Norepinephrine levels in experimental spinal cord trauma

Part 2: Histopathological study of hemorrhagic necrosis

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Alpha methyl tyrosine (AMT) or reserpine administered intravenously 24 hours before sacrifice in the nontraumatized cat resulted in significant reduction in tissue levels of norepinephrine (NE) tested at the T-5 spinal cord level. Phenoxybenzamine given 2 hours before sacrifice did not alter NE levels at T-5. Histological sections of spinal cord examined 1 hour after a 500 gm-cm trauma at the T-5 level in cats, pretreated 24 hours before trauma by a single dose of AMT or reserpine, demonstrated no reduction of gray or white matter hemorrhages when compared to controls. In cats pretreated with phenoxybenzamine 2 hours before trauma there was a marked reduction of hemorrhages at 1 hour posttrauma when compared to controls. The animals treated with phenoxybenzamine had a 32% reduction of systemic blood pressure before trauma, demonstrated no pressor response to spinal cord trauma, and were severely hypotensive posttrauma. It is concluded that posttraumatic blood pressure has greater etiological significance in the pathogenesis of experimental spinal cord hemorrhages than tissue levels of NE.

KEY WORDS □9 alpha methyl tyrosine □9 reserpine □9 phenoxybenzamine □9 norepinephrine □9 spinal cord injury □9 spinal cord hemorrhage □9 systemic blood pressure

Progressive hemorrhagic necrosis (HN) following experimental spinal cord trauma has been repeatedly demonstrated. A marked diminution of this process has been reported when various sympatholytic agents have been administered pre- or posttrauma. These histopathological alterations have been viewed as consistent with the hypothesis that local accumulation of norepinephrine (NE) with resulting ischemia and hemorrhages is etiologically significant in the pathogenesis of HN. This study was designed to study HN when spinal cord levels of NE had been reduced by pretreatment with agents that deplete catecholamines (CA) or drugs that block adrenergic receptors.

Methods and Materials

Animal Preparations

Adult cats weighing between 2.5 and 3.5 kg were used in the study. All animals were anesthetized with pentobarbital (35 mg/kg)
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intraperitoneally. Tracheostomy was performed and respirations were controlled by a small animal ventilator. A femoral artery and vein were cannulated for monitoring of systemic blood pressure by a Statham strain gauge transducer* and for the administration of intravenous fluids and medications. The end-tidal tracheal pCO₂ was monitored by a Beckman medical gas analyzer and body temperature was maintained at 36° to 38° C. The somatosensory cortical evoked response (CER) from stimulation of the lower extremities was monitored by the method described by D'Angelo, et al. At the termination of the experiment the cats were sacrificed by transection of the great thoracic vessels.

Control Studies

Cats were treated with either alpha methyl tyrosine methyl ester HCl (AMT), reserpine, or phenoxybenzamine prior to sacrifice to determine the effect of the drugs in reducing segmental NE concentration at the T-5 spinal cord level. Twenty cats were given 250 mg/kg of AMT intravenously over a 15- to 30-minute period and then sacrificed, four each at 1, 2, 4, 8, and 24 hours after infusion. Twenty cats were pretreated with an infusion of 2 mg/kg of reserpine intravenously over a 5-minute period and sacrificed at the same time intervals as the first group. Four cats were treated with 5 mg/kg of phenoxybenzamine intravenously over a 5-minute period and then sacrificed 2 hours later. Before sacrifice a laminectomy was performed from T-2 through T-6 and immediately after sacrifice the T-5 segment was removed, placed in 10% formalin, and subsequently sectioned in 20-μ segments and stained with hematoxylin and eosin.

Histological sections were studied under low power magnification (×10) and the severity of gray and white matter hemorrhages were graded. A Lovins field finder was used under medium power (×40) in order to quantitate the percentage involvement of both gray and white matter hemorrhages. Axonal and neuronal damage was graded under high power observation (×100).

Results

Pretreatment with AMT or reserpine resulted in a significant reduction from a control value of .077 μg/gm of NE at the T-5 vertebral level to .014 and .006 μg/gm of NE, respectively, by 24 hours. Significant reductions of NE were apparent by 2 hours with reserpine but only after 8 hours with AMT. The segmental spinal cord level of NE at T-5 after 2 hours of treatment with phenoxybenzamine was slightly higher than control values but was not a significant deviation from controls (Fig. 1 and Table 1).

Intravenous administration of AMT frequently resulted in a decrease of the systemic blood pressure but a return to normal levels occurred if the infusion was stopped (Fig. 2). The remaining quantity of AMT could then

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Hemorrhagic Necrosis Studies

Four groups of three cats each were used for the experimental study of progressive HN following trauma. One group was pretreated with AMT, and 24 hours later reanesthetized and subjected to experimental spinal cord trauma at the T-5 level. Another group was pretreated with reserpine and sustained similar trauma 24 hours later, while a third group received phenoxybenzamine 2 hours before trauma. A fourth group was traumatized without pretreatment and served as controls. Trauma was administered at the T-5 segmental level after a laminectomy had been performed by dropping a 25-gm weight with a 7.06 sq mm footplate impactor onto the exposed dura. One hour later the animals were sacrificed and the traumatized cord segment removed, placed in 10% formalin, and subsequently sectioned in 20-μ segments and stained with hematoxylin and eosin.

