Concentration of 3',5' cyclic adenosine monophosphate in ventricular CSF of patients following severe head trauma

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Previous studies have demonstrated that cerebrospinal fluid (CSF) from the lateral ventricle of patients without disturbance of sensorium or intracranial pressure, contains 15 to 30 nM 3',5' cyclic adenosine monophosphate (cAMP). The concentration of this cyclic nucleotide was measured by radioimmunoassay in 133 samples of CSF from the lateral ventricle of 26 patients who were comatose following acute head trauma for periods up to 40 days. Concentration of CSF cAMP in diminishing coma Grades V, IV, III, II, and I was 1.5 ± 0.1 nM; 1.24 ± 0.34 nM; 3.14 ± 0.7 nM; 10.06 ± 3.47 nM; and 13.36 ± 1.38 nM, respectively. After the sensorium cleared (coma Grade 0), cAMP was 22.0 ± 1.7 nM. The correlation between the grade of coma and cAMP concentration was -0.80 (p < 0.01). These results imply that alteration in the level of consciousness following head trauma is associated with a disturbance of cAMP metabolism within the central nervous system. Possible mechanisms explaining this observation as well as therapeutic implications are discussed.

KEY WORDS • head trauma • ventricular cerebrospinal fluid • cyclic AMP level • degree of coma

Cyclic adenosine 3',5' monophosphate (cAMP) is widespread in mammalian tissues along with the enzymes adenylate cyclase and phosphodiesterase, which control cAMP synthesis and degradation, respectively.1,24 Particularly high concentrations are observed in brain and cerebrospinal fluid (CSF).3,10,14,17 Adenylate cyclase is under hormonal control and is stimulated by catecholamines, histamine, serotonin, and melanotrophic peptides.2,7,15,20 The final role of cAMP in brain and other nervous tissue is not clear but increasing evidence suggests that cAMP is involved in the regulation of metabolism and function in these tissues.9 The involvement of cAMP in synaptic transmission has been confirmed by several investigators.15,26

Evidence suggests that measuring CSF cAMP concentration is more useful in studying alterations of brain cAMP than assaying the cAMP values of plasma or urine.11,12,97 A recent study in this laboratory21 showed that normal lumbar CSF contains 15 to 30 nM cAMP. Also ventricular CSF from patients with normal intracranial pressure and normal sensorium contained the same concentration of cAMP as normal lumbar CSF. In a preliminary report,18 we demonstrated a significant correlation between the level of consciousness and ventricular CSF cAMP levels in patients comatose following head trauma.
or intracranial hemorrhage. Return to normal sensorium was associated with cAMP levels returning toward normal values, whereas those patients who remained comatose had persistent, markedly diminished ventricular CSF cAMP levels. This study emphasized that prolonged coma is associated with a disturbance of cAMP metabolism within the central nervous system.

In the present study the relationship of CSF cAMP levels to the level of consciousness was further investigated in a larger, more homogeneous group of adult patients rendered comatose following severe craniocerebral trauma.

**Clinical Material and Methods**

Twenty-six patients, 16 to 49 years of age, were studied. All were admitted to the Neurosurgery Service of Grady Memorial Hospital between October, 1975, and September, 1976, in a comatose state after severe craniocerebral trauma. Twenty of these patients had blunt, closed head trauma and six patients had penetrating missile injuries. Level of consciousness was graded as follows:

Grade 0: normal
Grade I: drowsy, lethargic, indifferent and uninterested, or belligerent and uncooperative; does not lapse into sleep when left undisturbed
Grade II: stuporous; will lapse into sleep when not disturbed; may be disoriented to time, place, and person
Grade III: deep stupor; requires strong pain to evoke movement; may have focal neurological signs, but will respond appropriately to noxious stimuli
Grade IV: does not respond appropriately to any stimuli; may exhibit decerebrate or decorticate posturing; retains deep tendon reflexes; may have dilated pupils, absent corneal or oculocephalic reflexes
Grade V: does not respond appropriately to any stimuli; flaccid; no deep tendon reflexes; usually apneic.

