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Postischemic Changes in the Binding of Excitatory and Inhibitory Neurotransmitters in the Gerbil Brain

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ARAKI, T., Y. KANAI, F. MURAKAMI, H. KATO AND K. KOGURE. *Postischemic changes in the binding of excitatory and inhibitory neurotransmitters in the gerbil brain.* PHARMACOL BIOCHEM BEHAV 45(4) 945-949, 1993.— We performed receptor autoradiography to determine sequential changes in the binding of *N*-methyl-D-aspartate (NMDA) and γ-aminobutyric acid$_A$ (GABA$_A$) 1 h to 1 month after 10 min of transient cerebral ischemia in the gerbil. [^{3}H]MK-801 and [^{3}H]muscimol were used to label NMDA and GABA$_A$ receptors, respectively. [^{3}H]MK-801 binding showed no significant changes in the striatum and hippocampus at an early stage (1-24 h) after ischemia. Thereafter, [^{3}H]MK-801 binding exhibited a significant reduction in the dorsolateral striatum, most of hippocampal CA1 sector and dentate gyrus 48 h or 7 days of recirculation. However, [^{3}H]MK-801 binding progressively depressed in the hippocampal CA1 sector 1 month after ischemia, whereas other regions showed no significant alteration in the binding. By contrast, [^{3}H]muscimol binding was unchanged in all brain areas throughout the recirculation period. A histological study also demonstrated that transient ischemia caused severe neuronal damage in the striatum and hippocampus. These results demonstrate that NMDA and GABA$_A$ receptors are relatively resistant to severe degenerative processes. Furthermore, our finding suggests that transient ischemia may induce long-term changes in the properties of survival neurons or interneurons especially in the hippocampal CA1 sector.

Cerebral ischemia Neurotransmitter NMDA GABA$_A$ Receptor autoradiography Gerbil

GLUTAMATE and γ-aminobutyric acid (GABA) are major excitatory and inhibitory neurotransmitters in the central nervous system, respectively. These neurotransmitters are well known to play key roles in the pathogenesis of ischemic brain damage (7,8,13,23,24). The synaptic release of glutamate following cerebral ischemia is considered to be an important factor in the development of brain damage (7,8). By contrast, the enhancement of GABA activity ameliorates neuronal damage and abnormal neuronal activity after ischemia (13,16,24). Therefore, ischemia-induced neuronal damage may be partly caused by an imbalance between excitatory and inhibitory inputs.

Transient cerebral ischemia produces selective neuronal damage in specific brain areas. The dorsolateral striatum and hippocampal CA1 sector are most vulnerable to cerebral ischemia (2,17,21). Neuronal damage occurs quickly in the dorsolateral striatum. In the hippocampal CA1 sector, however, neuronal damage occurs after an interval of approximately 2-3 days following ischemia (17,22). Therefore, the mechanisms for the striatal damage produced by transient ischemia may be partly different from that for damage in the hippocampal region.

Recently, numerous studies suggest that postischemic alterations of second messenger systems may play an important role in the pathogenesis of neuronal damage after ischemia (1,11,15,19). Extracellular signals to neurons are transmitted by neurotransmitters that activate specific receptors on the cell surface, followed by the responses of receptor-linked second messenger systems (9,27,28). Therefore, the second messenger systems are initiated through activation of specific receptors such as *N*-methyl-D-aspartate (NMDA) receptor. In the present study, therefore, we focused on two major neurotransmitters (glutamate and GABA), and analyzed the postischemic time-course of these receptors using in vitro receptor autoradiography in the gerbil brain under the same experimental conditions.

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METHOD

Adult male Mongolian gerbils (Seiwa Experimental Animals, Fukuoka, Japan) weighing 60–95 g were used. The animals were anesthetized with 2% halothane in a mixture of 30% oxygen and 70% nitrous oxide. Bilateral common carotid arteries were exposed and anesthesia was discontinued to minimize its effect. The carotid arteries were clamped with aneurysm clips for 10 min, and then the animals were allowed to recover for 1, 5, 24 and 48 h, 7 days and 1 month after ischemia for receptor autoradiography. For histological study, the gerbils were allowed to survive 7 days after ischemia. In addition, five to six sham-operated animals for each study were also investigated in the same manner except for clipping of the bilateral common carotid arteries. The animals were kept on a thermostatted warming mat at 37–38°C following the procedure until they began to move again: food and water were available ad lib.

