Monoaminergic responses to spinal trauma

Participation of serotonin in posttraumatic progression of neural damage

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The monoaminergic neurotransmitters norepinephrine (NE), dopamine (DA), and serotonin (5-HT) appear to be involved in a number of spinal functions, because descending fibers containing these substances are distributed throughout the spinal cord. These descending neuronal systems influence the activity of spinal motoneurons, sensory neurons, and sympathetic preganglionic neurons. The monoamines have also long been known to be highly vasoactive at physiological, pharmacological, or pathological concentrations and as such have been extensively investigated in relation to cerebral ischemia and spinal cord ischemia and trauma. It has been proposed that the deleterious metabolic progression of events that occurs secondary to physical injury to the central nervous system involves the spasmogenic or other effects of NE, DA, or 5-HT that had been liberated from damaged nerve terminals.

Various studies of the effects of impact injury on spinal cord monoamine content have been performed in cats, dogs, monkeys, and sheep, and the results have been at variance. Some of these conflicts in data may be explained by species differences, by the variables related to the generation of spinal trauma, by circadian variations in spinal monoamine levels, and by differences in monoamine analytical methodology. The inherent lability of CNS monoaminergic systems makes them difficult to study even under normal conditions and renders the use of absolute measurements of transmitter level difficult to interpret.

For these reasons, we attempted to obtain an index of monoamine turnover by the concomitant analysis of neurotransmitter and metabolite concentrations. Additional measures of catecholamine turnover were calculated using the alpha-methylparatyrosine (AMT) method. Furthermore, we used a widely accepted analytical technique: liquid chromatography.
Definitions of Abbreviations

AMT = o-methylparatyrosine
DA = dopamine
5-HIAA = 5-hydroxyindole-3-acetic acid
5-HT = serotonin
HVA = homovanillic acid
LCEC = liquid chromatography with electro-chemical detection
MHPG = 3-methoxy-4-hydroxyphenethylen glycol
NE = norepinephrine

with electrochemical detection (LCEC). This method, if rigorously employed, allows the simultaneous determination of a wide range of chemical structures with a high degree of selectivity and sensitivity. We also attempted to account for the effects of injury-induced edema on the apparent monoamine concentration and to eliminate the effects of circadian variation in spinal monoamine content as potential confounding factors in the analysis. Finally, we extended the analysis of the monoamines from shortly after injury to 6 weeks postinjury, a time at which functional deficits from spinal trauma are clearly evident and differences between treatment groups are maximal.

Materials and Methods

Animal Preparation

Fifty male New Zealand rabbits (each weighing 2.0 to 2.5 kg) were included in these studies. The experimental animals were separated into five groups: Group 1 (five animals) was sacrificed 30 minutes after trauma; Group 2 (three animals) was sacrificed 30 minutes after injury and 60 minutes after AMT injection; Group 3 (three animals) was sacrificed 30 minutes after injury and 60 minutes after injection of AMT vehicle; Group 4 (five animals) was sacrificed 1 hour after injury; and Group 5 (five animals) was sacrificed 4 hours after injury. Five control groups (three animals each) were studied. These received a laminectomy but no trauma and were sacrificed at 30 minutes after the procedure, 30 minutes after the procedure and 60 minutes after AMT injection, 30 minutes after the procedure and 60 minutes after injection of AMT vehicle, or 1 hour or 4 hours after the procedure; otherwise they were handled exactly like the experimental groups. For the groups receiving AMT, the agent was prepared in distilled de-ionized water and a 250-mg/kg bolus was injected into an ear vein 30 minutes prior to laminectomy or impact injury. The water vehicle was administered identically. Spinal cord injury was accomplished by a modification of the method described by Allen. Animals were anesthetized with intravenous sodium pentobarbital (40 mg/kg) and a laminectomy was performed at T9-11 under sterile conditions to expose the intact cord and dura. A 10-gm weight was then dropped 10 cm through a guide tube directly onto the exposed dura. The impact variables were chosen from pilot studies such that severe spastic paraparesis was produced in all animals.

