ALTERATIONS OF neurotransmitter functions in cerebral ischemia and stroke have recently received increasing attention. Studies in various animal species have shown that catecholamine (CA), serotonin (5-HT) and amino acid (AA) biosynthesis in brain is dependent on arterial and tissue pO2. Severe ischemic conditions with derangement of the cerebral energy state markedly reduce monoamine and protein biosynthesis5-7 with depletion of noradrenaline (NA), dopamine (DA) and 5-HT and reduction of AA metabolism.24 After severe unilateral ischemia these modifications are present not only in the damaged tissue but also in remote "non-ischemic" areas and in the contralateral hemisphere.3-9 In the post-ischemic phase the main metabolites of DA, homovanillic acid (HVA) and of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), accumulate in the damaged tissue and in the adjacent edema zone.5,10

Human post-mortem studies confirmed the findings in animal models. After recent brain infarct severe depletion of CA, 5-HT and their metabolites was found in necrotic and intact areas.13 In older brain infarcts a reduction of 5-HT and HVA was still present in necrotic tissue while adjacent tissues showed almost normal levels indicating some recovery.13

Thus, both animal and human studies have shown that marked changes of neurotransmitter metabolism occur in ischemic brain tissue and that these changes may have a complex time pattern. It therefore appears important for the understanding of the relationships between ischemia and neuron function to study the temporal profile of neurochemical changes in the ischemic brain. In patients this can only be accomplished by the investigation of neurochemical indices in the CSF.

CSF levels of monoamines and their metabolites can be considered to reflect the neurotransmitter metabolism in the brain.14 Increased levels of NA and 5-HT were found in the CSF of patients with stroke,15,16 and the concentrations of these amines were inversely correlated with the duration of stroke and the severity of neurological deficit.16 Previous studies of 5-HIAA and/or HVA concentrations in CSF at various times after stroke were inconsistent, levels varying from high to undetectable and showing no correlation with other parameters, e.g. time or clinical deficit.17,18

The aims of our study were to determine the temporal profile of HVA and 5-HIAA in CSF of patients with stroke and the effects of persisting ischemia on acid metabolites in the CSF of patients with multi-infarct dementia (MID).

Patients and Methods

The study included thirty four patients who had had complete ischemic stroke of the superficial Sylvian territory, confirmed by clinical evaluation, computed tomographic (CT) scan, EEG, and in three cases by autopsy. Our standard diagnostic protocol also included a lumbar puncture for routine CSF examination, since at the time of the study, CT scans could not always be performed immediately upon admission. These patients were divided into three groups according to the time elapsed between the first signs of stroke and the lumbar puncture: group A, 22-47 h, 16 patients; group B, 48-71 h, 12 patients; group C, 72-96 h, 6 patients (table 1). Nineteen patients with MID were also studied (table 1). MID was diagnosed by clinical examination, extensive neuropsychological testing, the score on the Hachinski rating scale as modified by Rosen19 (mean ± S.D. = 8.4 ± 0.8), EEG, and CT scan. These patients had no signs or symptoms of acute stroke for at least six months.
Since HVA and 5-HIAA concentrations in the first and third CSF samples were never significantly different, the average value for the two determinations was used in the calculations.

In all groups of patients, HVA concentrations were significantly lower than in controls (table 2). Moreover, in groups B, C, and MID, the levels of HVA were also lower than in the group with the shortest duration after stroke (group A). The progressive decline of HVA levels in the first five days after stroke is further documented by a significant inverse correlation ($r = -0.49, p < 0.01$) between the time of the lumbar puncture after stroke and the HVA concentrations.

On the other hand, the concentrations of 5-HIAA in group B and MID were significantly lower than in controls and group A, and the 5-HIAA/HVA ratio was lower in groups A and B than in controls.

Regression analysis did not show any significant correlations between HVA, 5-HIAA, 5-HIAA/HVA and the Norris scores. The CSF levels of the acid metabolites were also not related to the outcome at six months.

Conclusions

The study of the temporal profile of effects of ischemia on brain transmitter function after acute stroke appears to constitute an important approach to the understanding of pathogenetic mechanisms of the disease.

Since for ethical reasons a longitudinal study could not be carried out, we performed our research in stroke patients similar for type of the lesion (e.g. ischemic) and vascular territory involved (e.g. superficial Sylvian) at different times after stroke.

In this respect our study is, to our knowledge, the first neurochemical investigation of CSF monoamine metabolites in such a well-defined condition. Previous reports of patients with stroke have not specified the type of lesion, the vascular territory, or the entity of edema, evaluated either directly by CT scan or indirectly by the degree of impairment of consciousness, EEG, or angiography.

We documented a clear time pattern of HVA and 5-HIAA levels both these substances significantly declining in the first five days after stroke. There may be more than one reason for altered concentrations of monoamine metabolites in CSF after cerebral ischemia.

<table>
<thead>
<tr>
<th>Groups</th>
<th>HVA (Mean ± SD)</th>
<th>5-HIAA (Mean ± SD)</th>
<th>5-HIAA/HVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>35.8 ± 13.8*</td>
<td>32.1 ± 11.2</td>
<td>1.04 ± 0.39†</td>
</tr>
<tr>
<td>group B</td>
<td>22.2 ± 10.4**$</td>
<td>21.0 ± 8.2$</td>
<td>1.20 ± 0.81$</td>
</tr>
<tr>
<td>group C</td>
<td>20.4 ± 8.2*$§</td>
<td>20.3 ± 11.8</td>
<td>1.03 ± 0.38</td>
</tr>
<tr>
<td>Mid</td>
<td>23.3 ± 10.3*†</td>
<td>18.8 ± 7.7*†</td>
<td>1.04 ± 0.83</td>
</tr>
<tr>
<td>Controls</td>
<td>61.7 ± 9.6</td>
<td>32.3 ± 4.5</td>
<td>0.53 ± 0.13</td>
</tr>
</tbody>
</table>

