Nerve Terminal Damage in Cerebral Ischemia: Protective Effect of alpha-Methyl-para-Tyrosine

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SUMMARY Mongolian gerbils were treated with alpha-methyl-para-tyrosine methyl ester (AMPT, a tyrosine hydroxylase inhibitor), in order to decrease brain levels of catecholamines. Six hours later, unilateral ischemic stroke was induced by ligation of the left common carotid artery. The delayed degeneration of nerve terminals was studied sixteen hours later by measuring the high-affinity uptake of radiolabeled transmitters by isolated synaptosomes. Dopamine, serotonin and glutamate terminals were studied. AMPT-treated gerbils were compared to untreated (no AMPT) animals; 220 gerbils were studied. AMPT pretreatment (100, 250 and 400 mg/kg) produced a dose-dependent protection of all three types of nerve terminals. In the absence of AMPT pretreatment, the uptake of radiolabeled transmitters by the ischemic hemisphere, expressed as a percentage of that seen in the contralateral (unaffected) side of the brain, was as follows (mean ± SEM): 27.3 ± 5.2% for dopamine terminals, 49.5 ± 6.2% for serotonin terminals, and 42.7 ± 5.3% for glutamate terminals. Protection was essentially complete at a dose of 400 mg AMPT per kg. The number of animals with significant damage to nerve terminals was reduced from 38.5% in untreated animals to 11.1% in animals treated with AMPT 400 mg/kg. Although the nerve terminals were protected, gerbils still showed the behavioral signs of unilateral stroke due to the permanent occlusion of the left carotid. These results indicate that endogenous dopamine may play a significant role in ischemic damage to nerve terminals in the cerebrum.

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Measurement of the levels of transmitters in the ischemic hemisphere of gerbils with irreversible unilateral carotid occlusion have shown a similar selective reduction of catecholamines relative to the other transmitters. The reduction occurred by one hour after carotid ligation and was attributed to release of the catecholamine transmitters due to depolarization of membranes in ischemia. The loss of catecholamines has been corroborated by histofluorescence studies, which have shown depletion of catecholamine-derived fluorescence from the ischemic striatum in gerbils with stroke.

The present study was instituted to determine whether the selective sensitivity of catecholamine nerve terminals to ischemia could reflect a toxic action mediated by the physical presence of the catecholamine transmitters. Alpha-methyl-para-tyrosine methyl ester (AMPT) was administered to gerbils in order to deplete the brain catecholamine stores. AMPT is a tyrosine hydroxylase inhibitor that prevents synthesis of catecholamines. AMPT reduces catecholamine levels because catecholamines turned over in the course of neurotransmission and metabolism cannot be replaced by resynthesis. Uptake of the transmitters dopamine, 5-HT and glutamate was measured in synaptosomes isolated from gerbils at sixteen hours after unilateral carotid artery ligation. Animals pretreated with AMPT at six hours prior to unilateral carotid artery ligation were compared to animals that were not pretreated. In this way, the role of endogenous catecholamines in nerve terminal damage could be assessed.

Materials and Methods

Studies were conducted with 220 gerbils. Male gerbils weighing 50 to 70 gm were injected i.p. with AMPT in dosages of 100 mg/kg, 250 mg/kg or 400 mg/kg six hours prior to carotid ligation. Untreated animals were injected with an equivalent volume of saline. The 400 mg/kg dose has been shown to reduce catecholamines from the cerebrum of gerbils 4 hours...
after injection. Time course studies in guinea pigs injected with 80 mg AMPT/kg i.p. show a peak effect on reduction of brain catecholamine levels at 8 hours, with resynthesis occurring at 24 hours. Gerbils were anesthetized with approximately 40 mg methohexitol/kg (i.p.), with the dosage titrated to the stage of surgical anesthesia for each animal. Animals could breathe spontaneously without a respirator. The left common carotid artery was exposed in the paratracheal region by blunt dissection so that there was no blood loss. After the animals exhibited partial recovery from anesthesia to the extent that they were responsive to leg pinch, the carotid artery was ligated with two ties. This method has been employed by Lust et al. to provide animals in whom behavioral changes associated with clinical stroke could be readily observed.

