Atrial Natriuretic Factor and Salt Wasting After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose: The causes of volume depletion and hyponatremia after subarachnoid hemorrhage are not fully understood but may be in part due to natriuresis or "cerebral salt wasting." Because previous studies using infrequent hormone sampling have given inconsistent results, we determined if elevations in atrial natriuretic factor concentrations preceded negative sodium and fluid balances.

Methods: We measured diurnal atrial natriuretic factor and vasopressin concentrations and sodium balance for 5 days in 14 consecutive patients after aneurysmal subarachnoid hemorrhage.

Results: Plasma concentrations of atrial natriuretic factor on admission were elevated in subarachnoid hemorrhage patients (mean±SD 106±59 pg/ml) compared with acutely ill controls (39±30 pg/ml). In eight patients, high peak concentrations of atrial natriuretic factor, greater than 300 pg/ml or a twofold increase above baseline, were followed by natriuresis and a negative sodium balance. Three patients, two of whom became hyponatremic, developed cerebral infarcts after natriuresis. Vasopressin concentrations were slightly elevated just after hemorrhage but subsequently declined to normal values.

Conclusions: A markedly increased atrial natriuretic factor concentration precedes natriuresis in some patients and, with other abnormalities of water handling possibly including a relatively diminished vasopressin concentration, may cause volume depletion. Patients with natriuresis appear to be at increased risk for delayed cerebral infarction after subarachnoid hemorrhage.

(Stroke 1991;22:1519-1524)

Intravascular volume depletion and fluid restriction have been shown to contribute to the development of delayed cerebral infarction from vasospasm, one of the leading causes of morbidity after subarachnoid hemorrhage.1,2 This is the basis for the currently recommended therapy of early volume expansion in patients at risk for vasospasm.3-5 A previous study has demonstrated that volume depletion after subarachnoid hemorrhage results from natriuresis ("cerebral salt wasting") associated with decreased plasma concentrations of vasopressin.1 Some preliminary studies have also shown elevated levels of atrial natriuretic factor early during the course of subarachnoid hemorrhage,6-8 but the relation of the atrial natriuretic factor concentration to the vasopressin concentration and to fluid and sodium balances has only recently been studied explicitly.9 Despite suggestions that atrial natriuretic factor is not responsible, we reasoned that atrial natriuretic factor, which exerts actions opposite those of vasopressin, might be the main cause of both natriuresis and volume loss in subarachnoid hemorrhage and that these changes occur independently of hyponatremia. We therefore prospectively studied the plasma levels of atrial natriuretic factor and vasopressin and the sodium balance beginning immediately after aneurysmal rupture.

Subjects and Methods

We studied 14 consecutive patients with clinical and computed tomographic (CT) evidence of aneurysmal subarachnoid hemorrhage admitted to the neurological-neurosurgical intensive care unit (ICU) within 12 hours after the ictus. Informed consent for phlebotomy was obtained from the patient or family. None of the patients were recently treated with diuretics or had renal or endocrine disease. All received at least 2 l fluid/day and intermittent doses of 5% albumin. Systolic blood pressure was maintained below 180 mm Hg with intravenous nitroglycerin or labetalol.

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Received December 31, 1990; accepted July 25, 1991.
For the 5 days of the study, we obtained 12-hour urine collections and recorded urine volume and sodium concentration. Sodium intake was calculated from intravenous fluids, medications, and, in appropriate patients, from food with known sodium content. Morning and evening samples for atrial natriuretic factor and vasopressin concentrations were obtained 8–12 hours apart beginning within 12 hours after the hemorrhage (day 0). We measured electrolyte levels, renal function tests, glucose content, and osmolality daily.

The amounts of subarachnoid blood and intraventricular blood were graded as described previously.10 Twelve patients had cerebral angiography. In these patients, the neck of the aneurysm was surgically occluded within 2 days after admission in four patients and in the other eight surgery was delayed for 8–10 days.

