Short report

Spinal trauma: pharmacological evidence for vasoconstrictor activity in cerebrospinal fluid

D J BOULLIN, P TAGARI, J T HUGHES AND J D YEO

From the Departments of Clinical Pharmacology and Neuropathology, Radcliffe Infirmary, Oxford, and the Spinal Injuries Unit, Royal North Shore Hospital, New South Wales, Australia

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 necrosis¹ 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,² and these are similar to those described in cerebral arteries after head injury³ and subarachnoid haemorrhage.⁴ These post mortem histological changes in subarachnoid haemorrhage were seen in arteries which had been shown angiographically to have been in spasm during life.⁴ 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.^{5,6} Freshly thawed CSF was added to the bath at concentrations ranging from 10 to 100 μ l/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.

Address for reprint requests: Dr DJ Boullin, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE, England.

Accepted 8 June 1981

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

Case no	Vasoconstrictor response (nmols/l PGE ₂) on day after injury					
	0	1	2	3	4	5
1		4.7	>100†			19
2		>100†	0			0
3		0	>100†			
4			5.8			
5		0	0			0
6			0	1		1
SAH*		17.4 ± 5.0 nmols/l PGE ₂				

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

*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.

Figure Vasoconstrictor response of isolated rat stomach fundus preparation to CSF from a patient with spinal cord trauma. At the arrow 0.5 ml CSF was added to the 5 ml organ bath, a contraction developed, was maximal after about 10 min and was sustained for at least 30 min. During this time the following pharmacological antagonists were added to the organ bath and failed to reverse the contractile response: a, acetylcholine antagonist, atropine; b, cimetidine, histamine receptor² antagonist; c, histamine receptor antagonist, mepyramine; d, angiotensin_{II} antagonist, saralasin; e, noradrenaline α -receptor antagonist,¹ phenoxybenzamine; f, serotonin antagonist, methysergide.

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

Antagonist	Concentration (nmols/l)	Specific drug effect (agonist) blocked
Atropine	20 000	Acetylcholine
Cimetidine	792	Histamine (H ₂ receptor)
Mepyramine	20 000	Histamine (H ₁ receptor)
Sarcosine ¹ -alanine ² -angiotensin _{II}	648	Angiotensin _{II}
Phenoxybenzamine	20 000	Noradrenaline (α -actions)
Methysergide	2000	Serotonin (5-HT)

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 histamine^{11 12} and noradrenaline¹³ (although the last mentioned has not been confirmed).^{7 8 14} Vaso-spasm 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.^{15 16} 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.^{5 18 19} Furthermore, specific neuropathological changes have been reported, postmortem, in arteries from SAH patients which were known to have been in spasm during life.⁴ As similar observations have been made in cases of spinal trauma,² 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

- Hughes JT. *Pathology of the Spinal Cord*. London: Lloyd-Luke, 1978; 91–104.
- Hughes JT, Tagari PC, Boullin DJ. Spinal cord trauma: vasoconstrictor substances in cerebrospinal fluid, correlated with necropsy changes in spinal arteries. In: J Cervos-Navarro, ed. *Proceedings of the Erwin Riesch Symposium on Cerebral Microcirculation and Metabolism. Pathology, Pathophysiology and Clinical Aspects*. New York: Raven Press, 1981. In press.
- Hughes JT. Morphological changes in human cerebral arteries in relation to intracranial arterial spasm. In: Wilkins RH, ed. *Cerebral Arterial Spasm*. Baltimore: Williams and Wilkins, 1980.
- Hughes JT, Schianchi PM. Cerebral arterial spasm: a histological study at necropsy of blood vessels in cases of subarachnoid haemorrhage. *J Neurosurg* 1978; **48**:515–25.
- Boullin DJ, Mohan J, Grahame-Smith DG. Evidence for the presence of a vasoactive substance (possibly involved in the aetiology of cerebral arterial spasm) in cerebrospinal fluid from patients with subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 1976; **39**:756–66.
- Boullin DJ, Hunt TM, Rogers AT. Models for investigating the aetiology of cerebral arterial spasm: comparative responses of the human basilar artery with rat colon, anococcygeus, stomach fundus and aorta, and guinea-pig ileum and colon. *Br J Clin Pharmacol* 1978; **63**:251–7.
- Hedeman LS, Schellenberger MK, Gordon JH. Studies in experimental spinal cord trauma. Part 1: alteration in catecholamine levels. *J Neurosurg* 1974; **40**:37–43.
- Nafteki NE, Demeny M, De Chreschito V *et al*. Biogenic amine concentrations in traumatised spinal cords in cats: effects of drug therapy. *J Neurosurg* 1974; **40**:52–7.
- Bingham WG, Ruffolo R, Freidman SJ. Catecholamine levels in the injured spinal cord of monkeys. *J Neurosurg* 1978; **42**:174–8.
- Zivin JA, Doppman JL, Reid JL *et al*. *Neurology (Minneapolis)* 1976; **26**:99–107.
- Kobrine AI, Doyle TF. Role of histamine in post traumatic spinal cord hyperemia and the luxury perfusion syndrome. *J Neurosurg* 1976; **44**:16–20.
- Kobrine AI, Doyle TF. Histamine in spinal cord injury. In: Harper AM, Jennet WB, Miller JD *et al*, eds. *Blood Flow and Metabolism in the Brain*. Edinburgh: Churchill Livingstone, 1975.
- Osterholm JL, Mathews GJ. Altered norepinephrine metabolism following experimental spinal cord injury. *J Neurosurg* 1972; **36**:386–94.
- de la Torre JC, Johnson CM, Harris LH. Monoamine changes in experimental head and spinal cord trauma: failure to confirm previous observations. *Surg Neurol* 1974; **2**:5–11.
- Assenmacher DR, Ducker TB. Experimental traumatic paraplegia: the vascular and pathological changes seen in reversible spinal cord lesions. *J Bone Joint Surg* 1971; **53A**:671–80.
- Ducker TB, Assenmacher DR. Microvascular response to experimental spinal cord trauma. *Surg Forum* 1969; **20**:428–30.
- Cawthorn DF, Senter HJ, Stewart WB. Comparison of hydrogen clearance and ¹⁴C-antipyrine autoradiography in the measurement of spinal cord blood flow after severe impact injury. *J Neurosurg* 1980; **52**:801–7.
- Boullin DJ, Blaso WP. Pharmacological vasoactivity of cerebrospinal fluid correlates with cerebral arterial spasm and clinical deterioration after subarachnoid haemorrhage. *Fed Proc* 1978; **37**:821.
- Blaso WP, Boullin DJ. Vasoconstrictor activity of cerebrospinal fluid from patients with cerebral arterial spasm. *J Physiol (Lond)* 1978; **282**:39P–40P.