The behavioral criteria for designation of stroke were similar to those described by Kahn, paucity of movement or spaying of the contralateral extremities (hemiparesis), torsion of the body and circling to the left, obtundation and a comatose-like motionless state. Animals that appeared otherwise normal but exhibited mild circling behavior generally associated with some lethargy were classified as “circling.” The “circling” category included some gerbils with such mild behavioral changes that the final categorization was difficult.

At sixteen hours after carotid ligation, the gerbils were decapitated with a guillotine. The cerebrum was removed and separated into left and right hemispheres, which were immediately immersed in ice cold isotonie (0.9%) saline. This procedure took approximately 30 seconds. Each hemisphere was weighed and then homogenized in 10 ml of 0.32M sucrose. Centrifugation was performed in a Sorvall RC 2B refrigerated centrifuge with a SS 34 head. The homogenates were centrifuged at 3000 rpm (1100 × g), for 10 minutes, to remove blood and cellular debris. The supernatant was centrifuged at 15,000 rpm (27,000 × g) for 30 minutes and the pellet retained. The pellet was then resuspended at a concentration of 150 mg wet weight of original tissue per ml in Krebs-Ringer phosphate buffer, pH 7.4, containing 0.05 mM pargyline and 1.7 mM ascorbic acid. This preparation has been used previously to provide a synaptosomal suspension which contains mitochondria, but is relatively free of glial elements and other subcellular particles.

Uptake measurements were based on prior studies by other investigators and were carried out in triplicate. Aliquots of 200 μl of the synaptosomal preparation in 5 ml of the Krebs-Ringer phosphate buffer were preincubated for 10 minutes at 37°C in a Precision Scientific GCA shaker bath. Radiolabeled neurotransmitters were added to a final concentration of 5 × 10^-9 M for DA and 5-HT and 8 × 10^-6 M for glutamate. After 10 minutes, one ml aliquots were removed from replicate flasks and passed through a 0.65 μm Millipore filter by means of suction filtration to isolate the synaptosomes. The filters with adhering synaptosomes were washed quickly with 1.0 ml saline. They were then suspended in 10 ml Scintiverse solution for scintillation counting of the radioactivity; radioactivity measurements were made 8–24 hours later in a Packard Model 2450 Tricarb Scintillation Spectrometer. The uptake of radiolabeled transmitters, corrected for radioactivity retained on the filter papers, was expressed as the DPM per mg wet weight of original tissue divided by the DPM in an equivalent volume of incubation medium, that is, a tissue-to-medium ratio. The uptake of transmitter in the ischemic left side versus the control right side was compared by expressing results as a ratio of left/right (L/R) ratio.

Statistical comparisons were made by paired Student “t” test for uptake of transmitters in each animal. The unpaired Student “t” test and the Mann-Whitney rank order U Test were employed for comparison of uptake between AMPT-treated and untreated animals. Chi square analysis was employed to determine if there were any significant behavioral differences in the various treatment groups. Significant reduction in uptake in the ischemic hemisphere of an individual animal was defined as an uptake value more than two standard deviations below the mean uptake in the left hemisphere of unaffected animals not treated with AMPT.

Radiolabeled neurotransmitters were obtained from New England Nuclear (Boston, Mass.): 3H-dopamine (22 Ci/mmol), 3H-5-HT (26.5 Ci/mmol) and 14C-glutamate (290 mCi/mmol). 14C-Glutamate was diluted with unlabeled glutamate to a specific activity of 0.18 mCi/mmol. Unlabeled L-glutamic acid was obtained from Sigma Chemical (St. Louis, MO). AMPT methyl ester was obtained from Regis Chemical Company, Morton Grove, Illinois. Scintiverse was from Fisher Scientific (Springfield, N.J.). Gerbils were obtained from Tumblebrook Farms (West Brookfield, Mass.).

