Neural Damage in the Rat Thalamus After Cortical Infarcts

Hideaki Iizuka, MD, Kaoru Sakatani, MD, and Wise Young, PhD, MD

Histopathologic changes in the thalamus of 23 rats after somatosensory cortical infarction produced by middle cerebral artery occlusion were examined using the Fink-Heimer silver staining method, immunohistochemistry with antibodies against glial fibrillary acidic protein and laminin, and conventional stains. Middle cerebral artery occlusion produced cortical infarcts in the lateral parietal region, with variable involvement of the frontoparietal parasagittal sensorimotor cortex. Within 3 days after occlusion, massive terminal degeneration but no neuronal changes were apparent in the ipsilateral thalamus. By 1 week after occlusion, abnormal neurons with darkly stained, shrunken nuclei and atrophic perikarya were present in the ipsilateral thalamic nuclei. These neurons were densely argyrophilic in Fink-Heimer sections. Rats with small lateral parietal cortical lesions had degenerating neurons limited to the medial ventroposteromedial nucleus. Large lesions involving the parasagittal sensorimotor cortex resulted in widespread neuronal damage in the ventroposteromedial, ventroposterolateral, intralaminar, and posterior nuclear regions but nowhere else. Immunoreactivity to laminin antibody decreased, and astrocytic proliferation was abundant in affected thalamic areas. These findings are consistent with retrograde neuronal degeneration due to thalamocortical fiber damage in ischemic cortical regions. Such lesions remote from the infarct may influence functional recovery in patients with stroke. (Stroke 1990;21:790–794)

Axonal lesions cause not only anterograde degeneration in distal segments of axons but also retrograde cell death in some neural centers.1,2 Central nervous system lesions thus can damage neural structures remote from the primary lesions. We have reported widespread degeneration of corticofugal axons and their terminals in rat brainstem and spinal cord after cortical infarction produced by middle cerebral artery (MCA) occlusion (MCAO).3 Several anatomic studies have shown retrograde neuronal degeneration in mammalian thalamus after decortication.1,2,4 Recent positron emission tomographic studies have revealed hypometabolic states in the ipsilateral thalamus of patients with focal cortical or capsular infarcts after MCAO.5,6 We consequently examined the thalamus in rats after unilateral MCAO. Our model consistently produces infarcts in the lateral parietal cortical area, with variable involvement of the parasagittal frontoparietal cortex but little direct ischemic damage to subcortical structures.5,7 The cortical regions that become infarcted contain the primary somatosensory cortex and receive thalamocortical fibers from specific thalamic nuclei, that is, the ventroposteromedial and ventroposterolateral nuclei.8 The ventroposteromedial nucleus is the specific somatosensory relay nucleus for face sensation, while the ventroposterolateral nucleus serves the body, fore limbs, and hind limbs.8

Materials and Methods

We studied 23 adult male Long-Evans hooded rats weighing 250–350 g. The rats were anesthetized with 40 mg/kg i.p. pentobarbital. The right MCA was exposed via a subtemporal craniotomy preserving the zygomatic arch so that the rats could feed after surgery.3,7 The MCA was exposed via a subtemporal craniotomy preserving the zygomatic arch so that the rats could feed after surgery.3,7 The MCA was occluded and divided 1–2 mm below the rhinal fissure. The rats usually showed mild contralateral hemiparesis and a tendency to circle toward the lesioned site after MCAO. Such symptoms, however, disappeared within 24 hours. The rats were housed in boxes containing sterile hardwood chips and fed ad libitum. They regained their preoperative weights within a week.

The rats were randomly sacrificed 1 (n=4), 2 (n=3), or 3 (n=3) days or 1 (n=6), 3 (n=3), or 6 (n=4) weeks after MCAO by transcardiac perfusion with 4% paraformaldehyde or 10% formalin in phosphate-buffered saline under anesthesia with 40 mg/kg i.p. pentobarbital. The brains were removed,
and 40-μm frozen sections or 10-μm paraffin-embedded sections were cut from tissue containing the infarct and thalamus.

Frozen sections were processed for immunohistochemistry using antibodies against glial fibrillary acidic protein (GFAP) (Boehringer Mannheim Biochemicals, Indianapolis, Indiana), laminin, or the avidin-biotin complex. Normal neurons are immunoreactive to the antibody against laminin in frozen sections. To detect degenerating axons and neurons, other frozen sections were stained using the Fink-Heimer method. Paraaffin-embedded sections were processed for hematoxylin and eosin staining and Klüver-Barrera staining. Brain structures were named according to the atlas of Paxinos and Watson.

Results

Infarcts were discernible by 1 day after MCAO and invariably involved the lateral parietal area (Parietal 1 and Parietal 2). The insular and anterior piriform cortices and the lateral caudoputamen were also consistently infarcted. In some rats, the lesion extended to the fore limb and hind limb regions of the frontoparietal sensorimotor cortex and to the anterior temporal area. The infarcts did not involve the thalamus or the internal capsule in any rat.

One week after MCAO, abnormal neurons with pyknotic nuclei and shrunken perikarya with indistinct Nissl substance were abundant in the ipsilateral thalamus (Figure 1). In Fink-Heimer sections, these abnormal shrunken neurons were densely argyrophilic (Figure 2). Laminin immunohistochemistry revealed decreased laminin-like immunoreactivity in damaged thalamic areas 1 week after MCAO (Figure 3) and later. Astrocytic proliferation was present in GFAP-stained sections. Three and 6 weeks after MCAO, degenerating neurons were more pyknotic and atrophic; GFAP reactions were more prominent (Figure 4).

