NOREPINEPHRINE, DOPAMINE AND SEROTONIN IN EXPERIMENTAL SPINAL CORD TRAUMA: CURRENT STATUS*

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Abstract. This is a review on norepinephrine, dopamine and serotonin with regard to their action following spinal cord injuries which reveals the controversies on this subject.

Key words: Norepinephrine; dopamine; serotonin.

Introduction

THE role of neurochemical factors in the pathophysiology of experimental spinal cord trauma has been widely studied, and recently considerable attention has been focused on the biogenic amines (Dohrmann, 1972; Osterholm, 1974). Much of the available data is inconsistent, with conflicting results being reported both in the basic pathophysiological studies as well as in the treatment studies.

The importance of a potentially reversible pathochemical substrate in spinal cord injury and its possible therapeutic implications are clear. The continued controversy concerning the role of the monoamines, norepinephrine, dopamine and serotonin, in spinal cord trauma has clouded the data and has rendered interpretation most difficult. In this paper, the function of monoamines in neural trauma is reviewed and the data discussed.

Norepinephrine

Osterholm and Mathews (1972) initially engendered much interest in the pathophysiology of spinal cord trauma by the demonstration of catecholamine alterations that may be responsible for destructive processes in traumatic paraplegia and also be amenable to therapeutic intervention. Using a 500 g-cm contusion, they found significant norepinephrine elevation in the injured cat spinal cord within the first 4 hours after trauma and correlated this with the presence of haemorrhagic necrosis of the central grey matter, the most prominent early pathological finding following spinal cord injury. Osterholm and Mathews (1972) proposed that toxic quantities of norepinephrine are released into the cord tissue after contusion resulting in vasoconstriction, ischemia and tissue necrosis with resultant vascular rupture and haemorrhage. The validity of this hypothesis was substantiated in part by the production of large central haemorrhages 2 hours after intraspinal norepinephrine injection (Osterholm and Mathews, 1972). In addition, the effects of several anti-norepinephrine agents on the contused feline spinal cord were studied, and all were found to have distinct protective action (Osterholm *et al.*, 1973). Every agent tested modified and minimised the tissue response to trauma, preventing post-traumatic haemorrhagic necrosis. From these findings, the authors postulated that trauma induces an excessive neuronal meta-

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bolic response, resulting in release of transmitter substances, particularly norepinephrine. These substances are thought to induce toxic vasospasm, hypoxia and subsequent necrosis of the tissue.

The pathogenic effect of norepinephrine on the traumatised spinal cord as described by Osterholm and Mathews (1972) has not been confirmed in the work of others. Several investigators (see Table I), have failed to find a significant elevation of norepinephrine in spinal cord tissue following trauma in cats, dogs or monkeys (Naftchi *et al.*, 1974; Hedeman *et al.*, 1974; Rawe *et al.*, 1974; de la Torre *et al.*, 1974; Bingham *et al.*, 1975; Tsubokawa *et al.*, 1975; Zivin *et al.*, 1976). De la Torre *et al.* (1974) did not observe an elevation in norepinephrine levels following a 500 g-cm spinal cord contusion. Alpha-methyl tyrosine (AMT), an inhibitor of catecholamine synthesis, did not appear to improve the rate of motor recovery or alter histopathological changes in cats when given 15 mins post-trauma (de la Torre *et al.*, 1974). Naftchi *et al.* (1974), Hedeman *et al.* (1974) and Tsubokawa *et al.* (1975) also failed to find any significant elevation in norepinephrine concentration following experimental spinal cord injury. Schoultz *et al.* (1976) found a norepinephrine elevation at the trauma site 1 hour after a 400 g-cm contusion of the feline spinal cord. No increase in norepinephrine concentration was noted, however, following experimental injury of adrenalectomised cats. The authors hypothesised that the origin of the elevated spinal cord norepinephrine seen 1 hour post-trauma was more related to a peripheral adrenal contribution and increased blood levels than to intrinsic cord sources. In a study of catecholamine levels in the spinal cords of monkeys following 300 g-cm trauma, Bingham *et al.* (1975) noted a progressive decrease in norepinephrine levels for 4 hours after trauma. Rawe *et al.* (1974) reported no increase in norepinephrine levels at the site of impact after a 500 g-cm contusion. Despite the efficacy of AMT to reduce norepinephrine to low levels, there was no significant difference in functional neurological recovery after trauma between AMT treated animals and controls (Rawe *et al.*, 1974). In addition, reserpine, a potent anti-norepinephrine agent, produced no significant post-traumatic improvement (Rawe *et al.*, 1974). Alpha-methyl tyrosine was found to increase the rate of motor recovery after experimental spinal cord injury in sheep by Yeo *et al.* (1975), although there was no significant