A precisely measured 3-cm length of spinal cord (centered at the impact site) was removed from each animal, corresponding to the segment proximal to the impact site (T-9), the impact site (T-10), and the segment located distally (T-11). This 3-cm segment was then carefully divided into six equal 5-mm lengths, weighed, and frozen at −90°C within 5 minutes of excision. The wet weights of these 5-mm long segments were compared in order to assess the contribution of traumatic edema to this value. The injured segment was easily identified by a hemorrhagic lesion.

In a separate study, 14 rabbits were maintained for 6 weeks after impact injury, as described above, for both biochemical measurement and neurological assessment. In spite of prophylactic treatment with antibiotics and daily bladder expression, urinary tract infections developed in many animals and several manifested signs of pulmonary edema. As a result, only three of the 14 animals in this group survived the 6 weeks. Samples of spinal cord were obtained from these animals as above.

All samples were stored at −90°C for up to 3 weeks prior to analysis. No degradation of analyte occurred under these conditions. All surgical manipulations and sampling procedures were performed at the same time of day. Furthermore, all rabbits were housed under identical light-dark conditions for a least 2 weeks prior to surgery in order to minimize out-of-phase circadian rhythms in spinal cord amine concentrations.

Liquid Chromatography

Standards were obtained for liquid chromatography, and working solutions were prepared weekly from frozen stock solutions (1 mg/ml 0.1 M HClO₄ or 3-methoxy-4-hydroxyphenethylen glycol (MHPG) in 1 mg/ml water). Water and methanol were of a grade suitable for high-performance liquid chromatography.

Biogenic amines (NE, DA, and 5-HT) and their major metabolites (MHPG, homovanillic acid (HVA), and 5-hydroxyindole-3-acetic acid (5-HIAA)) were measured by LCEC in the filtered supernatants of thawed spinal cord segments sonicated in 0.2 ml of 0.05 M HClO₄. A detailed description of the analytical methodology has been published elsewhere. Extensive verification of assay selectivity was carried out using four procedures to confirm peak identity: co-elution with authentic standards; comparison of peak height ratios at two applied potentials; duplicate determinations in two separate mobile-phase systems; and the exclusion by retention times of 22 electroactive species (including AMT) occurring in nervous tissue consisting of amines, acidic, basic, and neutral amine metabolites, and other acidic species (such as ascorbic and uric acid).

* Standards obtained from Sigma Chemical Co., St. Louis, Missouri.
† Methanol obtained from Fisher Scientific, Fairlawn, New Jersey.

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TABLE 1
Spinal cord tissue wet weights

<table>
<thead>
<tr>
<th>Cord Segment</th>
<th>Control Group</th>
<th>Injured Group (30 min-4 hrs)</th>
<th>Injured Group (6 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight (mg)</td>
<td>No.</td>
<td>Weight (mg)</td>
</tr>
<tr>
<td>all three</td>
<td>50.43 ± 1.12</td>
<td>90</td>
<td>59.56 ± 1.52†</td>
</tr>
<tr>
<td>injury site (T-10)</td>
<td>51.10 ± 1.44</td>
<td>30</td>
<td>61.83 ± 2.70‡</td>
</tr>
<tr>
<td>adjacent to injury (T-9, T-11)</td>
<td>50.54 ± 1.28</td>
<td>60</td>
<td>58.42 ± 1.83†</td>
</tr>
</tbody>
</table>

* Estimation of tissue fluid variation by analysis of wet weight. Values are means ± standard error of the means for the number of segments shown. Statistical comparisons with the control group, calculated by the two-tailed t-test, are indicated as follows: † = P < 0.001; ‡ = P < 0.005; § = P < 0.05.

Statistical Analysis

Final values were expressed as micrograms/gram of tissue wet weight. Mean values and standard errors of the mean are given. Statistical analyses included two-tailed t-tests and analysis of variance by Duncan's multiple-range test. A p value less than 0.05 was considered significant.

Results

The spinal cord was initially dissected into six 5-mm segments in order to insure that the injured segment was totally separated from the proximal and distal segments. Statistical analysis did not reveal differences in the concentrations of amines or metabolites in adjoining 5-mm segments at each laminar level. As a result, the values of the duplicate determinations in adjoining segments within a laminar level were averaged, and these values were employed for data analysis. In addition, statistical analysis of laminectomy control groups determined at 30 minutes, 30 minutes plus AMT vehicle, and 60 minutes and 4 hours after laminectomy did not reveal significant differences in analyte concentrations. These data were thus combined into one control group.