Results

Neurotransmitter uptake was measured in synaptosomes prepared from the ischemic left cerebral hemisphere and control right cerebral hemisphere of gerbils subjected to left carotid ligation (table 1). Uptake was measured at 16 hours after carotid ligation. Animals were separated into the following groups: those with no behavioral change (unaffected), those with mild behavioral changes such as slight lethargy and intermittent circling (circle), and those with hemiparesis and rotational movement (stroke). The behavioral characteristics of the animals are described in table 2.

Animals pretreated with AMPT were generally slightly lethargic six hours later when carotid ligation was performed. By 16 hours after ligation, animals treated with AMPT 100 mg/kg and 250 mg/kg that did not have a stroke were behaviorally indistinguishable from untreated animals without stroke. Animals without stroke that were pretreated with AMPT 400 mg/kg were hypokinetic, slightly lethargic, and tremulous 16 hours after carotid ligation, but would walk when prodded and could stand on their hind legs when disturbed.

Animals that were pretreated with AMPT 100 mg/kg and suffered a stroke after carotid ligation displayed the same behavioral activity as untreated animals with stroke (see methods). Animals with stroke pretreated with AMPT 400 mg/kg showed a somewhat
different behavior. Eight of these animals were curled in a ball, hypotonic and lying at the bottom of the cage because they could not support weight with their right extremities. Three animals that were standing, but hunched over, were classified as having a stroke because they had spastic extension of the right extremities when lifted by the tail and could not maintain standing balance when pushed. Four animals that also curled in a ball but had normal responses when lifted by the tail and good righting reflexes when pushed were put into the intermediate classification (circling). In these four animals, it could not be distinguished whether the paucity of movement was secondary to cerebral ischemia or to the metabolic effects of AMPT. None of the animals with stroke in the 400 mg AMPT/kg group exhibited rotational movement as caused by depletion of dopamine by AMPT in the unaffected striatum.

The uptake of DA, 5-HT and glutamate into synaptosomes from the ischemic (left) hemisphere and control (right) hemisphere is shown in Table 1. Uptake is expressed as the tissue to medium ratio: the disintegrations per minute (dpm)/mg wet weight of original tissue divided by the dpm in an equivalent volume of incubation medium. Figures in parentheses are the S.E.M.

†There is an apparent decrement in uptake of 5-HT in unaffected animals treated with AMPT 400 mg/kg. However, several untreated animals studied at the same time as controls had similar tissue to medium uptake ratios. The lower 5-HT uptake in these animals (both with and without AMPT) reflects decomposition of the 3H-5-HT tracer, rather than an effect of AMPT on uptake. Expression of the data as Left/Right ratio compensates for the effect of radiotracer decomposition and permits evaluation of the effects of ischemia in the various subgroups. It should be noted that earlier studies did not show bilateral change in uptake of neurotransmitters.24-25

<table>
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<th>Condition</th>
<th>No treatment</th>
<th>AMPT 100 mg/kg</th>
<th>AMPT 250 mg/kg</th>
<th>AMPT 400 mg/kg</th>
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<td>10</td>
<td>9</td>
<td>7</td>
<td>11</td>
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<td>Left/Right ratio</td>
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<td>(0.56)</td>
<td>(0.62)</td>
<td>(0.39)</td>
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<td>(0.29)</td>
</tr>
<tr>
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<td>(0.127)</td>
<td>(0.147)</td>
<td>(0.108)</td>
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<td>Left/Right ratio</td>
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<td>Left</td>
<td>(0.37)</td>
<td>(0.55)</td>
<td>(0.13)</td>
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<tr>
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<td>(0.053)</td>
<td>(0.104)</td>
<td>(0.19)</td>
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The uptake of DA, 5-HT and glutamate into synaptosomes from the ischemic (left) hemisphere and control (right) hemisphere is shown in Table 1. Uptake is expressed as the tissue to medium ratio: the disintegrations per minute (dpm)/mg wet weight of original tissue divided by the dpm in an equivalent volume of incubation medium. Figures in parentheses are the S.E.M.

*For animals showing no behavioral change after left carotid ligation (unaffected groups), uptake was measured in 22 out of 45 control animals (no AMPT), 8 out of 34 animals treated with 100 mg AMPT/kg, 10 out of 12 animals treated with 250 mg AMPT/kg, and 12 out of 20 animals treated with 400 mg AMPT/kg.

