COMT), increased 0 and 5 min after reperfusion. Normethanephrine (NMN), which is a metabolite of NE by COMT, also increased not only 5 min after but also up to 4 hr after ischemia-reperfusion, indicating a sustained increase in NE release. These results suggested that the neuronal activity of NE, which is supposed to exert a protective effect on ischemic damage, was enhanced for a longer period than that of DA after transient ischemia.

Keywords: Ischemia (transient forebrain, gerbil), Striatum, Microdialysis (brain), Normethanephrine

For the studies on cerebral ischemia, transient occlusion of carotid arteries in Mongolian gerbils has been employed extensively. Since gerbils frequently have an incomplete circle of Willis (1), they readily develop cerebral ischemia only with the occlusion of the carotid arteries. In this model, it was demonstrated that impairment of memory (2), abnormalities in the electromyogram (2), and degradation of hippocampal CA1 neurons (3) were produced.

The vulnerability of the striatum to forebrain ischemia appears to be related to dopaminergic hyperactivity during ischemia (4, 5). In contrast to the harmful effect of dopamine (DA), some evidence indicate that the adrenergic system might exert a protective influence against ischemic injury (6–8). Therefore, it is interesting to study the changes in monoaminergic functions after transient ischemia.

There have been many neurochemical studies on the monoaminergic systems showing the excessive releases of DA (9, 10), norepinephrine (NE) (11) and 5-hydroxytryptamine (5-HT) (12) by microdialysis methods. In these investigations, it appears that detailed changes in monoamine metabolism for a certain period of time after transient ischemia could not be precisely estimated. Although the microdialysis technique can measure the dynamic changes of neurotransmitters such as release and uptake, it cannot readily detect changes in static balance between synthesis, release, reuptake and metabolism in the nerve terminals. Therefore, to monitor the static and dynamic changes in monoaminergic systems, investigations of both the release and metabolism of monoamines in a single model are desirable. In this study, we observed the changes in extracellular levels and tissue contents of monoamines and their metabolites and the activities of monoamine-metabolizing enzymes in the striatum of gerbils whose carotid arteries were occluded bilaterally for 5 min.

MATERIALS AND METHODS

Male Mongolian gerbils (aged 15–20 weeks; Tumblebrook Farm, Inc., West Brookfield, MA, USA) were used
under urethane (1.0 g/kg, s.c.)-anesthesia throughout the experiments.

In the study of microdialysis, animals were placed in a stereotaxic frame, the skull was exposed, and a small hole was drilled to allow implantation of a guide cannula into the striatum. Coordinates were A: 0.8, L: 2.8 and V: 3.0 mm from the bregma. The implanted guide cannula was fixed with dental cement and two screws to the skull of the gerbils. After release from the stereotaxic frame, a U-shaped dialysis tube (M.W. cut-off: 50,000, membrane length: 2 mm; BDP-Ui-5-02, Eicom, Kyoto) was implanted, and Ringer’s solution (147 mM NaCl, 4 mM KCl and 2.3 mM CaCl₂) was perfused into the probe at a flow rate of 1 µl/min. To obtain stable levels of monoamines and their metabolites in the striatal dialysate, the dialysis probe was perfused for 2 hr. Thereafter, dialysate was collected at 20-min intervals and directly injected into an HPLC system. After the collection of basal samples, animals were subjected to transient ischemia by the following procedure: Gerbils were placed in the supine position, and an anterior midline cervical incision was made. Both common carotid arteries were exposed, and clamped with aneurysm clips simultaneously with the beginning of 20-min dialysate collection. After 5 min of clamping, the clips were removed, and the skin was sutured. In the control group, the animals were subjected to the same operation, but without clamping. Striatal dialysates were collected for a further 4 hr.

For the determination of monoamine contents in the striatal tissue, gerbils were decapitated at 0, 5, 60, 120 and 240 min after reperfusion. The brains were removed within 30 sec, and the striatum was dissected out on an ice-cold glass plate and immediately put into liquid nitrogen. The tissue was weighed and homogenized in 0.4 M perchloric acid containing 0.5% Na₂S₂O₅, 0.15% EDTA and internal standards (doxyepinephrine and N-methyl-5-hydroxytryptamine). The homogenate was centrifuged (2,000 × g for 20 min at 4°C) and 50 µl of the supernatant was filtered through a cellulose nitrate membrane (pore size of 0.45 µm; Gelman Sciences, Ann Arbor, MI, USA). The filtrate was stored at −80°C until the HPLC assay.