We also obtained control AM and PM samples for atrial natriuretic factor and vasopressin concentrations in 15 age- and sex-matched patients with acute neurological disease (Guillain-Barré syndrome, spinal cord injury) in the ICU during the epoch of the study.

Arterial blood samples collected in chilled plastic tubes containing 5 mg ethylenediaminetetraacetic acid and 1.5 units aprotinin per 12 ml were immediately separated by centrifugation at 500g for 15 minutes at 5°C. Plasma aliquots of 1 ml were stored at −70°C. The atrial natriuretic factor concentration was determined by direct radioimmunoassay after prior extraction of the plasma samples with Sep-pak C18 cartridges activated with 20 ml cold absolute methanol followed by 20 ml cold H2O. Samples were loaded with a 1:4 ratio of plasma:4% acetic acid (pH 2.5) and then washed with 10 ml of 4% acetic acid (pH 2.5). Atrial natriuretic factor was eluted with 4 ml of three parts acetonitrile and one part 4% acetic acid (pH 2.5), dried in a Speed-vac (Savant Co., Hicksville, N.Y.), and resuspended with atrial natriuretic factor human radioimmunoassay buffer (Peninsula Laboratories, Belmont, Calif.) to the original plasma volume. As determined using labeled samples of genuine α-human atrial natriuretic factor 1-26, the efficiency of recovery of the peptide extraction was 80%. Plasma atrial natriuretic factor concentrations were determined by specific radioimmunoassay from α-human atrial natriuretic polypeptide and corrected for recovery. The assay sensitivity was 1 pg/tube. Intra-assay and interassay coefficients of variation were 2.4% and 10.8%, respectively.

Plasma concentrations of vasopressin were assayed using aliquots of plasma extracted as described above. The vasopressin radioimmunoassay uses an antiserum generated in male New Zealand White rabbits immunized with vasopressin conjugated to bovine thyroglobulin, as previously described.11 The antiserum, used at a final dilution of 1:8×105, binds 30% of iodine-125–labeled vasopressin (8,000 cpm).

Iodine-125–labeled vasopressin was generated by reacting vasopressin (Peninsula Laboratories) with iodobeads (Pierce Chemical Co., Rockford, Ill.) under conditions outlined by the manufacturer. Labeled vasopressin was isolated by high-performance liquid chromatography on a C18 Bondapak column (Waters Assoc., Milford, Mass.) using a gradient of 0–50% acetonitrile in 0.1% trifluoroacetic acid. The peak fraction was diluted in 0.2% bovine serum albumin and 0.2N acetic acid and stored at 4°C. The sensitivity of the assay was 0.125 pg/tube. This antibody has minimal cross-reactivity with oxytocin (0.01%) and does not cross-react with other hypothalamic neuropeptides.11 The intra-assay and interassay coefficients of variation were 8.3% and 10.5%, respectively.

Results

The patient’s ages ranged from 36 to 71 (mean 53) years. Five patients were categorized as Hunt and Hess grade 1, six as grade 2, and three as grade 3 or 4.12 The initial CT scan demonstrated large collections of cisternal blood (sum score of greater than 15) in 11 of the 14 patients. Six patients had ventricular enlargement, including enlargement of the third ventricle, on the admission CT scan. Cerebral angiography, carried out in 12 patients, demonstrated an aneurysm from the anterior communicating artery in four, the carotid artery in five, and the posterior circulation in three. Three patients deteriorated due to delayed cerebral ischemia, resulting in brain death in two. One patient had fatal rebleeding 8 days after admission. Two comatose patients died of systemic complications. Six patients had a good recovery and three remained severely disabled, two because they did not recover from the initial hemorrhage.

Sodium balance could be calculated on 63 of 70 days. (In four patients urine collection was incomplete on the day of surgery, and in one patient furosemide was administered on 3 days because of mild heart failure.) There were no major changes in the blood urea nitrogen or creatinine concentrations during the epoch of the study in patients with subarachnoid hemorrhage, nor in the controls.

