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 biosynthesis with depletion of noradrenaline (NA), dopamine (DA) and 5-HT and reduction of AA metabolism. 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. In the post-ischemic phase the main metabolite 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.

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. In older brain infarcts a reduction of 5-HT and 5-HIAA was still present in necrotic tissue while adjacent tissues showed almost normal levels indicating some recovery.

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. Increased levels of NA and 5-HT were found in the CSF of patients with stroke, and the concentrations of these amines were inversely correlated with the duration of stroke and the severity of neurological deficit. 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.

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 examination, 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 Rosen (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.
Values for the MID group.

The MID or the stroke patients in the other groups (table

system.

columns of Sephadex G-10 as previously described.21

scans never showed any distortion of the ventricular

The second aliquot was used for routine laboratory

HVA and 5-HIAA concentrations were

of CSF were collected. The first and third were imme-

twelve hrs of fasting and bed rest. Three 5 ml samples

were also lower than in the group with the shortest
duration after stroke (group A). The progressive de-

cine of HVA levels in the first five days after stroke is

and the stroke patients were receiving corticosteroids

Drugs known to affect monoamine metabolism.

None of the MID patients and controls included in

Conclusions

The study of the temporal profile of effects of ische-

Since for ethical reasons a longitudinal study could

In this respect our study is, to our knowledge, the

Twenty patients were given antiaggregating agents

Lumbar punctures were performed at 8 A.M., after

None of the patients had severe impairment of alert-

Results

None of the patients had severe impairment of alert-

Patients in group A were slightly older, with more

Sheffield, insulin and strephathine were

or cardioactive drugs if previously taken were neither

Before CSF sampling. Antihypertensive, antidiabetic

and had normal diagnoses served as controls (table 1).

None of the MID patients and controls included in

The study took any psychotropic drugs for two weeks

CSF after cerebral ischemia

Since HVA and 5-HIAA concentrations in the first

Since HVA and 5-HIAA concentrations in the first and

were never significantly different, the average value for the two determinations was

In all groups of patients, HVA concentrations were

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 de-

cine of HVA levels in the first five days after stroke is

Further documented by a significant inverse correlation

and the Norris scores. The CSF levels of the acid

metabolites were also not related to the outcome at six months.

TABLE 1

Basic and Clinical Data for Controls and Patients with Stroke and MID

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>M</th>
<th>F</th>
<th>Age*</th>
<th>Norris Score*</th>
<th>6-Month follow up†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>16</td>
<td>7</td>
<td>9</td>
<td>72 ± 8‡</td>
<td>126 ± 60‡</td>
<td>4 10 — 2</td>
</tr>
<tr>
<td>group B</td>
<td>12</td>
<td>7</td>
<td>5</td>
<td>66 ± 11</td>
<td>85 ± 43</td>
<td>5 4 2 1</td>
</tr>
<tr>
<td>group C</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>60 ± 11</td>
<td>71 ± 58</td>
<td>2 3 1 —</td>
</tr>
<tr>
<td>Mid</td>
<td>19</td>
<td>15</td>
<td>4</td>
<td>60 ± 5</td>
<td>66 ± 40</td>
<td>15 3 1</td>
</tr>
<tr>
<td>Controls</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>64 ± 5</td>
<td>— — — —</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SD; †Number of cases; ‡p < 0.01 vs MID.

For all patients the severity of the neurological defi-

the Norris rating scale,20 slightly modified. Surviving stroke patients were reassessed

after six months with the same scale and evaluated as:

improved" (score decreased 10%), "worsened" (score

increased 10%), or "unchanged" (table 1).

Nine age-matched subjects who underwent myelog-

raphy for lumbar pain and had normal diagnoses

served as controls (table 1).

None of the MID patients and controls included in

the study took any psychotropic drugs for two weeks

before CSF sampling. Antihypertensive, antidiabetic

or cardioactive drugs if previously taken were neither

discontinued nor modified; but if such therapy had to

be started, diuretics, insulin and strophanthine were

been 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 Sylv-

ian) at different times after stroke.