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*Statham strain gauge transducer manufactured by Statham Laboratories, Inc., Hato Rey, Puerto Rico 00919.
†Beckman medical gas analyzer LB-2 manufactured by Beckman Instruments, Inc., 2500 Harbour Boulevard, Fullerton, California.
Fig. 1. Tissue level of NE in the T-5 spinal cord segment in the nontraumatized cat after treatment with AMT, reserpine, or phenoxybenzamine. Norepinephrine concentration is expressed in µg/gm of wet cord tissue.

### Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Cats</th>
<th>NE Levels* (µg/gm)</th>
<th>Range</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>untreated</td>
<td>4</td>
<td>0.077 ± 0.013</td>
<td>0.049–0.110</td>
<td></td>
</tr>
<tr>
<td>AMT pretreatment</td>
<td>4</td>
<td>0.079 ± 0.012</td>
<td>0.061–0.105</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>1 hr</td>
<td>4</td>
<td>0.053 ± 0.011</td>
<td>0.032–0.066</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>2 hrs</td>
<td>4</td>
<td>0.058 ± 0.011</td>
<td>0.033–0.078</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>4 hrs</td>
<td>4</td>
<td>0.043 ± 0.012</td>
<td>0.027–0.055</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>8 hrs</td>
<td>4</td>
<td>0.014 ± 0.007</td>
<td>0.000–0.030</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>reserpine pretreatment</td>
<td>4</td>
<td>0.059 ± 0.005</td>
<td>0.043–0.062</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>1 hr</td>
<td>4</td>
<td>0.023 ± 0.004</td>
<td>0.017–0.027</td>
<td>&lt;.01†</td>
</tr>
<tr>
<td>2 hrs</td>
<td>4</td>
<td>0.025 ± 0.015</td>
<td>0.007–0.040</td>
<td>&lt;.05†</td>
</tr>
<tr>
<td>8 hrs</td>
<td>4</td>
<td>0.003 ± 0.002</td>
<td>0.000–0.009</td>
<td>&lt;.01†</td>
</tr>
<tr>
<td>24 hrs</td>
<td>4</td>
<td>0.006 ± 0.003</td>
<td>0.000–0.012</td>
<td>&lt;.01†</td>
</tr>
<tr>
<td>phenoxybenzamine pretreatment</td>
<td>4</td>
<td>0.099 ± 0.017</td>
<td>0.064–0.133</td>
<td>&gt;.10</td>
</tr>
</tbody>
</table>

*Mean norepinephrine levels ± standard error of mean.
†Difference is significant.

Fig. 2. Transient reduction of systemic blood pressure observed during administration of AMT. A return to normal levels is observed with cessation of agent.

be infused without deterioration in the blood pressure and the maintenance of a normal pretrauma blood pressure was observed. The intravenous administration of reserpine did not result in any significant reduction of blood pressure either during its infusion or before trauma. Infusion of a 5-mg/kg dose of phenoxybenzamine did result in a 32% reduction of the systemic blood pressure before trauma (Fig. 3 and Table 2).

The administration of trauma in the control animals produced a pressor response, consisting of a sudden increase of systemic blood pressure up to 200 to 250 mm Hg with a latency of 2 to 3 seconds. The hypertensive phase persisted for 3 to 4 minutes and then was followed by a hypotensive period with the blood pressure remaining at 73% of the pretrauma level until sacrifice of the animal 1 hour later. In the animals pretreated with AMT or reserpine there was no alteration of this response except that the posttrauma blood pressure was somewhat higher. In the animals treated with phenoxybenzamine, the pretrauma blood pressure was diminished, the pressor response abolished, and the animals were hypotensive, experiencing a 50% reduction from pretreatment levels (Fig. 3 and Table 2).

Histological examination of the AMT and reserpine pretreated preparations under low power magnification (×10) revealed an increase rather than a diminution of the hemorrhages in the gray and white matter when compared to control sections (Fig. 4). Inspection of the cats pretreated with phenoxybenzamine, which did not significantly alter cord levels of NE at the T-5 level, showed a marked reduction of hemorrhages in both gray and white matter (Fig. 4 lower right).

Quantification of the gray and white matter hemorrhages at ×40 magnification confirmed the gross observations. The control values for hemorrhages at 1 hour posttrauma were 50% for gray matter and 7% for white matter. In the preparations treated with AMT or reserpine 53% and 70% gray matter hemorrhages, respectively, were observed. In the same preparations 9% and 17% hemorrhages in the white matter were calculated. The phenoxybenzamine pretreated animals showed 18% hemorrhages in the gray matter and 2% for white matter (Table 2).