In most patients with subarachnoid hemorrhage, atrial natriuretic factor concentrations were elevated on the day of admission (mean±SD 106±59 pg/ml) compared with the supine acutely ill ICU controls (mean±SD 39±30 pg/ml, p<0.01; Figure 1, Table 1). There was no significant difference between AM and PM atrial natriuretic factor values in the controls.

After the day of admission, eight patients had markedly increased atrial natriuretic factor concentrations (either greater than 300 pg/ml or twice baseline levels). The first peak of atrial natriuretic factor with the corresponding vasopressin level is shown in Figure 1. In four of these eight patients there was a second or third peak in the value of atrial natriuretic factor. During these peaks, mean±SD atrial natriuretic factor concentrations reached 374±180 (range 119–738) pg/ml. The first atrial natriuretic factor concentration peak in these eight patients occurred an average of 2.5 (range 2–5) days after the subarachnoid hemorrhage. Vasopressin

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Atrial natriuretic factor concentration peaks were not related to the angiographic dye load. None of the patients had a significant increase (to twice baseline levels) in the vasopressin concentration during the study. There was no correlation between the initial Hunt and Hess grade or the location of the aneurysm and the average or peak vasopressin concentrations.

The sodium balance was negative and there was a marked natriuresis on 8 of 13 days in the eight patients with an atrial natriuretic factor concentration peak compared with on 12 of 50 days in the six patients without a peak ($\chi^2 = 13.4, p < 0.01$). The mean±SD sodium balance on days with an atrial natriuretic factor concentration peak was $-246\pm143$ mmol compared with $-134\pm136$ mmol on days without a peak. Overall sodium balance did not differ significantly ($t$ test) in patients with and without atrial natriuretic factor concentration peaks. The patient with the highest atrial natriuretic factor concentration (738 pg/ml, patient 8) had a high sodium intake on that day, resulting in a slightly positive sodium balance. Sodium intake and natriuresis were higher on the 5 days in which atrial natriuretic factor concentration peaks were associated with a positive sodium balance (mean±SD 786±359 mmol and 781±501 mmol, respectively) than on the 8 days in which peaks were associated with a negative sodium balance (mean±SD 366±81 mmol and 566±165 mmol, respectively).

The vasopressin concentrations were similarly low in patients with negative ($15\pm14$ pg/ml) and positive ($14\pm14$ pg/ml) sodium balances. Data for a representative patient with an atrial natriuretic factor concentration peak followed by natriuresis are shown in Figure 2. In this patient, atrial natriuretic factor values were elevated approximately twofold above baseline during the first 2 days after aneurysmal rupture but rose to approximately 300 pg/ml on the third day, followed by natriuresis. Vasopressin concentrations were normal. Patients without an atrial natriuretic factor concentration peak all had cumulative positive sodium balances for the 5 days of the study. Data for a representative patient are shown in Figure 3.

Three patients with an abrupt increase in atrial natriuretic factor concentration (patients 6, 8, and 9) became hyponatremic (range 128–134 mmol/l), all after a marked natriuresis (mean±SD sodium balance $-347\pm157$ mmol). No other patient had serum sodium concentrations of less than 135 mmol/l. Mean peak atrial natriuretic factor concentration in the three patients who developed hyponatremia was greater than in those with normal serum sodium values (mean±SD 477±86 versus 210±185.5 pg/ml). Vasopressin concentrations were low or normal in all patients at the time of hyponatremia.

Three patients (patients 2, 6, and 9), two of whom had transient hyponatremia, developed delayed cerebral ischemia. All three had a marked increase in the atrial natriuretic factor concentration followed by natriuresis and a negative sodium balance preceding the cerebral infarction. CT scans demonstrated large

**Figure 1.** Atrial natriuretic factor (ANF) (left panel) and vasopressin (AVP) (right panel) serum concentrations on admission (ADM) and at peak ANF values (PV). Solid lines represent negative sodium balance on day of peak ANF value, interrupted lines represent positive sodium balance. Shaded areas represent 95% confidence intervals for control values. Top: Eight patients with ANF concentration peaks. Bottom: Six patients without marked ANF concentration elevations.
TABLE 1. Plasma ANF and AVP Concentrations in 14 Consecutive Patients With Subarachnoid Hemorrhage