All patients were studied with immediate cerebral angiography or computerized tomography (CT) scan. Sixteen patients required emergency craniotomy for evacuation of intracranial hematomas, contusions, or debridement of missile wounds. All 26 patients within 12 hours of admission had a ventricular catheter inserted into a lateral ventricle and connected to a closed Rickham reservoir* seated in the burr hole and buried subcutaneously. After wound closure, a No. 23 needle with a soft catheter† attached was inserted into the Rickham reservoir and connected to a Statham pressure transducer‡ for continuous recording of intracranial pressure (ICP) (Fig. 1). During the next 2 to 40 days, depending on the outcome in the individual patient, 1-ml to 2-ml samples of CSF were collected at intervals of 6 to 72 hours by percutaneous puncture of the subcutaneous reservoir. Grade of coma was recorded at the time of each sampling. Venous blood was obtained simultaneously with CSF in about one-third of the samples for measurement of plasma cAMP levels.

Each sample of CSF and blood was centrifuged immediately after collection and then stored at −20° C. Within 1 week the samples were analyzed for cAMP by radioimmunoassay. Experimental details of these analyses, and the verification of their specificities, have been described in previous reports. Cerebrospinal fluid was also analyzed for cyclic nucleotide phosphodiesterase activity.

For control purposes, cAMP was measured in plasma and in lumbar CSF of 14 patients aged 36 to 62 years old, with no neurological disease, who were undergoing spinal anesthesia. Ventricular fluid from patients without head trauma was not analyzed in this study, but in a previous investigation it was found that in ventricular fluid from adult patients with normal intracranial pressure and mentation, cAMP concentration averaged 22 nM. This did not differ significantly (p < 0.05 by Student’s t-test) from that in lumbar CSF from patients without neurological disease.

**Summary of Cases**

**Control Subjects**

In the 14 adults without neurological disease, plasma cAMP (mean ± SD) was

*Rickham reservoir manufactured by Cordis Corp., Miami, Florida.
†Abbott butterfly catheter made by Abbott Hospital Supplies, Chicago, Illinois.
‡Statham pressure transducer manufactured by Statham Manufacturing Company, San Juan, Puerto Rico.
13.8 ± 2.4 nM, and lumbar CSF cAMP was 23 ± 4 nM.

Head-Trauma Patients

The concentration of ventricular CSF cAMP was determined in 133 samples from 26 patients admitted to the hospital in a comatose state following head trauma. Sixteen patients recovered, four remained in a vegetative state for a prolonged period of time, and six patients died. When the data from all 26 patients were pooled (Fig. 2), the following values for CSF cAMP concentration (mean ± SEM) corresponding to each degree of coma were obtained: Grade V, 1.5 ± 0.1 nM; Grade IV, 1.24 ± 0.34 nM; Grade III, 3.14 ± 0.75 nM; Grade II, 10.06 ± 3.47 nM; Grade I, 13.36 ± 1.38 nM. After the sensorium became normal (Grade 0), cAMP was 22.0 ± 1.7 nM. The correlation between the grade of coma and cAMP concentration was −0.80 (p < 0.01).

For each patient, a change in degree of coma was usually associated with a similar change in cAMP level. In Grade IV coma, cAMP was always less than 6 nM. A rise from < 6 nM into the range of 6 to 12 nM in a patient with Grade IV coma was associated with a simultaneous or subsequent improvement of coma to Grade III or II. Yet, when cAMP remained < 6 nM, coma persisted at the Grade IV level and was associated with either persistent vegetative survival or death. When cAMP in Grade III or II patients increased above 10 nM, this rise was accompanied or followed within 4 days by improvement in level of consciousness to Grade I or 0. Whenever cAMP rose above 15 nM, the patient made a full recovery.

Eight plasma samples were analyzed in various patients during periods of Grade IV coma when ventricular CSF cAMP was < 6 nM, and all were within the normal range of 9 to 19 nM. Six ventricular CSF samples in patients manifesting Grade IV

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Fig. 2. The CSF cAMP levels in nM obtained in 133 samples in 26 head-trauma patients in relation to coma grade.

Fig. 3. Clinical course in Case 1, showing relationship of ventricular CSF cAMP level to coma grade and time.

Coma containing < 6 nM cAMP were analyzed for phosphodiesterase activity, which was undetectable.