Tissue Wet Weight

Analysis of the wet weight of spinal tissues excised from the experimental animals at 30 minutes, 1 hour, and 4 hours after trauma indicated the presence of edema. As shown in Table 1, 5-mm segments of tissue from injured animals averaged an 18% increase in wet weight in comparison to control tissues (p < 0.001, two-tailed t-test). Traumatized segments of the spinal cord displayed a 21% increase (p < 0.005), whereas adjacent segments showed an average 16% increase in wet weight (p < 0.001) compared to the corresponding control tissues.

In contrast, spinal tissues excised from animals at 6 weeks postinjury revealed an average 10% decrease in wet weight across the three segments analyzed as compared to control tissues (p < 0.05). This decrease was due to an average 20% decrease in wet weight (p < 0.05) in the injured segments of tissue. The wet weights of spinal cord segments adjacent to the injured tissue were not different from those of the corresponding control tissues at 6 weeks.

Serotonin

The mean concentrations of 5-HT in control animals were 0.397 ± 0.045 µg/gm tissue in the proximal segment (T-9), 0.281 ± 0.023 µg/gm tissue in the segment corresponding to T-10, and 0.350 ± 0.036 µg/gm tissue in the distal segment (T-11). These values are in close agreement to those reported by Zivin, et al.,6 who used a radioenzymatic assay.

Impact injury at the T-10 level resulted in significant increases in 5-HT concentration in all three segments analyzed, with levels reaching their zenith 4 hours after injury (see Fig. 1 for statistical data). At 6 weeks, the elevation in 5-HT concentration was maintained at a level similar to that at 4 hours in the proximal (p < 0.001, Duncan's multiple-range test) and injured segments (p < 0.02), and was not significantly different from that of the laminectomy group in the distal segment. Thus, by 6 weeks, a rostral to caudal 5-HT concentration gradient had developed (Fig. 1).

The mean control concentrations of 5-HIAA were 0.063 ± 0.006 µg/gm tissue at T-9, 0.052 ± 0.007 µg/gm tissue at T-10, and 0.053 ± 0.008 µg/gm tissue at T-11. The 5-HIAA level was significantly elevated in all segments at 30 minutes postinjury. By 60 minutes and 4 hours, however, 5-HIAA concentrations in all segments were no different from control values. At 6 weeks, the 5-HIAA content was again significantly elevated in the proximal and injured segments and slightly elevated distally as well. At this time, a rostral to caudal concentration gradient for 5-HIAA was also evident.

The 5-HIAA/5-HT ratio was significantly lowered in all segments at 4 hours due to an elevated 5-HT content in the absence of any alteration in the 5-HIAA level. At 6 weeks, this ratio was significantly elevated in the distal segment as a result of the significant fall in 5-HT concentration and slight increase in 5-HIAA concentration (Fig. 1).

Norepinephrine

The mean control concentrations of NE were 0.178 ± 0.012 µg/gm tissue at T-9, 0.155 ± 0.009 µg/gm tis-

Concentrations of NE were slightly but significantly depressed in the proximal and injured segments 30 minutes after trauma (p < 0.05 for both

![Fig. 1. Serotonergic response to spinal trauma at, above, and below the injury site. The concentrations in µg/gm of serotonin (5-HT, upper panel), 5-hydroxyindole-3-acetic acid (5-HIAA, center panel), and the ratio of these values (lower panel) are shown for nine laminectomized control animals and injured animals at each survival time studied (five animals in each group). The concentration data were not corrected for tissue fluid variation due to traumatic edema; however, based on the observed short-term increase in wet weights (Table 1), each 5-HT and 5-HIAA level at 30 minutes, 60 minutes, and 4 hours after injury was underestimated by 18% on average. In contrast, the average 20% loss of weight in injured segments at 6 weeks posttrauma indicates that the concentrations calculated in these tissues were correspondingly underestimated. Data were analyzed statistically by Duncan’s multiple-range test: * = p < 0.05; ** = p < 0.02; *** = p < 0.01; **** = p < 0.001.