†There is an apparent decrement in uptake of 5-HT in unaffected animals treated with AMPT 400 mg/kg. However, several untreated animals studied at the same time as controls had similar tissue to medium uptake ratios. The lower 5-HT uptake in these animals (both with and without AMPT) reflects decomposition of the 3H-5-HT tracer, rather than an effect of AMPT on uptake. Expression of the data as Left/Right ratio compensates for the effect of radiotracer decomposition and permits evaluation of the effects of ischemia in the various subgroups. It should be noted that earlier studies did not show bilateral change in uptake of neurotransmitters.24-25
glutamate was 42.7 ± 5.3%. Uptake of each transmitter was significantly reduced relative to control stroke animals. This was clearly evident on removing the cerebrum from the cranium and separating the hemispheres. The diminution in the extent of necrosis was present even in animals where uptake of transmitter was impaired.

Uptake of DA into synaptosomes prepared from the ischemic (left) hemisphere of 10 untreated gerbils with stroke was significantly more impaired than uptake of 5-HT or glutamate (table 1), (p < 0.001). These results confirm earlier observations on the selective sensitivity of DA neurons. Uptake of DA was 27.3 ± 5.2% of the control hemisphere, (see left/right ratio) while uptake of 5-HT was 49.5 ± 6.2% and uptake of glutamate was 42.7 ± 5.3%. Uptake of each transmitter was significantly reduced relative to control (p < 0.001).

In nine gerbils with stroke that were pretreated with the lower dose of AMPT (100 mg/kg), uptake of DA was 40.9 ± 12.7% of the control side. Uptake of 5-HT was 52.5 ± 9.3% and uptake of glutamate was 53.2 ± 10.4%. Uptake of all three transmitters was significantly lower in synaptosomes from the ischemic hemisphere than from the control hemisphere (DA p < 0.005, 5-HT p < 0.05, glutamate p < 0.025). However, the differences between relative uptake of the three transmitters were no longer statistically significant.

In seven gerbils with stroke treated with the intermediate dose of AMPT (250 mg/kg), uptake of DA into synaptosomes from the ischemic hemisphere was 54.2 ± 14.7% of control. Uptake of 5-HT was 67.5 ± 13.0% and uptake of glutamate was 63.7 ± 13.2%. Again, uptake of all three transmitters was significantly reduced compared to the control side (p < 0.05), but the differences between DA and the other transmitters did not achieve statistical significance.

In eleven gerbils with stroke that had been treated with the high dose of AMPT (400 mg/kg), uptake of DA into synaptosomes from the ischemic hemisphere was 81.8 ± 10.8% of control, uptake of 5-HT was 88.5 ± 7.9% and uptake of glutamate was 87.9 ± 9.1%. At this dosage of AMPT, uptake of each transmitter was not significantly different from its respective control. Moreover, AMPT provided significant protection for all three types of nerve terminals (DA p < 0.001, 5-HT p < 0.005, glutamate p < 0.001 by t-test; p < 0.01 by Mann-Whitney U Test).

There was no significant difference between untreated and AMPT-treated animals in the uptake of transmitters in unaffected animals (table 1). Thus, AMPT did not appear to have a direct effect on uptake. The reduction in the endogenous concentration of DA by AMPT does not alter the accumulation of H-DNA by synaptosomes because the concentration added to the medium is well below the Km of uptake for DA. In this range, transport is proportional to the concentration used.

The uptake of DA (fig. 1a), 5-HT (fig. 1b) and glutamate (fig. 1c) into synaptosomes prepared from each individual stroke animal in the various treatment groups can be seen in the accompanying figures. Seven of the ten control (not pretreated with AMPT) animals with stroke showed significant reduction in uptake of DA, 5-HT and glutamate, with significant selective reduction in uptake of DA (cf. table 1).

In stroke animals pretreated with 100 mg AMPT/kg, five of nine showed this same significant reduction in transmitter uptake with accentuation of damage to DA terminals. The remaining animals showed considerable preservation of DA nerve terminal function. Inspection of tabular data for individual animals (not shown), revealed that when uptake of DA was preserved, uptake of 5-HT and glutamate was also increased relative to control stroke animals.