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<th>Admission AVP (pg/ml)</th>
<th>Day of highest ANF value ANF (pg/ml)</th>
<th>Day of highest AVP (pg/ml)</th>
<th>Day of highest ANF value AVP (pg/ml)</th>
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ANF, atrial natriuretic factor; AVP, vasopressin.
*Highest ANF and AVP value on admission; subsequent plasma concentrations were lower.

infarcts in several watershed areas. Cerebral infarction resulted in brain death in two patients and severe disability in one. Data for a representative patient with natriuresis, a negative sodium balance, and infarction are shown in Figure 4. Clinical and CT features of the hemorrhage were similar in patients with and without atrial natriuretic factor concentration peaks (Table 2). No patient who developed cerebral infarction had thick clots in the subarachnoid cisterns (Table 2).

Figure 2. Data for patient 3 show twofold increases in plasma atrial natriuretic factor concentrations (ANF) (244 pg/ml) with normal or low plasma vasopressin concentrations (AVP) associated with net sodium loss (−162 mmol) 24 hours after ANF peak. Fluid balance was negative on that day (−1.1 L). N, negative; P, positive.

Figure 3. Data for representative patient (patient 4) with elevated plasma atrial natriuretic factor concentrations (ANF) compared with controls in intensive care unit and plasma vasopressin concentrations (AVP) close to normal. No ANF peaks were measured during 5 days of study. Cumulative sodium balance remained positive for 5 days of study. P, positive.
Over baseline concentration.

Delayed infarction

Acute hydrocephalus

Intraventricular hemorrhage

Much* subarachnoid blood

Factor Concentration Peaks

With Aneurysmal Rupture  With  and  Without Atrial Natriuretic

TABLE

Hunt and Hess grade

Loss of consciousness at ictus

1 or 2

3 or 4

Much* subarachnoid blood

on admission CT

Intraventricular hemorrhage

Acute hydrocephalus

Delayed infarction

Peak

Present (n=8)  Absent (n=6)

4  5

7  4

1  2

2  5

3  3

1  5

3  0

CT, computed tomogram; peak, >300 pg/ml or twofold increase over baseline concentration.

*At least five basal cisterns completely filled with clot.

Discussion

Patients with aneurysmal subarachnoid hemorrhage frequently have intravascular volume depletion due to natriuresis. Atrial natriuretic factor has been suggested as the cause of this cerebral salt wasting although no evidence linking this peptide to volume depletion has yet been found.7 We first confirmed previous findings that the atrial natriuretic factor concentration was greatly increased during the first few hours after aneurysmal rupture, but we also found a second abrupt increase in the atrial natriuretic factor serum concentration, greater than the

initial elevations, in eight of 14 patients. Moreover, these later elevations were often followed by natriuresis and a net sodium loss. The atrial natriuretic factor concentration elevation generally lasted less than 12 hours, the intersample interval in the study, suggesting that our intermittent sampling probably did not measure the highest atrial natriuretic factor concentrations. (Studies of fluid balance in subarachnoid hemorrhage that sample atrial natriuretic factor and vasopressin concentrations even less frequently than we did risk missing elevations in serum concentrations.) Atrial natriuretic factor concentration peaks may therefore explain previous observations of intravascular volume depletion, natriuresis, and decreased vasopressin concentrations in some patients during the first week after subarachnoid hemorrhage. This evidence is circumstantial, however, because we did not measure simultaneous plasma volumes.