*p < 0.01, vs controls; †p < 0.01, vs group A; §p < 0.05, vs controls; $p < 0.05 vs group A.
and infarction. Edema is one of the most important of these. Hachinski et al found decreased levels of HVA in lumbar CSF of patients with brainstem infarcts. We agree with them that the most likely explanation is that edema in the periaqueductal region may have reduced the outflow of HVA-rich CSF from the ventricles to the spinal cord. Moreover, edema may not only functionally block CSF from the ventricles but, when it is diffuse, it may provoke a compensatory displacement of CSF from intracranial spaces, which would contribute to increasing the levels of HVA in the spinal CSF. The large interindividual variability of HVA levels (4 to 207) found in patients with hemispheric infarcts can probably be explained by differences in the relative importance of these two mechanisms in a given patient.

Our results can be interpreted as showing they are the consequence of earlier DA and 5-HT depletion in the brain. Experimental and human post-mortem studies have clearly shown that in recent ischemia and infarcts 5-HT and DA are severely depleted not only in the focal and perifocal brain areas but also in the hemisphere contralateral to the injury. Thus, the reduced HVA and 5-HIAA CSF levels we observed between the second and fifth day after stroke may reflect a global depletion of brain amines in the early phases of brain ischemia. It has been suggested that the monoamines released in the early phase may contribute to some aspects of the pathogenetic processes, i.e. vasoconstriction, brain edema and reduction of regional cerebral blood flow (rCBF). The changes in monoamines can be either a cause or an effect of diaehasia, i.e. remote effects of a focal ischemia. The fact that there is diffuse cerebral dysfunction after unilateral infarction is further supported by observations of marked reductions of rCBF in the “non-ischemic” hemisphere soon after the onset of stroke.

On the other hand, human post-mortem studies show that in old infarcts monoamine depletion is still present in necrotic areas, but in intact areas levels are almost normal, indicating some recovery in the previously ischemic brain. However, in patients with recurrent cerebral ischemic attacks and consequent multiple infarcts (MID), our results show low concentrations of acid monoamine metabolites in the CSF. It can be supposed that in these patients the persistence of diffuse ischemia maintains a reduced amine turnover even in morphologically intact areas.

In a previous study we found that in patients who had a stroke but had been without further clinical evidence of ischemia for at least two months, HVA levels in CSF rose toward normal as the time after stroke lengthened. It appears therefore that the recovery of CSF metabolite levels can be considered a sign of functional recovery in intact areas and of the subsiding of ischemia.

The lack of correlation between the severity of neurologic deficit and HVA of 5-HIAA levels is not surprising considering that the severity of symptoms in patients with stroke depends mostly on the focal lesion while the reduced CSF HVA and 5-HIAA levels reflect diffuse brain dysfunction. Similarly, in MID the CSF changes might reflect not only tissue loss but also a state of diffuse ischemia which may not be clinically evident in patients with severe deficits due to multiple infarcts.

References
Diagnosis of Reversible Versus Irreversible Cerebral Ischemia by the Intravenous Administration of Naloxone

BRUNO ESTANOL, M.D., FRANCISCO AGUILAR, M.D., AND TERESA CORONA, M.D.

SUMMARY Naloxone was given as an i.v. bolus of 0.8 mgs to four groups of patients with stroke: 1) 20 patients with C.T. proven cerebral infarcts of longer than 7 days duration; 2) 20 patients with acute cerebral ischemia of less than 7 days duration; 3) 5 patients with C.T. proven intracerebral hemorrhage of less than 24 hours; 4) 3 patients with hyperacute cerebral ischemia of less than 24 hours. Two of their patients also had an intracerebral hemorrhage. Fallis et al gave intravenous naloxone in a double blind trial to 15 patients with symptoms between 8 and 60 hours in duration. None of the patients responded. One patient had an intracerebral hemorrhage. Faden suggested that the discrepancy of the different trials is partly due to a poor selection of patients, lack of early treatment and use of inadequate doses. In order to elucidate the time factor and the type of patients who respond to intravenous naloxone we conducted a trial in four different populations of stroke patients: 1) patients with an established cerebral infarction proven by C.T. scanner 48 hours after the onset of the cerebral ischemia and were asymptomatic when discharged. The 3 patients with hyperacute cerebral ischemia had a dramatic response to the injection of naloxone. These findings suggest that intravenous naloxone may differentiate reversible versus irreversible cerebral ischemia.

From the Department of Neurology, Hospital General, Centro Médico Nacional, Instituto Mexicano Del Seguro Social, Mexico.

Address correspondence to: Bruno Estañol, M.D., Department of Neurology, Hospital General, Centro Médico Nacional, Instituto Mexicano Del Seguro Social, Cuauhtemoc 330; Mexico 6, D.F.

Received July 23, 1984; revision #2 accepted March 21, 1985.

Address correspondence to: Bruno Estañol, M.D., Department of Neurology, Hospital General, Centro Médico Nacional, Instituto Mexicano Del Seguro Social, Cuauhtemoc 330; Mexico 6, D.F.

Received July 23, 1984; revision #2 accepted March 21, 1985.

Copyright © 1985 by the American Heart Association.
Homovanillic acid and 5-hydroxyindoleacetic acid modifications in CSF of patients with stroke and multi-infarct dementia.
S Smirne, M Franceschi, G Truci, M Camerlingo, R Pirola, L Ferini-Strambi and S R Bareggi

*Stroke*. 1985;16:1003-1006
doi: 10.1161/01.STR.16.6.1003

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/16/6/1003

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/