Histopathology

The gerbils were anesthetized with sodium pentobarbital (50 mg/kg) IP 7 days after ischemia. They were briefly subjected to transcardiac perfusion with heparinized saline, followed by perfusion-fixation with 10% formalin for 20 min. The fixed animals were then left at 4°C for 120 min. The brains were removed and immersed in the same fixative until they were embedded in paraffin. Paraffin sections, 5 μm thick, were stained with hematoxylin-eosin and cresyl violet. Stained sections were examined with a light microscope. Each group contained six to eight animals.

Receptor Autoradiography

The animals were decapitated 1, 5, 24 and 48 h, 7 days and 1 month after ischemia. The brains were removed quickly, frozen in powdered dry ice, and stored at −80°C. Coronal sections, 12 μm thick, were cut on a cryostat at −20°C and thaw-mounted onto gelatin-coated slides.

[^{3}H]MK-801 (noncompetitive NMDA receptor antagonist) binding. Autoradiographic distribution of the binding of MK-801 was determined according to the method of Bowery et al. (10) with minor modifications (3,5). Sections were rinsed in 50 mM Tris-HCl buffer (pH 7.4) containing 190 mM sucrose and dried in a cold air stream. They were then incubated for 20 min at room temperature in buffer containing 30 nM [^{3}H]MK-801 (specific activity 28.8 Ci/mmol, New England Nuclear, Newton, MA), after they were washed in the buffer twice for 20 s at room temperature. Nonspecific binding was determined with 100 μM MK-801 (Research Biochemicals Inc., Natick, MA).

[^{3}H]Muscimol binding. The method used for autoradiographic localization of muscimol ($GABA_A$) receptors has been described previously (3,5). To remove endogenous GABA, sections were subjected to a 20 min prewash at 4°C in 50 mM Tris-citrate buffer (pH 7.1): they were then incubated for 40 min at 4°C in buffer containing 30 nM [^{3}H]muscimol (specific activity 17.1 Ci/mmol, New England Nuclear). The sections were then washed in buffer for 1 min at 4°C. Nonspecific binding was determined in the presence of 10 μM GABA (Sigma Chemical Co., St. Louis, MO).

All procedures were performed under subdued lighting conditions. The sections were dried under a cold air stream