Analysis of monoamines and their metabolites was performed by HPLC with electrochemical and coulometric detection (13). The mobile phase consisted of 500 parts of water: methanol: acetonitrile (4:4:2), 0.1 mM sodium citrate-phosphate buffer, pH 3.0, containing 0.45 mM sodium 1-heptanesulfonate and 0.1 mM EDTA; 64.3 parts of methanol; and 25.7 parts of acetonitrile. This solution was filtered through a cellulose nitrate membrane (pore size of 0.45 µm; Millipore, Bedford, MA, USA) and degassed before use. A flow rate of 1.0 ml/min was maintained by a dual piston pump (Jasco 880-PU; Nihon-Bunko, Tokyo). A 4.6 × 150 mm reverse-phase column (Cosmosil, SC18-AR packed column; Nacalai Tesque, Kyoto) was used for the separation. The coulometric detectors (ESA, Bedford, MA, USA) consisted of a control module (model 5100A), a conditioning cell (model 5021), and a dual-electrode analytical cell (model 5011). The applied potentials were +0.45 V (conditioning cell), +0.04 V (detector 1) and −0.35 V (detector 2).

For the determination of the activities of monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), the striatum of gerbils was dissected, weighed and homogenized in 20 volumes of ice-cold 1.25% KCl. The resulting homogenates were used as enzyme sources for the assay of MAO activity, and the residual homogenates were stored at −80°C until the assay of COMT activity. MAO activity was radiochemically assayed as reported previously (14). Briefly, 220 µl of the homogenate was incubated in 80 µl of 0.1 M phosphate buffer (pH 7.4) with [14C]tyramine (100 µM) as a substrate for 15 min at 37°C, and the reaction was stopped by cooling the tubes on ice and acidifying with 20 µl of 3 N HCl. The incubation medium was extracted with toluene-ethylacetate (1 : 1), and an aliquot was taken for radioactivity measurement in a Packard Tri-Carb Liquid Scintillation Spectrometer (Packard, Meriden, CT, USA). In the assay of COMT activity, a procedure based on the method of Agarwal et al. (15), with modifications, was employed. The residual homogenate was centrifuged (20,000 × g for 30 min at 4°C) and 50 µl of the supernatant was incubated for 45 min at 37°C in 150 µl of 0.2 M phosphate buffer (pH 7.9, containing 8.3 mM KCl and 1.2 mM MgCl₂) with the substrates, [3H]S-adenosyl-L-methionine (50 µM) and epinephrine (500 µM). After stopping the reaction by adding 50 µl of 0.5 M boric acid (pH 10.0), the medium was extracted with toluene-isooamyl alcohol (3 : 2), and an aliquot was taken for radioactivity measurement.

Data are expressed as means±S.E.M. and they were analyzed by one-way analysis of variance and Student’s t-test. Differences with a P value less than 0.05 were considered statistically significant.

RESULTS

Changes in striatal extracellular levels of monoamines and their metabolites following transient ischemia (Figs. 1 and 2)

During the baseline period, the average levels in the dialysates were as follows: DA, 4.48±1.43; 3-methoxytyramine (3-MT), 3.70±0.44; 3,4-dihydroxyphenylacetic acid (DOPAC), 89.2±11.0; homovanillic acid (HVA), 210.3±20.2; 5-hydroxyindolacetic acid (5HIAA), 40.9±5.9 ng/ml. Over the experimental period, the control levels in the dialysates gradually decreased (DA and 3-MT) or increased (DOPAC, HVA and 5-HIAA), but the changes...
were not significant.

The bilateral occlusion of carotid arteries (BOCA) for 5 min followed by reperfusion elicited an abrupt and massive increase (144-fold) in the DA levels, which rapidly returned to the basal level. The 3-MT levels increased immediately after ischemia-reperfusion, and they reached a maximum (680%) at 40 min, followed by a gradual decrease. DOPAC levels also increased to 150% at 5 min. HVA levels decreased to approximately 80% immediately after ischemia-reperfusion, and so did the level of 5-HIAA (data not shown). Although NE and 5-HT could not be detected in the dialysates throughout the baseline period, after 5 min of BOCA and reperfusion, they all increased to detectable levels (NE, 2.00 ng/ml; 5-HT, 3.40 ng/ml, data not shown).

**Fig. 1.** Time course changes in DA and 3-MT levels in the dialysate sampled from the striatum in the control (-----) and ischemic (-----) gerbils. Striatal dialysate was collected at a 20-min interval. Ischemic gerbils subjected to 5-min bilateral occlusion of the carotid arteries (BOCA) during the time period shown by the open square, followed by reperfusion. Results are expressed as a percent of the basal level (samples prior to ischemia), and each point represents the mean ± S.E.M. (n=10). Statistical significance was assessed by Student's t-test, *: P < 0.05, **: P < 0.01, compared with control gerbils.