TABLE I

Concentration of catecholamines in the spinal cord after experimental spinal cord trauma*

Author and year	Animal	Region	Norepinephrine	Dopamine
Osterholm and Mathews (1972)	Cat	Thoracic	Increased	Decreased
de la Torre <i>et al.</i> (1974)	Dog, cat	Thoracic	Unchanged	Unchanged
Naftchi <i>et al.</i> (1974)	Cat	Thoracic	Unchanged	Increased
Hedeman <i>et al.</i> (1974)	Dog, cat	Thoracic	Decreased	Increased
Rawe <i>et al.</i> (1974)	Cat	Thoracic	Unchanged	Undetectable
Bingham <i>et al.</i> (1975)	Monkey	Thoracic	Decreased	Unchanged
Tsubokawa <i>et al.</i> (1975)	Dog	Thoraco-lumbar	Unchanged	—
Zivin <i>et al.</i> (1976)	Rabbit	Lumbar	Decreased	Unchanged
Schoultz <i>et al.</i> (1976)	Cat	Lumbar	Increased	—

* All measurements are at impact site.

difference in the extent of functional return at the end of 12 weeks. A recent report by Zivin *et al.* (1976) separately studied post-traumatic monoamine alterations in the contused grey and white matter. Their results showed norepinephrine to be decreased at the impact site in both the grey and white matter.

Dopamine

Concomitant with norepinephrine studies, another catecholamine, dopamine, has been investigated relative to its possible role in the pathophysiology of spinal cord injury (Osterholm and Mathews, 1972; Naftchi *et al.*, 1974; Hedeman *et al.*, 1974; de la Torre *et al.*, 1974; Bingham *et al.*, 1975; Zivin *et al.*, 1976) (Table I). Osterholm and Mathews (1972) found dopamine to be decreased by a factor of 4 at the site of spinal cord impact within 1 hour after trauma. Other investigators have noted no significant alteration in dopamine concentration in the contused spinal cord (de la Torre *et al.*, 1974; Bingham *et al.*, 1975; Zivin *et al.*, 1976). But Naftchi *et al.* (1974) and Hedeman *et al.* (1974) reported a significant elevation in dopamine concentration following experimental spinal cord injury. The latter authors (Hedeman *et al.*, 1974) also observed that the use of haloperidol, predominantly a dopaminergic blocker, lent a high degree of clinicopathological protection to the injured canine spinal cord, and hypothesised that the trauma-related dopamine elevation may induce intramedullary vasoconstriction through an alpha-adrenergic mechanism which is blocked by this agent. The administration of AMT 15 mins after injury did not prevent dopamine elevation and afforded no clinical or microscopic protection (Hedeman *et al.*, 1974). The lack of efficacy of AMT may be explained by the early and rapid post-trauma elevation of dopamine which would precede the onset of AMT action (Hedeman *et al.*, 1974). Twenty-four hour pretreatment with AMT, however, suppressed all spinal cord catecholamines, and did prevent trauma-induced dopamine elevation (Hedeman *et al.*, 1974).

Serotonin

Serotonin, a vasoactive biogenic amine, has been reported increased following central nervous system trauma both experimentally (Osterholm *et al.*, 1969; Tsubokawa *et al.*, 1975; Zivin *et al.*, 1976) and clinically (Misra *et al.*, 1967) (Table II). Osterholm *et al.* (1969) demonstrated significant elevation of serotonin in the brain and cerebrospinal fluid (CSF) after experimental cerebral trauma in cats. Elevated serotonin levels were noted in the traumatised canine spinal cord by Tsubokawa *et al.* (1975), who correlated these levels with the onset of vasoconstriction of the cord vessels and reduced vascular perfusion. Zivin *et al.* (1976) reported an increase in the white matter serotonin concentration both rostral and caudal to the impact lesion. Other investigators, however, have been unable to confirm serotonin elevation after neural trauma (de la Torre *et al.*, 1974; Naftchi *et al.*, 1974; Brodner *et al.*, 1977).

Brodner *et al.* (1976) have noted a significant decrease in the intramedullary serotonin levels 30 mins after injury, and have also reported a significant rise in CSF serotonin 1 hour after experimental spinal cord trauma. This elevation in CSF serotonin has been correlated with the appearance of vasoconstriction and reduced perfusion in the intramedullary microcirculation of the contused spinal cord (Brodner *et al.*, 1975). The authors postulated that release of serotonin during platelet aggregation and clot lysis in the subarachnoid space following trauma is responsible for the observed vascular changes.