![Fig. 2. Noradrenergic response to spinal trauma. The concentrations in µg/gm of norepinephrine (NE, top panel), 3-methoxy-4-hydroxyphenethylene glycol (MHPG, center panel), and the utilization ratios (lower panel) are shown as in Fig. 1. The concentrations of NE and MHPG calculated were not corrected for tissue fluid variation. Doing so would increase these calculated values by 18% on average in injured animals at 30 minutes, 60 minutes, and 4 hours posttrauma. Thus, while the depression of NE content at the site of injury may have been overestimated, the concomitant elevation of MHPG would have been underestimated, indicating that the increased utilization ratios observed were valid. The elevated NE and MHPG levels seen at 6 weeks in the injured tissue may have been overestimated by 20% on average. Statistical analysis and key to significance are as in Fig. 1.](image-url)
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measurements), and also at 60 minutes at the site of injury (p < 0.05). All other values at 60 minutes and 4 hours were not significantly altered. By 6 weeks, an increased NE concentration was observed proximally (p < 0.02), and a decreased concentration was seen distally (p < 0.01). A rostral to caudal NE concentration gradient was thus evident at 6 weeks.

The mean control concentrations of MHPG were 0.076 ± 0.011 μg/gm tissue at T-9, 0.060 ± 0.010 μg/gm tissue at T-10, and 0.069 ± 0.011 μg/gm tissue at T-11. No significant changes in MHPG concentration were seen over the short term (30 minutes, 60 minutes, and 4 hours postinjury). By 6 weeks, however, significant elevations in MHPG levels were seen in all segments (p < 0.01 for all measurements, Fig. 2).

The MHPG/NE ratio was elevated in the injured segment of spinal cord at 30 and 60 minutes postinjury (p < 0.05 for both measurements). Similarly, AMT-induced disappearance of NE was also augmented at 30 minutes at the site of injury, although this effect was not significant (Table 2). While the utilization ratio returned to control values by 4 hours, at 6 weeks postimpact it was significantly elevated in the injured and distal segments (p < 0.05 and 0.01, respectively). A caudal to rostral utilization gradient was thus evident (Fig. 2).

Dopamine

The mean control concentrations of DA were 0.016 ± 0.001 μg/gm tissue at T-9, 0.021 ± 0.004 μg/gm tissue at T-10, and 0.016 ± 0.002 μg/gm tissue at T-11 (Fig. 2). These values are in agreement with previous studies in the rabbit.61

Impact injury did not cause any alterations in DA content proximal or distal to the insult. At the site of injury, however, DA levels were depressed at 30 minutes and 4 hours (p < 0.02 for both measurements). At 6 weeks postinjury, DA concentrations were significantly elevated proximally (p < 0.01), had returned to control levels at the site of trauma, and were significantly lowered distally (p < 0.01). As a result, a rostral to caudal DA concentration gradient was evident.

Mean control concentrations of HVA were 0.038 ± 0.007 μg/gm tissue at T-9, 0.030 ± 0.005 μg/gm tissue at T-10, and 0.041 ± 0.009 μg/gm tissue at T-11. The concentration of HVA was not affected by spinal trauma over the short term. At 6 weeks after impact injury, significant HVA elevations were seen in all segments (see Fig. 3 for statistical data). Dopamine utilization (HVA/DA ratio) was decreased proximally at 30 and 60 minutes (Fig. 3). The utilization ratio increased dramatically at 6 weeks in all segments and in the traumatized and distal segments in particular. A caudal to rostral utilization gradient was thus evident at 6 weeks (Fig. 3).

Of the three animals that survived the 6-week period, two displayed paralysis and one had severe spastic paraparesis in their hindlimbs. In the paralyzed animals, atrophy of the hindlimb muscles and incontinence had developed. The animal with paraparesis displayed some spontaneous movement, but was unable to walk. Biochemical differences between these animals could not be reliably discerned.

Discussion

Consistent with previous reports,30,66 we found that impact injury to the spinal cord resulted in edema formation, as measured by increased tissue wet weight/unit length of spinal cord. These increases were seen in spinal tissues excised 30 minutes, 60 minutes, and 4 hours after trauma both at the site of injury and in the tissue 1 cm above and below the injury. There were no significant differences in wet weight between the injured segments and the adjacent segments of spinal cord. Correction of the calculated concentrations of amines and metabolites for these apparent short-term increases in tissue fluid would, on average, magnify measured elevations (5-HT) and minimize measured depressions (NE and DA) in analyte concentration.