There was no diuresis with the immediate posthemorrhage atrial natriuretic factor concentration elevation, perhaps because the vasopressin concentration was also elevated or remained normal in some patients. In contrast, the delayed atrial natriuretic factor concentration peak was accompanied by depressed levels of vasopressin, allowing varying degrees of water loss. The initial rise of the vasopressin concentration may have resulted from the stress of the hemorrhage, and the subsequent sharp decline, from direct inhibition of vasopressin by atrial natriuretic factor. An inhibitory effect of atrial natriuretic factor on vasopressin, demonstrated in atrial natriuretic factor infusion studies,12-14 might be anticipated from a natriuretic factor.

The most salient finding of our study was that all three patients with cerebral infarction had had an atrial natriuretic factor–associated natriuresis on the previous day. The amount of blood in the cerebral cisterns was similar in patients with and without infarcts and therefore did not alone explain the strokes due to vasospasm. Our findings raise the possibility that natriuresis caused volume reduction and decreased cerebral perfusion in regions with vasospasm. Blocking atrial natriuretic factor may, therefore, be an alternative therapy to volume loading in preventing infarction from vasospasm. Winquist and others15 have suggested that atrial natriuretic factor concentration elevation is a protective response after subarachnoid hemorrhage because it may dilate large vessels and reduce vasospasm. Two recent animal experiments, however, failed to demonstrate a direct effect of atrial natriuretic factor on cerebral vessels.16,17

This study supplements recent reports with single atrial natriuretic factor samples7-6 in which the atrial natriuretic factor concentration was also initially elevated in all patients after hemorrhage. These studies focused on the similarity of atrial natriuretic factor concentrations in hyponatremic and eu-
FIGURE 1. Plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in control subjects and in patients with brain hemorrhage or brain infarction. Blood samples were withdrawn within 72 hours after onset. Bars indicate mean±SEM.

of Kitasato University Hospital within 72 hours after onset. Fifty patients (mean age 59 years) were found to have brain hemorrhage, and the remaining 57 patients (mean age 64 years) had brain infarction. Patients who were in a state of peripheral circulatory collapse and had already received drugs that might affect monoamine metabolism were excluded from the study. Computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed in all patients. In the patients with brain hemorrhage, localization of the hematomas classified from the CT findings was putaminal in 20, thalamic in 15, cerebellar in six, pontine in five, and lobar in four. Location of the brain infarcts was supratentorial in 44 and infratentorial in 13 patients. State of consciousness on admission was categorized as alert, obtunded/stuporous, or comatose.12 Fifteen patients with brain hemorrhage and eight patients with brain infarction died within 2 weeks after onset.

The concentration of MHPG in the CSF was measured in an additional 37 patients with acute brain infarction (mean age 65 years). In all of these patients, the infarcts were located supratentorially in 44 and infratentorial in 13 patients. State of consciousness on admission was categorized as alert, obtunded/stuporous, or comatose.12 Fifteen patients with brain hemorrhage and eight patients with brain infarction died within 2 weeks after onset.

Prior to the sampling of blood or CSF, the patients were maintained in a supine position for at least 30 minutes. Informed consent was obtained from all patients before the sampling of blood and CSF. Blood samples for the measurement of plasma levels of MHPG were withdrawn from an indwelling catheter within a cubital vein. The CSF samples were obtained by lumbar puncture in the lateral recumbent position between 10 AM and noon. The initial 5 ml of CSF was used for routine examination, and an additional 3 ml was stored for determination of the MHPG level. Blood was sampled simultaneously with removal of CSF. The first CSF samples were withdrawn during the acute stage (within 7 days after onset). In patients who were hospitalized beyond 2 weeks, subacute CSF samples were taken 15–30 days after stroke onset. In all patients with brain infarction, the CSF was clear and colorless.

Control blood samples for the measurement of plasma levels of MHPG were obtained from 32 healthy subjects (mean age 50 years). Control CSF samples were taken from eight patients (mean age 42 years) who were neurologically normal but had indications for lumbar puncture. Blood or CSF for the control measurements was sampled after the subjects had been supine for a length of time equal to that of the patients. In the control patients, CT and MRI examinations revealed no organic lesions of the brain or spinal cord.