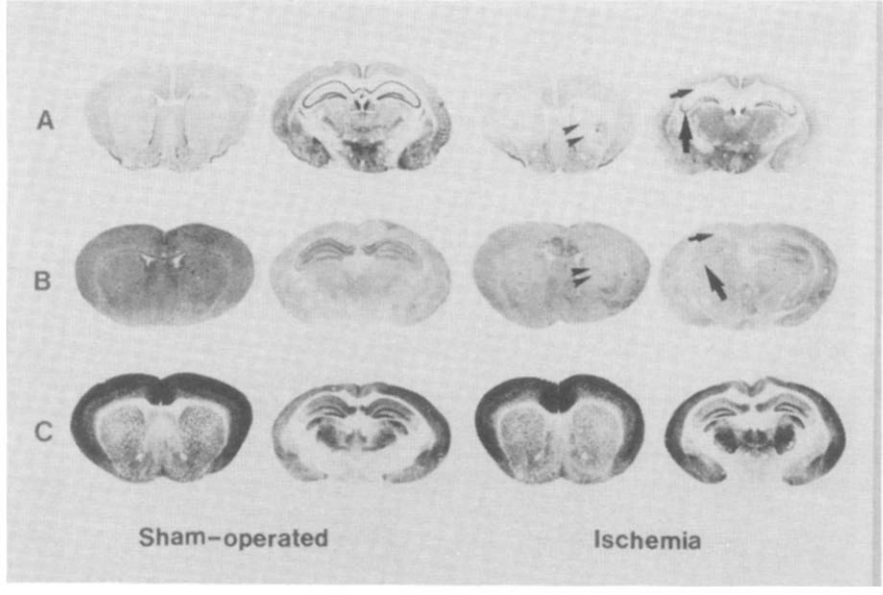

FIG. 1. Representative histological photographs (A) and autoradiograms of [^{3}H]MK-801 (B) and [^{3}H]muscimol (C) binding sites in the gerbil brain 7 days after transient cerebral ischemia. Sham-operated gerbils revealed no conspicuous neuronal damage in the brain. In contrast, gerbils subjected to 10-min ischemia showed severe reduction in the striatum (A, arrowheads), hippocampal CA1 sector (A, small arrow), and hippocampal CA3 sector (A, large arrow). In sham-operated animals, [^{3}H]MK-801 and [^{3}H]muscimol binding activities were found in the striatum and hippocampus. Gerbils subjected to 10-min ischemia showed severe reduction in [^{3}H]MK-801 binding in the striatum (B, arrowheads), hippocampal CA1 sector (B, small arrow), and dentate gyrus (B, large arrow). In contrast, [^{3}H]muscimol binding showed no significant alteration in the brain (C).

TABLE 1

REGIONAL DISTRIBUTION OF [^{3}H]MK-801 BINDING IN THE GERBIL BRAIN FOLLOWING TRANSIENT CEREBRAL ISCHEMIA

		Recirculation Time					
	Sham-operated (5)	1 h(3)	5 h(4)	24 h(7)	48 h(5)	7 days(5)	1 month(5)
Striatum							
Lateral	200 ± 22	138 ± 33	176 ± 5	130 ± 29	101 ± 30*	92 ± 25*	118 ± 30
Medial	197 ± 30	127 ± 38	168 ± 7	133 ± 29	144 ± 27	119 ± 17	165 ± 30
Hippocampus							
CA1 sector							
Stratum oriens	363 ± 25	366 ± 60	328 ± 26	310 ± 42	283 ± 34	176 ± 37†	129 ± 18†
Stratum radiatum	351 ± 31	360 ± 62	340 ± 30	324 ± 46	280 ± 27	210 ± 40	159 ± 22†
Stratum lacunosum-moleculare	234 ± 32	222 ± 45	257 ± 25	214 ± 29	204 ± 11	128 ± 22*	109 ± 20*
CA3 sector	199 ± 46	218 ± 42	210 ± 24	199 ± 15	173 ± 11	102 ± 10	136 ± 32
Dentate gyrus	335 ± 47	297 ± 57	306 ± 26	292 ± 34	234 ± 11	178 ± 17†	287 ± 19

Optical density was converted to fmol/mg tissue using [^{3}H]microscales. Values are expressed as means ± SE.
*$p < 0.05$, †$p < 0.01$ vs. sham-operated group (Dunnett's multiple range test). The number of animals is in parentheses. Striatum (Lateral), the dorsolateral part of striatum; striatum (Medial), the ventromedial part of striatum.

and were exposed to Hyperfilm-^{3}H (Amersham Corp., Arlington Heights, IL) for 2–4 weeks in X-ray cassettes with a set of tritium standards. The optical density of the brain regions was measured with a computer-assisted image analyzer as described previously (1,3,4). The relationship between optical density and radioactivity was obtained with reference to the [^{3}H] microscales (Amersham) co-exposed with the tissue sections, using a third-order polynomial function. Anatomical structures were verified by the examination of cresyl violet-stained sections, and comparison with the gerbil brain atlas of Loskota et al. (18).

Binding assays were performed in duplicate. Nonspecific binding, which is negligible in [^{3}H]muscimol and is relatively high in [^{3}H]MK-801 binding, was subtracted from the total binding. Statistical comparisons were made by Dunnett's multiple range test. Each group contained three to seven animals.

