Effect of Experimental Ischemia on Neurotransmitter Amines in the Gerbil Brain


SUMMARY In the gerbil cerebral infarction was produced by unilateral carotid ligation. 3.5 hours later, when the neurological deficit was fully developed, hemisphere dopamine (DA) showed little change from normal. It seems unlikely that changes in DA are the direct cause of the turning behavior shown by these animals. Slight changes in norepinephrine (NE) occurred on the operated side but 4 hydroxy-3-methoxy phenylethylenglycol sulphate (MOPEG-SO4) levels were not affected. Significant falls in 5-hydroxytryptamine (5-HT) and 5-hydroxyindole acetic acid (5-HIAA) were found on the operated side but there was also a trend for both 5HT and 5-HIAA to fall on the unoperated side. These changes occurred in clinically affected and unaffected animals and their clinical significance is unproven.

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TABLE 2
Levels of NE in Right and Left Cerebral Hemispheres 3.5 Hours After Carotid Ligation on the Right

<table>
<thead>
<tr>
<th>Animals</th>
<th>No.</th>
<th>Right hemisphere</th>
<th>NE ng/g</th>
<th>± S.E.</th>
<th>Left hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation</td>
<td>8</td>
<td>802.8</td>
<td>N.S.</td>
<td>±157.2</td>
<td>919.4</td>
</tr>
<tr>
<td>Operated but no neurological deficit</td>
<td>4</td>
<td>808.8</td>
<td>N.S.</td>
<td>±191.6</td>
<td>760.5</td>
</tr>
<tr>
<td>Operated and showing deficit</td>
<td>12</td>
<td>838.5</td>
<td>N.S.</td>
<td>±56.0</td>
<td>1025.0</td>
</tr>
</tbody>
</table>

*Each sample obtained by combining hemispheres from 2 animals.

*Student’s t- or Wilcoxon rank test for paired data. None of the differences between operated and sham animals is significant at the p <0.05 level (Student’s t- or Mann Whitney U-Test for unpaired data).

Discussion

The failure to find consistent changes in DA levels in the ischemic hemisphere is of interest. Zervas et al.11 found a significant depletion of DA on the ischemic side 24 hours after carotid ligation in this model. The fall in DA appears, therefore, to develop slowly although Kogure et al.6 have suggested that in the rat the change is biphasic with an early rise in DA depletion having perhaps account for the failure of the present study to find any abnormality at 3.5 hours. Welch et al.,15 however, in a recent study, have reported a significant reduction in dopamine in the gerbil hemisphere cortex at 3 hours. There are methodological differences which may explain this discrepancy. Welch’s data showed a bilateral change in clinically affected and unaffected animals, although the greatest change was recorded in the infarcted hemisphere of symptomatic animals.

It has been suggested that the fall in dopamine detected by Zervas11 is related to the turning behavior of the gerbils with unilateral cerebral infarction because of its role as a neurotransmitter in the basal ganglia. However, the present study shows no clearcut change in DA at a time after carotid ligation when turning behavior is well developed and Welch’s study showed bilateral changes. It is much more prominent at an early stage than at the later time when the more severe DA depletion has been described. The animals turning toward the damaged side may represent the physiological effect of damage to the striopallidal outflow pathways, for both the caudate-putamen and the globus pallidus are involved.

Minor changes in norepinephrine were seen though they are not statistically significant when compared with sham-operated animals. The tendency appeared to be for a small bilateral drop in levels of NE as also found by Welch15 but the clinically normal and abnormal animals were all affected and MOPEG sulphate levels were identical between affected and unaffected groups.

TABLE 3
Levels of MOPEG-SO4 in the Right and Left Cerebral Hemispheres 3.5 Hours After Carotid Ligation on the Right

<table>
<thead>
<tr>
<th>Animals</th>
<th>No. of pairs</th>
<th>Right hemisphere</th>
<th>MOPEG-SO4 ng/g</th>
<th>± S.E.</th>
<th>Left hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation</td>
<td>6</td>
<td>49.8</td>
<td>N.S.</td>
<td>±4.9</td>
<td>56.2</td>
</tr>
<tr>
<td>Operated but no neurological deficit</td>
<td>5</td>
<td>48.9</td>
<td>N.S.</td>
<td>±8.97</td>
<td>50.2</td>
</tr>
<tr>
<td>Operated and showing deficit</td>
<td>7</td>
<td>44.7</td>
<td>N.S.</td>
<td>±14.1</td>
<td>52.4</td>
</tr>
</tbody>
</table>

*Each sample obtained by combining hemispheres from 2 animals.

None of the differences between operated and sham animals is significant except the level of NE in operated animals showing a deficit compared with sham operated animals (p <0.05, Mann Whitney U-test for unpaired data).
The reduction of cerebral 5-HT level, the evidence for an important pathogenic effect is slender. The fall in tissue 5-HT level, the evidence for an important pathogenic effect is slender. The fall in 5-HT reflects release of transmitter 5-HT into symmetrical animals. In our study the changes were indicated.