In stroke animals pretreated with 250 mg AMPT/kg,
only two of seven animals showed a significant reduction in DA uptake. For three animals, DA uptake approached equality with uptake in the non-ischemic right hemisphere. In these animals, uptake of 5-HT and glutamate also were elevated to the level seen in the control hemisphere.

In stroke animals that had been pretreated with 400 mg AMPT/kg, only two of eleven animals had significant reduction in DA uptake into synaptosomes from the ischemic hemisphere, and one animal had intermediate reduction. These three animals correspond to the lowest data points for 5-HT and glutamate uptake in Figs. 1b and 1c. In the remaining eight animals, uptake of DA, 5-HT and glutamate in the ischemic hemispheres were all in the same range as in the corresponding non-ischemic hemispheres.

We considered the possibility that the sedative effect of AMPT 400 mg/kg may have caused animals with mild stroke to appear as if they had a more severe stroke. In such an event, mildly affected animals would be placed into the "stroke" category and the mean uptake value in the stroke category would give an appearance of protection. However, this possibility can be excluded: Only 3 of 27 animals treated with AMPT 400 mg/kg had significant impairment of uptake of DA in the ischemic hemisphere. For animals not pretreated with AMPT, all 10 with stroke and 5 of 7 with mild circling behavior had significant reduction of uptake of DA in the ischemic hemisphere. A comparison of the AMPT-pretreated and untreated groups shows that the total number of animals with significant damage to nerve terminals in the pretreated group (3/27 11.1%) was significantly lower than among untreated animals (15/39 38.5%) (p < 0.01), irrespective of the extent of stroke behavior.

In summary, when there was prevention of damage to DA nerve terminals by AMPT, there was also prevention of damage to 5-HT and glutamate terminals. Protection by AMPT was dose-dependent upon the administered amount of AMPT: Both the mean uptake values for animals in the stroke category (table 1), and the number of animals exhibiting preservation of neurotransmitter uptake (fig. 1), increased with increasing dose of AMPT. Although AMPT protected against the loss of neurotransmitter uptake, it did not prevent behavioral change associated with stroke after permanent ligation of the carotid artery (table 2).

With regard to the possibility of selective protection of DA terminals by AMPT, the simultaneous effects

**FIGURE 1.** a) The uptake of dopamine into synaptosomes from the ischemic left hemisphere compared to the control right hemisphere is expressed as the ratio of left/right in gerbils exhibiting signs of stroke after left carotid ligation. The left right ratio is shown for each animal with no pretreatment and for animals pretreated with 100 mg/kg, 250 mg/kg or 400 mg/kg AMPT i.p. at 6 hours prior to left carotid ligation. The horizontal bars represent the mean uptake for each group of animals. b) The uptake of 5-HT is shown as per the legend to figure 1a. c) The uptake of glutamate is shown as per the legend to figure 1a.
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on DA, 5-HT, and glutamate terminals makes a clear evaluation difficult. It is noted that for the lowest dose of AMPT (100 mg/kg), where selectivity in action might be more readily assessed, DA uptake remained less than that for 5-HT or glutamate (table 1, L/R ratio, stroke category), but differences between DA and the other transmitters were no longer significant statistically. Increments in mean uptake of DA and glutamate with increasing AMPT were apparent (table 1, DA from 0.27 ± 0.05 to 0.40 ± 0.12, and glutamate from 0.42 ± 0.05 to 0.53 ± 0.10), while the mean uptake of 5-HT was relatively unchanged (from 0.49 ± 0.06 to 0.52 ± 0.09). The increase in SEM for each transmitter (table 1, L/R ratio, 100 mg AMPT/kg), compared to no pretreatment, relates to the greater spread of data, due in large measure to the strong protection seen in some animals (Cf. figs. 1a, b, c).