RESULTS

Histopathology

Representative photographs in the brain 7 days after ischemia are shown in Fig. 1. Sham-operated gerbils showed no neuronal damage throughout the brain. Gerbils subjected to 10-min ischemia revealed severe neuronal damage in the brain. The most frequently affected regions were the hippocampal CA1 sector and dorsolateral striatum, followed by the hippocampal CA3 sector. In the thalamus and neocortex, mild damage was found. However, the dentate gyrus was intact.

Receptor Autoradiography

Representative autoradiograms of [^{3}H]MK-801 and [^{3}H]muscimol binding are shown in Fig. 1. Postischemic alteration

TABLE 2

REGIONAL DISTRIBUTION OF [^{3}H]MUSCIMOL BINDING IN THE GERBIL BRAIN FOLLOWING TRANSIENT CEREBRAL ISCHEMIA

		Recirculation Time					
	Sham-operated (5)	1 h(4)	5 h(6)	24 h(3)	48 h(4)	7 days(5)	1 month(5)
Striatum							
Lateral	101 ± 10	101 ± 27	92 ± 3	102 ± 9	139 ± 8	96 ± 12	76 ± 20
Medial	109 ± 17	67 ± 17	95 ± 4	117 ± 16	142 ± 23	108 ± 14	99 ± 15
Hippocampus							
CA1 sector							
Stratum oriens	197 ± 10	220 ± 7	179 ± 16	211 ± 9	221 ± 43	202 ± 38	148 ± 32
Stratum radiatum	194 ± 12	221 ± 7	178 ± 16	209 ± 7	233 ± 46	197 ± 21	135 ± 26
Stratum lacunosum-moleculare	138 ± 10	163 ± 6	142 ± 12	164 ± 7	201 ± 46	162 ± 20	121 ± 21
CA3 sector	96 ± 6	96 ± 10	83 ± 7	92 ± 2	100 ± 12	63 ± 11	89 ± 18
Dentate gyrus	287 ± 16	275 ± 8	257 ± 18	312 ± 13	308 ± 52	248 ± 22	291 ± 24

Optical density was converted to fmol/mg tissue using [^{3}H]microscales. Values are expressed as means ± SE. The number of animals is in parentheses. Striatum (Lateral), the dorsolateral part of striatum; striatum (Medial), the ventromedial part of striatum.

of [^{3}H]MK-801 and [^{3}H]muscimol binding is summarized in Tables 1 and 2.

[^{3}H]MK-801 Binding

In sham-operated gerbils, [^{3}H]MK-801 binding was greatest in the dendritic fields of hippocampal CA1 sector. However, densities in the CA1 pyramidal cell layer were very low. The dentate gyrus also exhibited a high gray density of the binding. The striatum and hippocampal CA3 sector had relatively low [^{3}H]MK-801 binding sites. In gerbils subjected to 10-min ischemia, [^{3}H]MK-801 binding showed no significant alteration in all brain regions up to 24 h after recirculation. At 48 h after ischemia, a significant reduction in [^{3}H]MK-801 binding was seen only in the dorsolateral striatum. Thereafter, [^{3}H]MK-801 binding markedly decreased in the dorsolateral striatum, stratum oriens and stratum lacunosum-moleculare of the hippocampal CA1 sector and dentate gyrus 7 days after recirculation. At 1 month after ischemia, the hippocampal CA1 sector revealed severe decline in [^{3}H]MK-801 binding, whereas other regions showed no significant alteration in the binding.

[^{3}H]Muscimol Binding

In sham-operated gerbils, [^{3}H]muscimol binding was greatest in the dentate gyrus, followed by the hippocampal CA1 sector. The striatum and hippocampal CA3 sector exhibited a relatively low density of [^{3}H]muscimol binding sites. Ten minutes of ischemia caused no significant alterations in [^{3}H]muscimol binding in the brain throughout the recirculation period. However, the hippocampal CA1 sector revealed a tendency for reduction in [^{3}H]muscimol binding 1 month after ischemia. The dorsolateral striatum also showed a reduction in [^{3}H]muscimol binding in two of five animals 1 month after ischemia.