**Fig. 2.** Time course changes in DOPAC and HVA levels in the dialysate sampled from the striatum in the control (-----) and ischemic (-----) gerbils. See the legend of Fig. 1 for details. Each point represents the mean ± S.E.M. (n=10). Statistical significance was assessed by Student's t-test, *: P < 0.05, **: P < 0.01, compared with control gerbils.

**Influence of transient ischemia on striatal tissue contents of monoamines and their metabolites (Figs. 3 and 4)**

In urethane-anesthetized gerbils, the basal striatal tissue contents of monoamines and their metabolites were as follows: DA, 8282.6±313.5; 3-MT, 164.8±19.5; DOPAC, 1001.6±85.5; HVA, 2334.1±152.9; 5-HT, 922.5±30.2; 5-HIAA, 662.1±47.0; NE, 345.0±22.6 ng/g tissue.

After transient ischemia, DA did not change markedly; only a slight increase was found at 240 min. 3-MT rose to 280 and 390% of the control level at 0 and 5 min, respectively, after reperfusion. DOPAC increased by 20% at 5 min. HVA also increased to 140–170% at 60, 120 and 240 min. On the other hand, 5-HT decreased to 70% at 5 min after the reperfusion and during the subsequent period. 5-HIAA decreased to 75–80% initially (at 0 and 5 min), but tended to increase after 60 min. NE also decreased to 70–80% at 0, 5 and 240 min. NMN rose to about 360% at 5 min and remained at a high level (260–280%) up to 240 min.
Fig. 3. Time course changes in tissue contents of DA, 3-MT, DOPAC and HVA in the striatum of gerbils. Transient ischemia was achieved by bilateral occlusion of the carotid arteries for 5 min followed by reperfusion in urethane-anesthetized gerbils. The animals were decapitated 0, 5, 60, 120 and 240 min after the end of ischemia or without ischemia (control). Results are expressed as ng/g tissue, and each column represents the mean ± S.E.M. (n=5–11). Statistical significance was assessed by Student's t-test, *: P < 0.05, **: P < 0.01, compared with the control group.

Fig. 4. Time course changes in tissue contents of 5-HT, 5-HIAA, NE and NMN in the striatum of gerbils. See the legend of Fig. 3 for details. Each column represents the mean ± S.E.M. (n=5–11). Statistical significance was assessed by Student's t-test, *: P < 0.05, **: P < 0.01, compared with the control group.
Table 1. Effects of anesthesia and ischemia on MAO and COMT activities in gerbils

|            | Control     | Anesthetized | Ischemia   |
|------------|-------------|--------------|------------|
| MAO        | 56.8±1.9    | 55.5±1.4     | 54.1±1.2   |
| COMT       | 0.59±0.03   | 0.63±0.02    | 0.56±0.03  |

MAO and COMT activities were expressed as pmol/min/mg tissue. Each value represents the mean±S.E.M. Gerbils in the anesthetized group were treated with urethane (1.0 g/kg, s.c.) 4 hr before sacrifice. Those in the ischemic group were subjected to 5-min bilateral occlusion of the carotid arteries 2 hr after urethane treatment and were sacrificed 2 hr later. The striatum was dissected from the brains, and MAO and COMT activities were measured radiochemically. There were no significant differences in MAO and COMT activities between the groups (control vs. anesthetized or ischemic gerbils).

**Influence of transient ischemia on the activities of MAO and COMT (Table 1)**

The control activity of MAO in the striatum was 56.8±1.9 pmol/min/mg tissue. Two hours after ischemia-reperfusion, there was no significant change in MAO activity in the region. The activity of COMT was 0.59±0.03 pmol/min/mg tissue in the control striatum, and it was also not affected by transient ischemia. Furthermore, urethane-anesthesia itself did not have any effects on either MAO or COMT activities.