No obvious inflammatory reactions were observed in any rat. Degenerative changes of neurons were not seen elsewhere in the brain.

The degenerating thalamic neurons were distributed in a characteristic pattern. Table 1 summarizes the relation between location of the cortical infarct and the extent of thalamic degeneration. Rats with small cortical infarcts limited to the lateral region of Parietal 1 had degenerating neurons in the medial portion of the ventroposteromedial nucleus. Rats with large infarcts including Parietal 1 and extending into the fore limb and hind limb areas of the frontoparietal sensorimotor cortex and the temporal cortical area had degenerating neurons in most of the ipsilateral ventroposteromedial nucleus. Degenerating neurons were also present in the ventroposterolateral, ventromedial, intralaminar, and posterior nuclear regions.

Discussion

We demonstrate delayed degeneration of ipsilateral thalamic neurons after somatosensory cortical infarcts. These pathologic changes in the thalamus might have resulted from ischemic damage due to thalamic compression by edema after cortical infarction. The following findings, however, strongly sug-
gest retrograde neuronal degeneration secondary to axonal damage in the cortical infarct.

First, no pathologic changes were seen in the thalamus 1–3 days after MCAO. In our previous studies, selective neuronal death in the peri-infarct cortex and subcortical area was obvious in Fink-Heimer sections as early as 6 hours after MCAO and reached a maximum within 24 hours. Kataoka et al have reported decreased succinate dehydrogenase activity in ipsilateral thalamic neurons 5 days after MCAO. Although reports of human autopsy cases are few, neuronal degeneration or cell loss with GFAP reactions has been observed in the ipsilateral thalamus after cortical lesions including stroke, injury, and surgical interventions.

Second, the distribution of thalamic neuronal degeneration correlated anatomically with cortical involvement. Our results indicate that the ventroposteromedial nucleus neurons, which send axons to the Parietal 1 cortical region, were most frequently affected. Also, rats with small infarcts involving only the lateral part of Parietal 1 had neuronal degeneration limited to the medial area of the ventroposteromedial nucleus. The infarcts consistently involved the Parietal 1 region, and medial ventroposteromedial neurons send axons to the lateral part of Parietal 1.
Two negative findings are noteworthy. We did not find reactive chromatolytic changes in the thalamic neurons after cortical infarction. Holmes described degeneration and disappearance of central nervous system neurons after axonal interruptions without reactive chromatolysis. It is known that thalamic neurons do not undergo chromatolysis but degenerate rapidly after axonal damage. Furthermore, retrograde degeneration did not occur elsewhere in the brain, even though other neural structures must innervate the lateral parietal cortex. This suggests that thalamic neurons are particularly vulnerable.

Several factors may influence the death of axotomized neurons. Our data suggest that retrograde neuronal death is more likely if a substantial proportion of the cellular projections are lost and if neurons project to only a few targets. Thalamic nuclei neurons appear to send their axons to the cortex without extracortical collaterals. In cats and monkeys with hemidecortication, Nashold et al have ob-

<table>
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<th>Location</th>
<th>Degeneration</th>
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<tbody>
<tr>
<td>VPM</td>
<td>**</td>
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<td>VPL</td>
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TABLE 1. Location of Cortical Infarct and Extent of Thalamic Degeneration in Rats After Middle Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th>Rat</th>
<th>Location</th>
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<tr>
<td></td>
<td>FrM</td>
<td>Par1</td>
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<tr>
<td>1 week after MCAO</td>
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<td>3 weeks after MCAO</td>
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<td>6 weeks after MCAO</td>
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MCAO, middle cerebral artery occlusion; FrM, frontal motor area; Par1, parietal 1 area; FL, fore limb area of sensorimotor cortex; HL, hind limb area of sensorimotor cortex; Par2, parietal 2 area; Te, temporal cortex; Occ, occipital cortex; VPM, ventroposteromedial nucleus; VPL, ventroposterolateral nucleus; IL, intralaminar nuclear group; Po, posterior nuclear group; ++, severe cortical infarct; +, partial involvement by infarct; -, no infarct; **, many neurons degenerating throughout entire nuclear region; *, few neurons degenerating; -, no neurons degenerating.
served more neuronal degeneration and extensive gliosis in thalamic nuclei with specific projections than in nuclei with nonspecific projections.

Our results indicate that focal cortical stroke produces widespread neuronal degeneration in the thalamus. This degeneration appears to be retrograde as opposed to the anterograde degeneration that we found earlier.3 These observations may have implications for functional recovery after and therapeutic approaches to stroke. Retrograde degeneration of thalamic neurons implies deafferentation of the cortex. Even if some neurons in the ischemic cortex were spared, deafferentation may prevent functional recovery. It would be of interest to find out whether transplantation of neural tissue20 or introduction of growth factors21 into the infarct reduces retrograde thalamic degeneration. Finally, our results suggest that survival of some thalamic neurons depends on their projections to target neurons in the cortex.

Acknowledgment

We thank T. Yamamoto, MD, of the Department of Neurology, Fukushima Medical College, Fukushima, Japan, for the generous gift of the antilaminin antibody.

References


KEY WORDS • cerebral ischemia • neurons • thalamus • rats
Neural damage in the rat thalamus after cortical infarcts.
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Stroke. 1990;21:790-794
doi: 10.1161/01.STR.21.5.790

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