DISCUSSION

Our study showed that [^{3}H]MK-801 binding decreased in the dorsolateral striatum and hippocampus, which were most vulnerable to ischemia, whereas [^{3}H]muscimol binding was unchanged in all regions throughout the recirculation period. Thus, [^{3}H]MK-801 and [^{3}H]muscimol binding was differentially affected by the ischemic insult, despite an extensive degeneration of neurons in the dorsolateral striatum and hippocampus. Furthermore, there was no clear connection between neuronal necrosis and reduction in [^{3}H]MK-801 and [^{3}H]muscimol binding. These results suggest that the NMDA and $GABA_A$ receptors are relatively resistant to severe degenerative processes. Furthermore, our findings suggest that, apart from a detrimental effect of ischemia on the integrity of cellular structures that ultimately leads to neuronal cell loss, ischemia may induce slowly progressive changes on survival neurons or interneurons especially in the hippocampal CA1 region.

Previous reports have shown the temporal profile of histopathological changes in the gerbil brain following transient ischemia (17,21). The neurons in the neocortex, striatum, hippocampus, and thalamus are selectively vulnerable to ischemia. Within specific populations, there is a hierarchy of susceptibility to ischemic insult (2). Pyramidal neurons of the hippocampal CA1 sector and small- and medium-sized neurons of the striatum are most vulnerable to ischemia (21), whereas the interneurons in the hippocampus are resistant (14). The present study also showed that transient ischemia can produce severe neuronal damage in the dorsolateral striatum and hippocampal regions. This histological finding is consistent with previous reports (2,17,21).

In the present study, [^{3}H]MK-801 binding in the hippocampal CA1 sector decreased 7 days after ischemia, when the CA1 pyramidal neurons were destroyed. Thereafter, a progressive loss of [^{3}H]MK-801 binding was seen in all layers of hippocampal CA1 sector. On the other hand, the dorsolateral striatum revealed a significant reduction in [^{3}H]MK-801 binding 48 h and 7 days after ischemia. However, this reduction was no longer present 1 month postischemia. For this reason, it is conceivable that the relative recovery of [^{3}H]MK-801 binding may be due to an increase in the number of receptors per survival striatal neuron after ischemia. Dentate gyrus also showed a significant decrease in [^{3}H]MK-801 binding only 7 days after ischemia. But, this postischemic decline was not observed after 1 month of recovery. These observations are consistent with a previous report (25). Interestingly, although extensive neuronal damage was seen in the striatum and hippocampus, [^{3}H]MK-801 binding in those areas was relatively resistant to degenerative processes after ischemia. The reason for this is presently unclear. However, this phenomenon could be explained by [^{3}H]MK-801 binding to remaining postsynaptic sites including quite large membrane fragments and presynaptic sites, as previously reported (25).

In contrast, [^{3}H]muscimol binding was unchanged during the recirculation period in all layers of the hippocampal CA1 sector, where neuronal damage was seen. Other regions also showed no significant alteration in the striatum, hippocampal CA3 sector and dentate gyrus throughout the recirculation period. Therefore, recognition sites labeled by [^{3}H]muscimol seem to be strikingly resistant to severe degradation processes. The present data also demonstrated that there was no clear connection between neuronal damage and reduction in [^{3}H]muscimol binding following ischemia. Furthermore, the present study showed that [^{3}H]muscimol binding may be predominantly distributed on presynaptic sites and interneurons. These findings are consistent with previous reports (13,20).