Utilization of neurotransmitter was assessed by calculating the ratio of metabolite concentration to neurotransmitter.37 Being a relative value, these ratios are independent of variations in tissue fluid. Measurement

<table>
<thead>
<tr>
<th>Cord Segment</th>
<th>Norepinephrine (μg/gm)</th>
<th>Dopamine (μg/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>proximal (T-9)</td>
<td>0.180 ± 0.010</td>
<td>0.118 ± 0.022</td>
</tr>
<tr>
<td>injury site (T-10)</td>
<td>0.159 ± 0.007</td>
<td>0.105 ± 0.015</td>
</tr>
<tr>
<td>distal (T-11)</td>
<td>0.165 ± 0.010</td>
<td>0.124 ± 0.023</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means. For the groups receiving α-methylparatyrosine (AMT, 250 mg/kg), the agent was injected into an ear vein 30 minutes prior to laminectomy or impact injury. Animals were sacrificed 30 minutes after laminectomy or injury. Vehicle for AMT was given similarly before laminectomy. Administration of vehicle did not alter concentrations found after laminectomy alone. Administration of vehicle to injured animals did not alter concentrations found after impact injury alone (data not shown).
of neurotransmitter metabolite levels does provide insight into neurotransmitter release and metabolism under physiological conditions, as well as in certain pathological conditions. The fact that the catecholamine turnover rates calculated by the AMT method were in qualitative agreement with the corresponding utilization ratios supports the validity of these measurements under the conditions of this study.

**Serotonin**

In agreement with certain previous findings, but not others, we found that spinal trauma resulted in an increased spinal 5-HT concentration at and adjacent to the injury site. Each segment of spinal cord analyzed up to 4 hours after the injury displayed significant 5-HT elevations. These elevations were of even greater magnitude when the contribution of edema to the measurement of tissue weight was considered. Similarly, 5-HIAA concentrations were elevated at 30 and 60 minutes posttrauma, but had returned to control levels by 4 hours, resulting in a significant decrease in the 5-HT utilization ratio.

The marked elevation in spinal 5-HT concentration observed after spinal cord injury is not easily explained by neuronal mechanisms. An increased 5-HT synthesis is not likely to occur posttrauma in the presence of ischemic hypoxia. Contribution to spinal 5-HT stores from supraspinal sites can be excluded based on the known rates of axoplasmic transport. An exaggerated release or leakage of 5-HT from raphe-spinal neurons would be expected to result in a loss of 5-HT from the spinal cord, as has been observed for central DA after carotid ligation. While it is possible that a decreased oxidative metabolism of 5-HT prevented such a circumstance, the aforementioned DA depletion following carotid ligation was also associated with a diminished oxidation of DA. Furthermore, the concentrations of 5-HIAA measured in this study did not fall below the control level to 4 hours, and were in fact elevated at 30 and 60 minutes postinjury. Although it is conceivable, due to a lack of acid-transport activity, that the initial increase in 5-HIAA concentration reflected an accumulation rather than production of this metabolite, a similar accumulation of HVA, subject to the same transport mechanism, was not observed.

A distinct possibility is that 5-HT was released from blood platelets activated by injury and entered spinal tissue as a result of posttraumatic hemorrhage and blood-brain barrier injury. Platelet 5-HT concentration in the rabbit, among the highest found in mammals, has been estimated to be 26.8 μmol/ml (5 x 10⁸ platelets). This concentration is four orders of magnitude greater than the average 5-HT concentration found in the spinal cord in this study. Clearly, there was a sufficient amount of 5-HT already existing in blood platelets prior to trauma to account for the increased level of spinal 5-HT observed.

The pharmacological actions of 5-HT in the circulation include the initiation of vasoconstriction and blood-brain barrier injury. Platelet 5-HT concentration in the rabbit, among the highest found in mammals, has been estimated to be 26.8 μmol/ml (5 x 10⁸ platelets). This concentration is four orders of magnitude greater than the average 5-HT concentration found in the spinal cord in this study. Clearly, there was a sufficient amount of 5-HT already existing in blood platelets prior to trauma to account for the increased level of spinal 5-HT observed.