Representative Cases

Case 1

This 26-year-old woman sustained multiple facial fractures in an automobile accident and was admitted in Grade IV coma (Fig. 3). Cerebral angiography was normal. A Rickham reservoir was inserted under local anesthesia in the right lateral ventricle. Continuous monitoring of ICP over a 1-week period did not reveal any pressure elevation, thus suggesting a clinical diagnosis of brain-stem contusion. After a few days of transient improvement following a tracheostomy, she regressed to Grade IV coma and remained in a persistent vegetative state for several weeks after the last CSF cAMP sample, which was obtained on the 20th hospital day, before dying of pulmonary complications. Her CSF cAMP levels remained consistently below 6 nM throughout the sampling period.

Case 2

This 49-year-old woman suffered head trauma in an automobile accident and was admitted in Grade III coma (Fig. 4). Cerebral angiography disclosed an avascular left temporal mass lesion with a 3-mm shift of the midline structures. A Rickham reservoir was placed in the right lateral ventricle shortly after admission and a CSF specimen obtained immediately disclosed a normal cAMP level, which fell precipitously shortly thereafter. The ICP was initially elevated in the 20 to 25 mm Hg range and responded to intermittent mannitol infusion returning to normal. The patient deteriorated on the third hospital day to Grade IV coma, associated with increasing ICP elevations. Repeat angiography disclosed an increase in the left temporal mass effect and a temporal lobectomy was performed with some transient improvement to Grade III level postoperatively. Despite con-
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trol of ICP with therapy including steroids, hyperventilation, and mannitol, the patient deteriorated to Grade IV and V coma and remained in a vegetative state throughout 60 days of hospitalization. After the initial normal cAMP level was obtained, CSF cAMP never exceeded 2 nM.

Case 3

This 24-year-old man was admitted in Grade IV coma following a wound from a large caliber gun to the right frontal-temporal region (Fig. 5). Immediate cerebral angiography disclosed a right acute subdural hematoma of moderate size and evidence of an avascular intracerebral mass. The subdural and intracerebral hematomas were immediately evacuated and a catheter placed in the left lateral ventricle and connected to a Rickham reservoir. Transient, minimal neurological improvement ensued, however the patient died on the 10th hospital day after remaining in Grade IV coma. Pre-plateau and plateau waves were treated as they developed with intermittent mannitol infusion, hyperventilation, steroids, and CSF aspiration. The ventricular CSF cAMP never exceeded 3 nM.

Case 4

This 49-year-old alcoholic man was found unresponsive in jail with evidence of facial contusions. On admission to Grady Memorial Hospital, the patient was in Grade III coma with an associated left hemiparesis (Fig. 6). Cerebral angiography revealed a right acute subdural hematoma and an avascular right temporal lobe mass. At surgery the subdural hematoma was evacuated and a sub-total temporal lobectomy performed for hemorrhagic contusion. A Rickham reservoir

Fig. 4. Clinical course in Case 2, showing relationship of ventricular CSF cAMP level to coma grade and time.

Fig. 5. Clinical course in Case 3, showing relationship of ventricular CSF cAMP level to coma grade and time.

Fig. 6. Clinical course in Case 4, showing relationship of ventricular CSF cAMP level to coma grade and time.
was inserted in the left lateral ventricle. Postoperatively he remained stable for the first 3 days with transient ICP elevations requiring medical therapy. By the fifth postoperative day he had improved to Grade II coma, and by the 20th hospital day was fully recovered. Changes in ventricular CSF cAMP paralleled his clinical course.

Case 5

This 41-year-old man had a generalized seizure after a blow to the head and was admitted to Grady Memorial Hospital in Grade IV coma (Fig. 7). Cerebral angiography revealed a small right subdural hematoma and an avascular left intratemporal mass without an associated shift of the midline structures. A Rickham reservoir was inserted into the right lateral ventricle under local anesthesia to monitor ICP, which was normal initially. On the third day, ICP rose to 35 mm Hg in a sustained manner refractory to standard medical therapy. He remained unchanged clinically, however, with CSF cAMP levels below 4 nM. On the fourth day, bilateral subtemporal craniectomies were performed with evacuation of a right subacute subdural hematoma and a subtotal left temporal lobectomy for contusion. The patient's level of consciousness improved progressively from the fifth day, and his sensorium was normal 20 days after admission. The CSF cAMP levels returned to normal.