Both [^{3}H]MK-801 and [^{3}H]muscimol binding was unchanged throughout the early recirculation period. However, the unaltered binding does not always suggest that neuronal transmission via NMDA and GABA receptors are intact. These bindings may simply reflect the resistance of the binding sites to severe degenerative processes. However, [^{3}H]MK-801 binding decreased 48 h and/or 7 days after ischemia when neuronal damage was obvious in the striatum and hippocampus, whereas [^{3}H]muscimol binding showed no significant alteration in these sites. Thus, the decrease in [^{3}H]MK-801 binding was more pronounced than that in [^{3}H]muscimol binding in the brain following ischemia. Interestingly, a progressive loss of [^{3}H]MK-801 binding was found only in the hippocampal CA1 sector, presumably related to neuronal cell loss. This finding suggests that ischemia may also induce long-term changes in the properties of the surviving neurons or interneurons. Glutamate is well known to cause ischemic neuronal damage by acting at excitatory NMDA receptors (23), which play an important physiological role in long-term potentiation (LTP), learning and memory (6,12,26). The high concentration of NMDA receptors was noted in the dendritic fields of hippocampal CA1 pyramidal neurons. Therefore, a progressive loss of NMDA binding in the hippocampal CA1 sector may be expressed as functional changes in neuronal transmission and animals or human behavior after ischemic insult. However, further studies are needed to investigate the biochemical mechanism of this phenomenon.

In conclusion, the present study demonstrates that NMDA and $GABA_A$ receptors are relatively resistant to degenerative processes. They also demonstrate that there is no clear connection between neuronal necrosis and reduction in NMDA and $GABA_A$ receptors. Furthermore, our results suggest that transient cerebral ischemia may induce long-term alterations in the properties of the surviving neurons or interneurons. These findings may help to further elucidate the relationships between ischemic brain damage and behavioral pharmacology.