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![Figure 3. Dopaminergic response to spinal trauma. The concentrations of dopamine (DA, upper panel), homovanillic acid (HVA, center panel), and the resulting utilization ratios (lower panel) are shown as in Figs. 1 and 2.](image-url)
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possibly the decreased utilization of 5-HT observed at 4 hours posttrauma in this study. More significantly, because these neurons also contain thyrotropin-releasing hormone, it is conceivable that release of this neurotransmitter would also be depressed. Based on this hypothesis, the beneficial effects of exogenous thyrotropin-releasing hormone in reducing posttraumatic paralysis would result from a bypass of the 5-HT-induced presynaptic inhibition. Similarly, 5-HT receptor antagonists have been shown to have an ameliorative effect on spinal function after experimental spinal trauma. These actions are consistent with the proposed interaction of platelet-derived 5-HT with raphe-spinal neurons. Blockade of the 5-HT receptor inhibits platelet aggregation and release reactions and should reverse 5-HT-mediated autoreceptor stimulation.

Norepinephrine

In accord with previous studies, NE concentration was decreased 30 minutes postinjury proximal to and at the trauma site and MHPG content was elevated at 30 minutes only at the site of injury. Correcting these data for the trauma-induced increase in weight negated the NE effect but enhanced the significance of the MHPG effect. Accordingly, the NE utilization ratio in the impact-injured tissue was significantly elevated up to 60 minutes after injury. The NE turnover rate at 30 minutes, calculated by the AMT method, was also elevated but not significantly. These data are consistent with a small and transient increased release or leak of NE from nerve terminals at the site of injury with its subsequent metabolism to MHPG. The relevance of this effect to the pathophysiology of spinal trauma would thus appear to be small and transient as well.

Dopamine

The short-term effects of spinal impact injury on DA observed in this study are at variance with some findings but in general agreement with others. There were no remarkable postinjury alterations in DA concentration over the short term except at the impact site, where DA content was lowered. This decrease was overestimated, however, due to the local increase in tissue fluid. No dramatic changes in HVA concentration were observed, but there was a trend toward decreased HVA levels and HVA/DA utilization ratios in all segments, probably as a result of decreased oxidative metabolism. These data do not support a significant role for DA in the primary pathophysiology of spinal trauma.

Long-Term Response to Injury

The similarity of effects of chronic spinal injury upon all three monoaminergic systems studied implies a common mechanism. At this time period of study, a restriction of axoplasmic transport could account for the increased transmitter and metabolite concentrations proximal to the injury site and for the rostral to caudal concentration gradient observed for all of the monoamines and metabolites. Consistent with previous observations, depleted monoamine stores displayed an augmented utilization distal to the injury. The mechanism of this response may involve either a release from supraspinal inhibition secondary to injury-induced deafferentation or an intrinsic neuronal response to neurotransmitter depletion. The presence and degree of neurotransmitter gradients after spinal trauma may be quantitative neurochemical markers of spinal dysfunction.

Conclusions

The data presented provide support for a primary role of 5-HT, possibly from vascular sources, and the raphe-spinal tract, in the short-term pathophysiology of spinal cord trauma. The definitive role of the blood platelet in the posttraumatic progression is currently under investigation. Evidence has also been presented that significant monoaminergic activity can remain 6 weeks after spinal trauma and, in fact, will be enhanced below the lesion in spared fibers. These descending systems retain the ability to modulate their function during the chronic phase of injury, which implies that therapeutic intervention may be of some benefit long after the initial trauma.

Acknowledgments

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References

groups in the lower brain stem of the rabbit projecting to the spinal cord, with special reference to catecholamine-containing neurons. Brain Res 221:35–55, 1981
46. Osterholm JL, Mathews GJ: Altered norpinyinphyline metabolism following experimental spinal cord injury. Part 1: Relationship to hemorrhagic necrosis and post-wounding neurologic deficits. Part 2: Protection against trau-
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matic spinal cord hemorrhagic necrosis by norepinephrine synthesis blockade with alpha methyl tyrosine. J Neurosurg 36:386-401, 1972


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