Short report

Spinal trauma: pharmacological evidence for vasoconstrictor activity in cerebrospinal fluid

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Summary  Cerebrospinal fluid from six cases of acute spinal trauma collected 0–6 days after injury was examined for vasoconstrictor activity using both human isolated cerebral arteries and animal tissues. The cerebrospinal fluid of four out of six patients was vasoactive. The identities of the vasoconstrictor substances were not established, but experiments with pharmacological antagonists showed that arterial contractions were not due to serotonin, histamine, noradrenaline, acetylcholine or angiotensin II, substances which are known potent spastic agents on cerebral arteries. Our findings would explain by the mechanism of arterial spasm, principally in the anterior spinal artery, the neuropathological appearance of central haemorrhagic necrosis in spinal cord injury. The infarction of the core of the spinal cord could be caused by vasoconstrictor substances, reported here, in the cerebrospinal fluid after spinal injury. If the identities of the substances could be established, drug therapy to prevent or relieve the spasm would be possible.

The neuropathology of the acute spinal cord traumatic lesion is that of a progressive central haemorrhagic necrosis and this directs attention to the involvement of the main spinal cord arteries in the production of the lesion. There is histological evidence of distinctive changes in spinal cord arteries after trauma, and these are similar to those described in cerebral arteries after head injury and subarachnoid haemorrhage. These post mortem histological changes in subarachnoid haemorrhage were seen in arteries which had been shown angiographically to have been in spasm during life. In cases of subarachnoid haemorrhage (SAH), not only have histological changes been found in arteries at necropsy, but during life, vasoactive substances have been demonstrated in the cerebrospinal fluid (CSF). Accordingly, we have examined CSF for vasoconstrictor substances in cases of spinal trauma taken 0–6 days after injury.

Materials and methods

Isolated tissues
Human basilar and vertebral arteries and rat stomach fundus strips were mounted in 5 ml organ baths as previously described. Freshly thawed CSF was added to the bath at concentrations ranging from 10 to 100 μl/ml. Contractile responses were measured for up to two hours using isotonic recording. The effect of various pharmacological antagonists on fully developed contractions was investigated. Because the identities of the vasoconstrictor factors are not yet established (see Results), responses were expressed in terms of prostaglandin E2 (PGE2).

Patients
The patients, four males and two females, with ages ranging from 18 to 31 years, all with spinal fracture dislocations causing paraparesis or paraplegia, were admitted to the Spinal Injuries Unit of the Royal North Shore Hospital, Sydney Australia. CSF samples were collected at various times by lumbar puncture from below the site of injury, frozen immediately at −70°C, and subsequently flown to England for pharmacological investigation.
Results

Using human basilar and vertebral arteries, vasoconstrictor activity was detected in CSF from four out of six patients (table 1). In some instances (cases 1, 2, and 3), activity was substantially greater than the mean value obtained from the examination of 29 samples from eight cases of subarachnoid haemorrhage (table 1). Attempted identification of the substances responsible for the contractions was carried out using specific pharmacological antagonists. All these substances were ineffective in reversing fully developed contractions (figure and table 2).

Table 1  Vasoconstrictor activity in spinal trauma CSF

<table>
<thead>
<tr>
<th>Case no</th>
<th>Vasopressor response (nmols/l PGE2) on day after injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>&gt;100†</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

SAH* 17.4 ± 5.0 nmols/l PGE2

Data were obtained by bioassay on human isolated basilar or vertebral arteries using PGE2 as a standard.4

*These values were obtained at the same time during bioassay of 29 samples of CSF collected from 8 SAH patients, some of whom had angiographically demonstrated cerebral vasospasm.
†The values were too great for accurate determination.

Table 2  Pharmacological antagonists which failed to reverse contractions produced by spinal trauma CSF

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Concentration (nmols/l)</th>
<th>Specific drug effect (agonist) blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>20 000</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>792</td>
<td>Histamine (H2 receptor)</td>
</tr>
<tr>
<td>Mepyramine</td>
<td>20 000</td>
<td>Histamine (H1 receptor)</td>
</tr>
<tr>
<td>Sarcosine-alanine</td>
<td>648</td>
<td>Angiotensin1</td>
</tr>
<tr>
<td>Angiotensin2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>20 000</td>
<td>Noradrenaline (α-actions)</td>
</tr>
<tr>
<td>Methysergide</td>
<td>2000</td>
<td>Serotonin (5-HT)</td>
</tr>
</tbody>
</table>

The above results were obtained using the rat stomach fundus preparation. All agonists (right column) are potent vasoconstrictor agents on this tissue.

Discussion

The magnitude of the neurological deficit caused by spinal trauma may have an important pharmacological factor. Experimentally induced spinal cord trauma has been associated with increased concentrations of various vasoconstrictor substances. These include dopamine,7–9 serotonin,10 histamine11 12 and noradrenaline13 (although the last mentioned has not been confirmed).7–8 14 Vasoconstriction of surface vessels has been seen under the operating microscope in animals following experimental spinal cord trauma.15 16 In similar experiments, changes occurred in spinal cord blood flow leading to ischaemia17; the appearance of haemorrhagic necrosis after such experimental
injuries is well documented. We present here pharmacological evidence in support of the view that spinal trauma is associated with spasm of the spinal cord arteries. Four out of six of our patients had vasoconstrictor substances in their CSF, able to produce slowly developing and sustained contractions of isolated human cerebral arteries. In our earlier, more extensive studies with CSF from SAH patients with angiographically proven arterial spasm, we also found vasoconstrictor substances which produced qualitatively similar pharmacological effects to those described here. Furthermore, specific neuropathological changes have been reported, postmortem, in arteries from SAH patients which were known to have been in spasm during life. As similar observations have been made in cases of spinal trauma, we may reasonably postulate that the infarction of the core of the spinal cord is caused by spasm of the spinal arteries.

If the vasoconstrictor substances in the CSF could be isolated and identified, then specific antagonists could be developed to prevent or reverse any spasm of the spinal cord arteries, alleviate the magnitude of the neurological deficit and prevent the vascular part of the histological changes associated with spinal trauma.

We are grateful to the staff of the Royal North Shore Hospital, New South Wales, Australia for the collection and preservation of the CSF specimens.

References