**DISCUSSION**

In this study, we evaluated changes in the levels of monoamines and their metabolites both in the tissue and the extracellular space in the striatum of gerbils in the same ischemic model. Increases in extracellular levels of DA (144-fold), NE and 5-HT (from subdetectable levels to detectable ones) were observed immediately after 5 min of BOCA and reperfusion, being consistent with many other reports (9–12). On the contrary, the tissue contents of DA did not change markedly in the early period, namely at 0 and 5 min after reperfusion, and slightly increased only at 240 min, while the tissue contents of NE and 5-HT decreased, or tended to decrease, both immediately after ischemia-reperfusion and during the subsequent period. Similar changes in tissue contents of monoamines, i.e., no change or increase in DA and decrease in 5-HT and NE, were reported in the striatum in several ischemic models (16–19). A previous study (20) reported that the in vivo activity of tyrosine hydroxylase, but not tryptophan hydroxylase, was accelerated after ischemia-reperfusion in anesthetized rats. Moreover, McMillen et al. indicated that there were functional differences in the properties of tyrosine hydroxylase between dopaminergic and noradrenergic neurons (21). Considering these findings in evaluating our data, unchanged or slightly increased tissue DA contents after transient ischemia, contrary to massive DA release into the extracellular space, might reflect the enhanced synthesis of DA.

Since 3-MT is a metabolite of DA by COMT that exists mainly in the extracellular space (22), its increased level is regarded as an indication of DA release (23). In the present study, the striatal tissue contents of 3-MT increased 0 and 5 min after reperfusion, and its extracellular level also did, as previously reported in other ischemic models (16, 24). Thus, the excessive release of DA following cerebral ischemia could be proved by not only the increase in extracellular DA level but also the changes in the tissue contents of 3-MT. NMN is a similar type of metabolite of NE by COMT. In this study, the increase in tissue content of NMN was observed 5 min after reperfusion, coinciding with the remarkable increase in the extracellular level of NE, and it also seems to be a sensitive indicator of NE release (23).

Even in the later period after transient ischemia, namely 1, 2 and 4 hr after reperfusion, the tissue contents of NMN, but not 3-MT, were found to remain at a higher level compared with the control. Since we could not detect the basal extracellular level of NE, it is uncertain whether NE release was enhanced 4 hr after reperfusion in the microdialysis study. However, considering the sustained decrease in the tissue contents of NE and the unchanged activities of MAO and COMT, the increases in NMN contents in the later period should be evidence for increased NE release, i.e., enhanced neuronal activity, although it is not obvious why the neuronal activity of NE is continuously enhanced after reperfusion. These findings support the speculation presented by others (25, 26) that NE release might be stimulated for a while after transient ischemia. Several workers reported the protective activity of NE against ischemic injury; an α1-agonist (6) or α2-agonist (7) showed protective effects, while the lesions of the locus coeruleus (8) had an aggravating effect on the ischemic damage. Taking into account these findings, we postulated that the enhanced neuronal activity of NE might exert a protective effect against ischemic injury.

The extracellular levels of DOPAC increased significantly 40 to 60 min after, but did not change immediately after the transient ischemia. However, it seems that a 20-min collection time interval was too long for the 5-min ischemic period in this study, and therefore the transient decrease in extracellular level of DOPAC as previously reported (27) may have been obscured by the subsequent increase. On the other hand, the tissue contents of DOPAC transiently increased at 5 min. Since DOPAC is produced by MAO in the cytosol of dopaminergic nerve terminals mainly from non-vesicular DA (reuptaken (28) or newly synthesized (29)), the probable increase in DA reuptake or activated DA synthesis that followed excessive
DA release during ischemia may have resulted in the increase in the production of DOPAC. DOPAC is thought to be passively diffused from the nerve terminal to the extracellular space. Thus, the time lag of increase in DOPAC between the tissue content and the extracellular level might indicate the period that was necessary for this diffusion process.

Immediately after 5 min of BOCA, the extracellular levels of HVA significantly decreased to approximately 80% of the basal level. It is assumed that because of the excessive release of DA, the quantity of DA makes it a preferable substrate to DOPAC for the metabolic conversion by extracellular COMT, resulting in the diminished conversion of DOPAC to HVA and enhanced conversion of DA to 3-MT, and eventually lowering of the extracellular HVA level in the period immediately after the transient ischemia. Of course, the suppression of MAO activity due to deprivation of oxygen might also be involved in this decreased HVA level.

In summary, changes in the release and metabolism in monoaminergic neurons during transient ischemia and after reperfusion in gerbils were investigated by measuring both the tissue contents and the extracellular levels of monoamines and their metabolites in the striatum. Excessive releases of DA, NE and 5-HT were observed immediately after the transient ischemia, evidenced also by the increased tissue contents of 3-MT and NMN in the cases of DA and NE. Contrary to the tissue content of 3-MT, those of NMN showed a sustained increase up to 4 hr after reperfusion. These results suggested that the release of NE, i.e., the neuronal activity, which is supposed to exert a protective modulation on ischemic injury, was enhanced for several hours after transient ischemia in the striatum of gerbils, whereas the DA release returned to the basal level shortly after a remarkable increase.

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