The study of the temporal profile of effects of ische-

mia on brain transmitter function after acute stroke appears to constitute an important approach to the

understanding of pathogenetic mechanisms of the
disease.

Since HVA and 5-HIAA levels both these substances significantly de-

edema,17–18 evaluated either directly by CT scan or

indirectly by the degree of impairment of conscious-

ness, EEG, or angiography.

We documented a clear time pattern of HVA and 5-

HIAA levels both these substances significantly de-

clining in the first five days after stroke. There may be

more than one reason for altered concentrations of

monoamine metabolites in such a well-defined condition. Previous

first neurochemical investigation of CSF monoamine

metabolites in such a well-defined condition. Previous

were not specified the type of lesion, the vascular territory,17 or the entity of edema,17,18 evaluated either directly by CT scan or

indirectly by the degree of impairment of conscious-

ness, EEG, or angiography.

We documented a clear time pattern of HVA and 5-

HIAA in other studies23–25 and our present findings are

consistent with and confirm this time pattern. The

most consistent finding was a progressive decline in both

HVA and 5-HIAA during the first five days after stroke.

In the present study, we investigated the temporal profile of both

HVA and 5-HIAA in the first five days after stroke. The two

substances were measured by the isotope dilution

method. 

Since the HVA and 5-HIAA concentrations in the first

and third CSF samples were never significantly differ-

ent, 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). Mor-

over, 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 de-

cline 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.

<table>
<thead>
<tr>
<th>Groups</th>
<th>HVA</th>
<th>5-HIAA</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>1.00±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.14 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,22 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 infarcts18 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 studies3-13 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. vasogenic edema and edema formation.23 The changes in monoamines can be either a cause or an effect of diaschisis, 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” hemispheric soon after the onset of stroke.24, 25

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 ischémic 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.28 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 less than 24 hours duration; 2) 20 patients with acute cerebral ischemia of less than 24 hours; 3) 5 patients with C.T. proven intracerebral hemorrhage of less than 24 hours; and 4) 3 patients with hyperacute cerebral ischemia which occurred during the performance of a cerebral angiogram. The patients with established cerebral infarctions of more than 7 days duration and the patients with intracerebral hematomas had no response to intravenous naloxone. Of 20 patients with acute cerebral ischemia of less than 24 hours duration, 7 had prompt, complete and long-lasting recovery. These patients had no subsequent evidence of cerebral infarct 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 secondary to cerebral angiography had a dramatic response to the injection of naloxone. These findings suggest that intravenous naloxone may differentiate reversible versus irreversible cerebral ischemia.

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SEVERAL CONTROVERSIAL REPORTS regarding the use of naloxone in acute cerebral ischemia have recently appeared.1,2,3,9 Baskin and Hosobuchi1 found that two patients with focal cerebral ischemia had dramatic improvement with the intravenous administration of naloxone. Jabaily and Davis2 gave intravenous naloxone to thirteen patients with acute stroke, treatment given between 4 and 24 hours after the cerebral event. Three out of thirteen patients improved suggesting that naloxone reversal of ischemic cerebral deficits was a rare event. Two had intracerebral hemorrhages that did not respond and one had an immediate and long lasting recovery and was subsequently shown to have a C.T. scan without evidence of a cerebral infarction.

Cutler et al3 gave intravenous naloxone to nineteen patients with cerebral ischemia of less than seventy-two hours duration. None of the patients responded to the intravenous naloxone. Two of their patients also had an intracerebral hemorrhage. Fallis, et al9 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. Faden8 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. with symptoms longer than 7 days duration (range 7–15 days); 2) patients with hypertensive intracerebral hematomas proven by C.T. the naloxone being given within the first 24 hours of the inception of the symptoms; 3) patients with acute cerebral ischemia of less than twenty-four hours duration (normal C.T. and lumbar puncture in the first 24 hours); 4) patients with hyperacute focal cerebral ischemia secondary to angiographic accidents; the naloxone was given within the first ten minutes of the onset of the ischemia.

Patients and Methods

The first group were 20 patients with C.T. proven cerebral infarct of more than 7 days’ duration (range
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

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