TABLE II

Experimental central nervous system trauma: concentration of serotonin in tissue and cerebrospinal fluid*

Author and year	Animal	Region	Serotonin	
			Tissue	CSF
Osterholm <i>et al.</i> (1969)	Cat	Brain	Increased†	Increased
de la Torre <i>et al.</i> (1975)	Dog, cat	Thoracic spinal cord	Unchanged	—
Naftchi <i>et al.</i> (1974)	Cat	Thoracic spinal cord	Unchanged	—
Tsubokawa <i>et al.</i> (1975)	Dog	Thoraco-lumbar spinal cord	Increased	—
Brodner <i>et al.</i> (1976)	Cat	Thoracic spinal cord	Unchanged‡	Increased§
Zivin <i>et al.</i> (1976)	Rabbit	Lumbar spinal cord	Increased	—

* All measurements are at impact site.

† Measurements are from cerebrum and brain stem.

‡ No change at 5 min, 15 min, 1, 4 and 12 hours post-trauma; decreased ($p < 0.05$) at 30 min after injury.

§ Increased ($p < 0.025$) at 1 hour post trauma.

|| Increased in white matter; decreased in grey matter.

Osterholm *et al.* (1969) have shown that minute quantities of serotonin injected intracerebrally cause severe neurological alterations and cerebral oedema. They hypothesised that, when released from an intracellular site, serotonin acts on other neurons to cause post-traumatic neurological damage. De la Torre *et al.* (1974) used higher concentrations of serotonin for intracerebral injection of cats and monkeys and found no alteration in either neurological or behavioural parameters.

Serotonin may play an important role in the propagation and development of the spinal cord lesion following trauma. All arguments advanced favouring norepinephrine as a mediator of secondary spinal cord injury could apply equally to serotonin. If pretreatment with reserpine retards damage, serotonin depletion may be an important factor. Howitt and Turnbull (1972) did not find methysergide, a serotonin antagonist, to be effective in lessening the effects of spinal cord injury. Pretreatment with parachlorophenylalanine (PCPA) has been shown by Brodner and Roth (1977) to increase perfusion and improve the microcirculatory dynamics of the traumatised spinal cord. Similarly, Němeček *et al.* (1975) have reported functional improvement in the experimentally contused rabbit spinal cord after pretreatment with PCPA.

The findings to date do not support the hypothesis that the catecholamines, norepinephrine and dopamine, play a direct and major role in the pathophysiology of spinal cord trauma. Similarly, the place that serotonin may have in this process is unclear. Factors contributing to the inconsistencies in biochemical and histochemical studies of spinal cord injury are the limitations of the models and methods used as well as technical problems with the measurement of biogenic amines. Of concern is the high variability in normal and post-traumatic catecholamine values. Variability is all the more prominent in the traumatised animals because of the lack of standardisation of the spinal cord trauma model using the weight-dropping technique (Dohrmann & Panjabi, 1976), and the lack of control of the major physiological parameters at the time of injury (Brodner *et al.*, 1976).

SUMMARY

The status and function of monoamines in experimental spinal cord trauma remains a subject of controversy and continued debate. The norepinephrine hypothesis has been severely weakened by its lack of reproducibility. Dopamine results are too variable to draw meaningful conclusions. The role of serotonin, particularly with reference to its vasoactive properties and the physiological importance of its effects, remains to be determined.

RÉSUMÉ

Le rôle et la fonction des monoamines dans les traumatismes expérimentaux de la moelle épinière restent l'objet de controverses et de débats continuels. L'hypothèse de la norépinéphrine a été considérablement affaiblie par son manque de reproductibilité. Les résultats de la dopamine sont trop variables pour permettre de tirer des conclusions valables. Le rôle de la sérotonine, en particulier concernant ses propriétés vasoactives et l'importance physiologique de ses effets, reste à déterminer.

ZUSAMMENFASSUNG

Der Status und die Funktion von Monoaminen in experimentell verursachten Rückenmarksverletzungen ist umstritten. Die Norepinephrinhypothese wurde erheblich geschwächt durch den Mangel an Reproduzierbarkeit. Dopamine Resultate sind zu variabel, um gültige Schlüsse zu ermöglichen. Die Rolle von Serotonin bezüglich seiner vasoaktiven Wirkung ist noch zu untersuchen.

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