REFERENCES

1. Araki, T.; Kato, H.; Hara, H.; Kogure, K. Postischemic binding of [^{3}H]phorbol 12,13-dibutyrate and [^{3}H]inositol 1,4,5-trisphosphate in the gerbil brain: An autoradiographic study. Neuroscience 46:973–980; 1992.
2. Araki, T.; Kato, H.; Kogure, K. Selective neuronal vulnerability following transient cerebral ischemia in the gerbil: Distribution and time course. Acta Neurol. Scand. 80:548–553; 1989.
3. Araki, T.; Kato, H.; Kogure, K.; Kanai, Y. Long-term changes in gerbil brain neurotransmitter receptors following transient cerebral ischaemia. Br. J. Pharmacol. 107:437–442; 1992.
4. Araki, T.; Kato, H.; Kogure, K.; Saito, T. Postischemic alteration of muscarinic acetylcholine, adenosine A_1 and calcium antagonist binding sites in selectively vulnerable areas: An autoradiographic study of gerbil brain. J. Neurol. Sci. 106:206–212; 1991.
5. Araki, T.; Kato, H.; Kogure, K.; Shuto, K.; Ishida, Y. Autoradiographic mapping of neurotransmitter system receptors in mammalian brain. Pharmacol. Biochem. Behav. 41:539–542; 1992.
6. Auer, R.; Jensen, M. L.; Whishaw, I. Q. Neurobehavioral deficit due to ischemic brain damage limited to half of the CA1 sector of the hippocampus. J. Neurosci. 9:1641–1647; 1989.
7. Benveniste, H.; Drejer, J.; Schousboe, A.; Diemer, N. H. Elevation of the extracellular concentrations of glutamate and aspartate in the rat hippocampus during transient cerebral ischemia monitored by microdialysis. J. Neurochem. 43:1369–1376; 1984.
8. Benveniste, H.; Jorgensen, M.; Sandberg, M.; Christensen, T.; Hanberg, H.; Diemer, N. H. Ischemic damage in hippocampal CA1 is dependent on glutamate release and intact innervation from CA3. J. Cereb. Blood Flow Metab. 9:629–639; 1989.
9. Berride, M. J. Inositol trisphosphate and diacylglcerol: Two interacting second messengers. A. Rev. Biochem. 56:615–649; 1987.
10. Bowery, N. G.; Wong, E. H. F.; Hundson, A. L. Quantitative autoradiography of [^{3}H]-MK-801 binding sites in mammalian brain. Br. J. Pharmacol. 93:944–954; 1988.
11. Cardell, M.; Bingren, H.; Wieloch, T.; Zivin, J.; Saitoh, T. Protein kinase C is translocated to cell membranes during cerebral ischemia. Neurosci. Lett. 119:228–232; 1990.
12. Collingride, G. L. S.; Kehl, S. J.; McLennan, H. The antagonism of amino acid-induced excitations of rat hippocampal CA1 neurones in vitro. J. Physiol. (Lond.) 334:19–31; 1983.
13. Johansen, F. F.; Christensen, T.; Jensen, M. S.; Valente, E.; Jensen, C. V.; Nathan, T.; Lambert, J. D. C.; Diemer, N. H. Inhibition in postischemic rat hippocampus: GABA receptors, GABA release, and inhibitory postsynaptic potentials. Exp. Brain Res. 84:529–537; 1991.
14. Johansen, F. F.; Jorgensen, M. B.; Diemer, N. H. Resistance of hippocampal CA-1 interneurons to 20 min of transient cerebral ischemia in the rat. Acta Neuropathol. (Berl.) 61:135–140; 1983.
15. Jorgensen, M. B.; Deckert, J.; Wright, D. C. Binding of [^{3}H]-inositoltrisphosphate and [^{3}H]phorbol 12,13-dibutyrate in rat hippocampus following transient global ischemia: A quantitative autoradiographic study. Neurosci. Lett. 103:219–224; 1989.
16. Johansen, F. F.; Diemer, N. H. Enhancement of GABA neurotransmission after cerebral ischemia in the rat reduces loss of hippocampal CA1 pyramidal cells. Acta Neurol. Scand. 84:1–6; 1991.
17. Kirino, T. Delayed neuronal death in the gerbil hippocampus following ischemia. Brain Res. 239:57–69; 1982.
18. Loskota, W. A.; Lomax, P.; Verity, M. A. A stereotoxic atlas of the Mongolian gerbil brain. Ann Arbor, MI: Ann Arbor Science; 1974.
19. Onodera, H.; Araki, T.; Kogure, K. Protein kinase C activity in the rat hippocampus after forebrain ischemia: Autoradiographic analysis by [^{3}H]phorbol 12,13-dibutyrate. Brain Res. 481:1–7; 1989.
20. Onodera, H.; Sato, G.; Kogure, K. GABA and benzodiazepine receptors in the gerbil brain after transient ischemia: Demonstration by quantitative receptor autoradiography. J. Cereb. Blood Flow Metab. 7:82–88; 1987.
21. Pulsinelli, W. A.; Brierley, J. B.; Plum, F. Temporal profile of neuronal damage in a model of transient forebrain ischemia. Ann. Neurol. 11:491–498; 1982.
22. Pulsinelli, W. A.; Duffy, T. E. Regional energy balance in rat brain after transient forebrain ischemia. J. Neurochem. 40:1500–1503; 1983.
23. Simon, R. P.; Swan, J. H.; Griffiths, T.; Meldrum, B. S. Blockade of *N*-methyl-D-aspartate receptors may protect against ischemic damage in the brain. Science 226:850–852; 1984.
24. Sternau, L. L.; Lust, W. D.; Ricci, A. J.; Ratcheson, R. Role for γ-aminobutyric acid in selective vulnerability in gerbils. Stroke 20:281–287; 1989.
25. Westerberg, E.; Monaghan, D. T.; Kalimo, H.; Cotman, C. W.; Wieloch, T. W. Dynamic changes of excitatory amino acid receptors in the rat hippocampus following transient cerebral ischemia. J. Neurosci. 9:798–805; 1989.
26. Wigstrom, H. B.; Gustafsson, B.; Huang, Y.-Y. Mode of action of excitatory amino acid receptor antagonists on hippocampal long lasting potentiation. Neuroscience 17:1105–1115; 1986.
27. Worley, P. F.; Baraban, J. M.; Colvin, J. S.; Snyder, S. H. Inositol trisphosphate receptor localization in brain: Variable stoichiometry with protein kinase C. Nature 325:159–161; 1987.
28. Worley, P. F.; Baraban, J. M.; Souza, E. B.; Snyder, S. H. Mapping second messenger systems in the brain: Differential localizations of adenylate cyclase and protein kinase C. Pro. Natl. Acad. Sci. U.S.A. 83:4053–4507; 1986.