Blood samples were collected into tubes containing 100 mmol ethylenediaminetetraacetic acid, disodium salt (EDTA-2Na) and cooled in ice until centrifugation at 4°C. Plasma and CSF samples were stored at ~40°C until assayed. Free MHPG was measured using high-performance liquid chromatography (HPLC) with electrochemical detection.13 One milliliter of plasma or CSF was mixed with 150 μl of 100 mmol EDTA-2Na and 200 μl of 1,000 mmol sodium acetate buffer (pH 6.0). The samples were transferred to columns containing Bond Elut PH (Analytchem International, Harbor City, Calif.) and the columns were washed with distilled water. Then, 1.5 ml reaction mixture consisting of acetonitrile and 2 mmol KH₂PO₄ was added. The eluate was evaporated at 35°C employing a rotary evaporator. The residue was added to 500 ml of 100 mmol HCl, and MHPG was extracted with 3 ml ethyl acetate by mixing. The ethyl acetate phase was evaporated, and the residue was dissolved in 60 μl of the mobile phase. A 30-μl aliquot of the sample was injected into the HPLC system (model 860-CO, Nihonbunko Co., Tokyo, Japan). Free MHPG was determined using an electrochemical detector (model 840-EC, Nihonbunko Co.).

Statistical analysis was performed using Student's t test and linear regression; p<0.05 was regarded as significant. Data are presented as mean±SEM.
Results

The plasma level of MHPG in the 32 control subjects was 4.6±0.3 ng/ml. The value of MHPG in plasma obtained from the patients with brain hemorrhage (7.3±0.5 ng/ml) was significantly greater than that in plasma obtained from the patients with brain infarction (6.6±0.5 ng/ml, p<0.01) as well as from the control subjects (p<0.01) (Figure 1). The plasma level of MHPG in the patients with brain infarction was also significantly greater than that in the control subjects (p<0.01). Within the brain infarction group, the plasma level of MHPG in patients with cardiogenic embolism (8.7±1.0 ng/ml, n=22) was significantly greater than that in patients with nonembolic infarction (5.7±0.5 ng/ml, n=35; p<0.01). Three patients with cardiogenic embolism had severe heart failure. The level of plasma MHPG in these three patients was 8.5±2.0 ng/ml.

Levels of plasma MHPG for patients who were alert, obtunded/stuporous, or comatose were 5.0±0.4 ng/ml (n=28), 6.1±0.4 ng/ml (n=57), and 11.9±1.2 ng/ml (n=22), respectively (Figure 2). The level in comatose patients was significantly greater than that for any other group of patients. Figure 2 also illustrates the association between clinical diagnosis and plasma levels of MHPG obtained within 72 hours after the onset of stroke. The level of plasma MHPG in samples collected from the 23 patients who subsequently died ranged from 4.3 to 21.6 ng/ml, and the mean±SEM value (11.7±0.8 ng/ml) was significantly greater than that for the 84 patients who survived (5.7±0.3 ng/ml, p<0.01).

The CSF levels for MHPG in patients with brain infarction and in control patients are compared in Figure 3. The mean±SEM MHPG value for CSF obtained during the acute stage from the patients with brain infarction (10.9±0.6 mg/ml) was significantly greater than that for CSF from the eight control patients (7.9±0.6 mg/ml, p<0.01).

Table 1 shows CSF MHPG levels in the 26 patients with brain infarction who were still hospitalized 2 weeks after the stroke. Samples were obtained twice from the same patients. Mean values for CSF MHPG decreased significantly over time (p<0.01). When these results were corrected for the plasma contribu-

| Table 1. CSF Levels of MHPG in Patients With Brain Infarction |
|-----------------|-----------------|-----------------|
| Level           | Patients with brain infarction (n=26) | Controls (n=8) |
| CSF MHPG        | 11.5±0.7*       | 7.9±0.6         |
| Corrected CSF MHPG | 6.9±0.6*       | 4.9±0.6         |
| Plasma MHPG     | 5.1±0.5         | 3.3±0.2         |

CSF, cerebrospinal fluid; MHPG, 3-methoxy-4-hydroxyphenylglycol; acute stage (within 7 days after onset; subacute stage at 15-30 days. Corrected CSF MHPG includes correction for contributions of plasma MHPG as proposed by Kopin.11 Data are mean±SEM ng/ml. *p<0.01 different from subacute stage by paired t test. † † p<0.01, 0.05, respectively, different from acute stage.
FIGURE 3. Cerebrospinal fluid (CSF) levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in 37 patients with brain infarction and eight control patients. CSF samples were collected within 7 days after onset. Bars indicate mean±SEM.