There is a general agreement about 5-HT in that most workers have confirmed a fall in ischemic cerebral tissue with or without seizures. There are important discrepancies between the present results and those of Welch et al.14 who have suggested that DA and NE levels only fall in those animals that develop seizures as a result of infarction. Our study included such animals (with seizures) and others with only circling behavior and no seizures as a single category of neurologically affected animals. In future studies a separation of subgroups according to the nature of the clinical deficit is clearly indicated.

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<table>
<thead>
<tr>
<th>Animals</th>
<th>No.</th>
<th>Right hemisphere</th>
<th>SHIAA μg/g</th>
<th>S.E.</th>
<th>Left hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation</td>
<td>6</td>
<td>1204</td>
<td>N.S.</td>
<td></td>
<td>1105</td>
</tr>
<tr>
<td>Operated but no neurological</td>
<td>6</td>
<td>744.8*</td>
<td>N.S.</td>
<td>708.8</td>
<td></td>
</tr>
<tr>
<td>deficit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operated and showing deficit</td>
<td>6</td>
<td>754.9*</td>
<td>N.S.</td>
<td>746.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Levels of 5-HIAA in the Right and Left Cerebral Hemispheres 5.5 Hours After Carotid Ligation on the Right.

Difference from level in sham animals: Student's t- or Mann Whitney U-test unpaired data. *p < 0.01.

hemintheses in both sets of operated animals. Zervas11 found no difference in NE at 24 hours. Kogure6 found an initial fall in the ischemic rat brain which tended to recover toward normal by 4 hours, perhaps accounting for the minor differences in the present study at 3.5 hours.

The clinical implication of the NE changes is uncertain since the differences are small, and are equally present in clinically affected and clinically unaffected animals.

Some of the variability in DA and NE findings may relate to the nature of the neurological abnormality produced in individual animals. Thus, Welch et al.14 have suggested that DA and NE levels only fall in those animals that develop seizures as a result of infarction. Our study included such animals (with seizures) and others with only circling behavior and no seizures as a single category of neurologically affected animals. In future studies a separation of subgroups according to the nature of the clinical deficit is clearly indicated.

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Serum Dopamine-β-Hydroxylase Activity in Acute Stroke

TADASHI KANDA, M.D., FUMIO GOTOH, M.D., MASAHIRO YAMAMOTO, M.D., FUMIHIKO SAKAI, M.D., TSUNEYUKI TAKEOKA, M.D., AND YASUYUKI TAKAGI, M.D.

SUMMARY Serum dopamine-β-hydroxylase (DBH) activity was measured in 34 patients with acute cerebrovascular disease. The serum level of DBH activity showed its highest value soon after the onset of stroke and then gradually decreased over the next few days. After reaching its lowest level, the DBH activity again showed a slight increase. There was no direct relationship between serum DBH activity and total serum protein, or blood pressure. In 8 of 12 patients, DBH activity in the cerebral venous blood was higher than that in the arterial blood. These results suggest that rapid release of DBH into the circulating blood occurred after stroke, presumably from sympathetic nerve endings in the vessels or organs, including the brain.

DOPAMINE-β-HYDROXYLASE (DBH), the enzyme needed for the final step of norepinephrine synthesis, is known to be present in synaptic vesicles in sympathetic nerve endings and to be released together with norepinephrine by a process of exocytosis from the stimulated nerve endings. Thus, DBH in circulating blood may be derived mainly from sympathetic nerve terminals and the level of DBH activity in the blood may reflect alterations in sympathetic nerve activity. In clinical studies of migraine, in which a cerebral vasomotor disturbance is known to exist, elevated levels of DBH activity in the circulating blood have been seen in headache-free intervals.

In patients with stroke, elevated levels of plasma and urinary catecholamines have been reported during the acute state of cerebrovascular disease, suggesting increased activity in the sympathetic nervous system after ictus. Recent observations of experimental subarachnoid hemorrhage have suggested the possible participation of cerebrovascular nerves in the generalized response of the autonomic nervous system. Since the autonomic nervous system may play a role in the regulation of cerebral blood flow, the cerebral vasomotor disturbance observed at the acute stage of stroke could be associated with the release of norepinephrine from nerve endings in cerebral vessels. Measurements of DBH levels in arterial and cerebral venous blood, as well as in the systemic venous blood of patients with stroke, may thus provide some insight into the pathophysiology of stroke.

The purpose of the present study was to determine whether or not perceptible amounts of DBH were released into the circulating blood from sympathetic nerve endings in the vessel of the brain or other organs during an acute stroke.

Subjects and Methods

Serum DBH activity was measured in 34 patients with various types of acute cerebrovascular disease, admitted within 24 hours of onset. Their ages ranged from 28 to 89 (mean 53) years. Ten patients were found to have cerebral infarction, 17 intracerebral hemorrhage, and 7 subarachnoid hemorrhage resulting from ruptured intracranial aneurysms. The diagnosis was based on the clinical examinations, lumbar puncture, cerebral angiography and/or computed tomography. Four patients died within 4 days after the onset and 2 died between 5 to 30 days.

Initial blood samples were drawn 40 minutes to 23 hours after onset. The second and third samples were then obtained at 3–4 days and 5–10 days after onset. In 12 patients, simultaneous blood samples were obtained within 48 hours after onset from the femoral
Effect of experimental ischemia on neurotransmitter amines in the gerbil brain.
M J Harrison, C D Marsden and P Jenner

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