Case 6

This 46-year-old man sustained blunt head trauma and was admitted to the hospital in Grade IV coma with a fixed, dilated right pupil and left-sided decerebration (Fig. 8). Cerebral angiography disclosed an acute right subdural hematoma, which was immediately evacuated. A Rickham reservoir was inserted into his left lateral ventricle. Postoperatively he was initially unchanged and ICP elevations to 60 mm Hg were successfully treated with standard medical measures. By the seventh day his level of consciousness improved to Grade III with an associated elevation of CSF cAMP from 3 nM to 12 nM. He continued to improve slowly, and at the time of the last cAMP sample, 27 days after admission, he was in Grade I stupor with a CSF cAMP of 15 nM. Over the ensuing 40 days of hospitalization, he made a full recovery.

Discussion

The mechanism of prolonged coma following head trauma is not understood and the pathophysiological and biochemical changes responsible remain the object of intense investigation. The use of an implanted intraventricular catheter attached to a subcutaneous reservoir, as described in this report, not only permits continuous monitoring of ICP, but also ready access to ventricular CSF for biochemical analyses in both the acute and chronic phases following head injury when lumbar puncture might be contraindicated.

Previous reports have demonstrated changes in cyclic nucleotide levels in brain tissue and CSF in various neurological disorders. One minute after stab trauma to the
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cerebrum of the mouse, brain cAMP concentration rose to seven times normal. In 15 patients, 1 to 15 days after cerebral thrombosis without altered level of consciousness, cAMP concentration in lumbar CSF was significantly elevated. In addition, lumbar CSF cAMP remains significantly elevated for 3 days in awake epileptic patients following seizures. Rudman, et al., first attempted to relate CSF cAMP levels to sensorium, and demonstrated subnormal concentrations in children with diffuse brain disease causing severe psychomotor retardation. This same study demonstrated a direct correlation between ICP and CSF cyclic guanosine monophosphate (cGMP). A preliminary report from our laboratory revealed markedly reduced ventricular CSF cAMP levels in six patients who were comatose following either head trauma or spontaneous intracranial hemorrhage; in those cases cAMP returned to normal levels with improvement in sensorium.

The present study expands upon the correlation of ventricular CSF cAMP and level of consciousness in a larger, homogeneous group of patients rendered comatose as a result of severe acute head trauma. These previous reports and our own observations suggest that the subnormal level of cAMP in the ventricular fluid of the present series of 26 patients does not represent a nonspecific effect of brain damage, but may reflect instead a depletion of brain cAMP that is uniquely associated with severe and prolonged coma after trauma or intracranial hemorrhage.

The plasma cAMP level of these comatose patients was normal. Therefore, their subnormal level of CSF cAMP was probably not caused by diminished transport of cAMP into CSF from plasma, but presumably resulted instead from a disorder of cAMP metabolism within the central nervous system. One possible cause of disorder might be decreased production of cAMP by brain adenylate cyclase, which could result from damage to the cyclase enzyme, from inadequate delivery of cyclase-activating hormones (catecholamines, histamine, serotonin, or melanotropic peptides), from deficiency of the enzyme's substrate adenosine triphosphate (ATP), or from deficiency of the endogenous cyclase-activating metabolic intermediate adenosine, which is derived from ATP.

Another possible explanation is accelerated transport of cAMP out of CSF by the probenecid-sensitive active transport system. The possibility of increased degradation of cAMP in CSF is unlikely because of the absence of the enzyme phosphodiesterase in the samples tested.

Therapeutic implications of these findings may be important. If the diminished CSF cAMP levels in comatose patients following head trauma do not represent an epiphenomenon, then it is possible that the low levels may be the cause of the diminished consciousness. There are several methods of increasing CSF cAMP that may be of potential therapeutic value. Probenecid has been demonstrated in the experimental animal and in man to increase the CSF content of cAMP. In addition, any of the many adenylate cyclase stimulating agents or phosphodiesterase inhibitors may conceivably accomplish the same result. A synthetic cAMP, dibutyryl cAMP, may be instilled directly into the CSF. Some of these studies are currently in progress in animal models in our laboratory.

Whether or not of therapeutic significance, the correlation of CSF cAMP level with degree of coma may serve as an excellent prognosticating factor in severe head trauma. No patient in this series recovered whose CSF cAMP level remained below 6 nM for longer than 10 days, whereas all patients whose CSF cAMP level exceeded 15 nM recovered.

References

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Cyclic nucleotide activities: Cyclic adenosine 3',5'-monophosphate (cAMP) is a cyclic nucleotide that plays a role in processes such as cellular signaling, gene expression, and intracellular messenger systems.


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