Assuming that the corrected CSF MHPG level obtained during the acute stage was still significantly greater than that obtained during the subacute stage, patients with brain infarction were divided into two groups according to the location of the infarct, designated as cortical infarcts or deep subcortical infarcts. Cortical infarcts consisted of medium-sized lesions (>2 cm in diameter) involving the cerebral cortex, while deep infarcts comprised small lesions (<2 cm in diameter) in deep areas of the brain supplied by penetrating arteries. During the acute stage, the CSF MHPG level in patients with cortical infarcts (12.0±0.6 ng/ml, n=25) was significantly greater than that in patients with deep infarcts (8.5±0.8 ng/ml, n=12; p<0.05). There was a significant difference in the corrected CSF MHPG level between the groups (7.1±0.5 and 5.2±0.3 ng/ml, respectively; p<0.05). With regard to state of consciousness, the value for CSF MHPG of the eight patients who were obtunded (14.6±1.1 ng/ml) was significantly greater than that of the 29 alert patients (9.8±0.5 ng/ml, p<0.01).

The CSF MHPG levels were consistently greater than the plasma MHPG levels. A significant correlation was noted between the plasma and CSF levels of MHPG collected during the acute stage (r=0.67, p<0.01). A significant correlation was also noted among samples obtained later from 26 patients during the subacute stage (r=0.63, p<0.01) (Figure 4).

Discussion

We found that the concentration of MHPG in the CSF as well as that in the plasma was significantly elevated during the acute stage of stroke. Assuming that plasma and CSF levels of MHPG do, in fact, reflect the activity of central noradrenergic neurons, our results imply that the stroke enhanced the activity of noradrenergic neurons in the brain. Previous work on cerebral infarction by Meyer et al14 demonstrated that CSF levels of norepinephrine were elevated during the acute stage.

Since the CSF level of MHPG may be influenced by plasma MHPG converted from plasma norepinephrine,11 Kopin et al11,15 proposed a correction for the plasma contribution to the CSF level to more...
precisely determine the amount of CSF MHPG that is derived from the central noradrenergic system. When our CSF data were corrected using that formula, corrected CSF MHPG levels for samples obtained during the acute stage of cerebral infarction were still significantly greater than those for samples obtained during the subacute stage (Table 1). These observations suggest that central noradrenergic neurons may be activated during the acute stage of stroke, and the amount of released norepinephrine in the brain increases. In addition, an increase in the CSF levels of MHPG was noted in obtunded patients as opposed to alert patients, while differences in the plasma levels were not significant. These findings might also represent evidence of a brain source for MHPG in the CSF. Although the exact mechanism responsible for the increase in plasma and CSF levels of MHPG following stroke is not entirely clear, the stress of a stroke may activate the central noradrenergic system as well as the peripheral sympathetic nervous system.

While further studies are needed to elucidate the precise role of the released norepinephrine in the pathophysiology of acute stroke, our results indicate that significant correlations exist between the plasma and CSF levels of MHPG and the clinical state of the patient. These observations also suggest that measurements of plasma and CSF levels of MHPG may to some extent provide useful information concerning the clinical status and prognosis of stroke patients, although in some patients control levels of plasma MHPG may be associated with a poor outcome.

References


Key Words • glycols • norepinephrine • cerebrovascular disorders
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Stroke. 1991;22:1519-1524
doi: 10.1161/01.STR.22.12.1519
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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