Discussion

Treatment of gerbils with AMPT prior to carotid ligation reduced the amount of ischemic damage to the uptake mechanism of DA nerve terminals, as well as to those of 5-HT and glutamate terminals. The number of animals with significant impairment of uptake was reduced from 38.5% in untreated animals to 11.1% in animals treated with AMPT 400 mg/kg. This reduction in damage was significant (p < 0.01). Depletion of the catecholamines did not completely prevent stroke, since animals still exhibited severe behavioral abnormalities. There was also damage to tissue in the cerebral hemispheres on gross inspection, though perhaps to a lesser extent than untreated animals. Since AMPT depletes cerebral catecholamines, these results suggest that the catecholamines are in some way deleterious to nerve terminals after an ischemic insult.

An initial goal of this study was to assess whether or not AMPT could prevent the accentuated damage to DA nerve terminals. As noted, however, the main finding was that AMPT protected all three of the terminal types that were studied. The simultaneous action on DA, 5-HT and glutamate makes it difficult to evaluate any selective degree of protection for DA nerve terminals.

Other authors have reported release of endogenous catecholamines from the brain, shortly after the onset of ischemia. This could result in vasoconstriction, and in a consequent worsening of the ischemic insult. Furthermore, there is some evidence that extraneuronal catecholamines may be toxic to neuronal structures: When norepinephrine is injected into the capillaries of a pial window, regional necrosis of cerebral tissue occurs. Necrosis does not occur when 5-HT is injected, even with an equivalent amount of regional ischemia. Acute release of endogenous catecholamine does not explain the delayed damage to nerve terminals that occurs after eight hours of ischemia, though it may be involved in the initial damaging process. Indeed, histofluorescence studies have shown almost complete depletion of catecholamine from the ipsilateral striatum early after carotid occlusion in the gerbil. At this time, the structure of the striatum and the function of nerve terminals remain intact. Even though there is depletion of catecholamine in the ischemic hemisphere, there is evidence that catecholamine metabolism and turnover proceed. The levels of catecholamines fall initially and do not rise. However, AMPT 400 mg/kg administered two hours prior to the carotid ligation produces a further decrement in catecholamine level two hours after ligation. Similarly, the administration of the monoamine oxidase (MAO) inhibitor pargyline 75 mg/kg two hours prior to ligation produces a rise in catecholamine levels in the ischemic hemisphere two hours after ligation. These observations also imply that some circulation and oxygen are present in the ischemic hemisphere, since both tyrosine hydroxylase and MAO require molecular oxygen to function.

Disruption of nerve terminal function by an ischemic insult appears to be a delayed process analogous to the histologic finding of ripening of ischemic infarction, which occurs in a similar time frame. Some acute injury does occur to neuronal membranes. This can be seen ultrastructurally as a breakdown of ribosomal units and swelling of rough endoplasmic reticulum and Golgi complexes. This initial vacuolization may cause leakage of catecholamine transmitters either into the cytoplasm or extracellularly. Extracellular catecholamines may penetrate into the cytoplasm of neurons and glia. Cytosolic catecholamines would be exposed to MAO which produces H2O2 as a product of oxidative deamination. H2O2 is a known neurotoxin and could possibly be involved in the ripening if ischemic damage. Extracellular catecholamines may also exert toxic effects via autooxidation or other mechanisms. Prior depletion of catecholamines and inhibition of catecholamine resynthesis in the ischemic hemisphere may lessen or prevent this damage.

Synaptic activity appears to be necessary to mediate the death of hypoxic neurons in tissue culture. When young hippocampal neurons without synaptic activity are exposed to sodium cyanide or hypoxia, no effect is noted. Death occurs only in more mature neurons that have developed synaptic activity. This hypoxic death can be blocked by MgCl2, which inhibits synaptic activity. Our data indicate that catecholamine transmitters are involved in the delayed degeneration of nerve terminals in the ischemic hemisphere of Mongolian gerbils. Depletion of the catecholamines by pretreatment with AMPT exerted a strong protective effect at 16 hours after carotid ligation. The toxicity of catecholamines may be due to a direct action or to some byproduct of catecholamine metabolism. Glutamate and 5-HT nerve terminals were protected along with DA terminals, suggesting that catecholamines may be involved in the spread of ischemic damage to adjacent nerve terminals.

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