Inspection of the traumatized sections under ×100 magnification when compared to nontraumatized areas of the cord revealed
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![Graph showing systemic blood pressure response to 500 gm-cm trauma at the T-5 spinal cord level in control cats and cats pretreated with AMT, reserpine, or phenoxybenzamine. Points on the graph represent mean values for systolic blood pressure.](image)

that at 1 hour after the injury most of the white matter had a lacunar honeycombed appearance resulting from an increase in periaxonal spaces. Many axons were swollen, and distortion and disruption of myelin sheaths were evident in many areas. Neuronal changes consisted of angulation, shrinkage, swelling, and a reduction in the number of cell bodies. Loss of nucleoli, absence of Nissl substance, and the appearance of occasional ghost remnants of cell bodies were frequently observed. These alterations were noted regardless of the pretreatment agent used, and were also seen in the untreated, traumatized controls.

**Discussion**

Alpha methyl tyrosine (AMT) is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the initial step of the biosynthetic pathway of the conversion of tyrosine to norepinephrine (NE) in the central nervous system. A reduction in the content of NE by AMT has been demonstrated in the caudate nucleus and brain stem of guinea pigs, hypothalamus of rabbits, and cerebral

**TABLE 2**

*Systemic blood pressure and cord hemorrhages in control and pretreated cats with 500 gm-cm trauma at T-5*

<table>
<thead>
<tr>
<th></th>
<th>Control (3 cats)</th>
<th>AMT (3 cats)</th>
<th>Reserpine (3 cats)</th>
<th>Phenoxybenzamine (3 cats)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mean systolic blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at pretreatment</td>
<td>123</td>
<td>123</td>
<td>117</td>
<td>123</td>
</tr>
<tr>
<td>posttrauma</td>
<td>123</td>
<td>120</td>
<td>133</td>
<td>83</td>
</tr>
<tr>
<td>at trauma</td>
<td>240</td>
<td>220</td>
<td>233</td>
<td>70</td>
</tr>
<tr>
<td>15 min posttrauma</td>
<td>80</td>
<td>93</td>
<td>97</td>
<td>62</td>
</tr>
<tr>
<td>30 min posttrauma</td>
<td>87</td>
<td>103</td>
<td>98</td>
<td>60</td>
</tr>
<tr>
<td>45 min posttrauma</td>
<td>90</td>
<td>107</td>
<td>108</td>
<td>60</td>
</tr>
<tr>
<td>60 min posttrauma</td>
<td>90</td>
<td>110</td>
<td>135</td>
<td>62</td>
</tr>
<tr>
<td><strong>percentage cord hemorrhages 1 hr posttrauma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gray matter (%)</td>
<td>50</td>
<td>53</td>
<td>70</td>
<td>18*</td>
</tr>
<tr>
<td>white matter (%)</td>
<td>7</td>
<td>9</td>
<td>17</td>
<td>2*</td>
</tr>
</tbody>
</table>

*Significantly different from control values, p <0.05.
Fig. 4. Cross sections of spinal cord in animals 1 hour after receiving 500 gm-cm injury at the T-5 level. H & E, × 7.5. Upper Left: Cord from an untreated control cat. Calculated hemorrhagic involvement is 50% for gray and 7% for white matter. Upper Right: Cord from a cat pretreated with AMT. Calculated hemorrhagic involvement is 53% for gray and 9% for white matter. Lower Left: Cord from a cat pretreated with reserpine. Calculated hemorrhagic involvement is 70% for gray and 17% for white matter. Lower Right: Cord from a cat pretreated with phenoxybenzamine. Calculated hemorrhagic involvement is 18% for gray and 2% for white matter.

cortex, caudate nucleus, hypothalamus, brain stem, and spinal cord of cats.13,17,32,33 Although studies in other species indicate a more rapid disappearance of NE after one dose of AMT,5 our results in the cat demonstrate that by 24 hours there is a marked depletion of NE at the T-5 segmental level. This is in agreement with Hedeman's finding of non-detectable NE levels in dogs after 24 hours of pretreatment with AMT.19

Reserpine, a rauwolfia alkaloid, depletes stores of catecholamines (NE and dopamine) and serotonin in many organs including brain, blood vessels, heart, and the adrenal medulla.21 This agent interferes with intraneuronal storage of NE but also decreases NE synthesis by blocking the uptake of dopamine (DA) by storage granules that contain the hydroxylation enzyme, dopamine-beta-hydroxylase, necessary for conversion of DA to NE.31 This may lead to diminished DA levels as well, since DA is then more susceptible to rapid metabolism by monoamine oxidase.31 Reserpine has been effective in reducing the concentration of NE in the brain stem of rats,6 spinal cord of rats,12 and hypothalamus and spinal cord of cats.2,18 Reduced concentrations of NE can be measured within an hour after intravenous administration and depletion is maximal by 24 hours.21 Our
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studies confirm these findings at the T-5 segmental level in cats.

Phenoxybenzamine, a haloalkylamine, is an alpha adrenergic blocking agent whose full blockade power develops slowly; the peak effect is usually not reached until approximately 1 hour after administration. Its action is unrelated to any effects on adrenergic nerve function but instead to the intermediate step of neurotransmission that is mediated by catecholamines at the receptor site. It also exerts important effects on NE metabolism by inhibiting the access of NE to inactivating enzymes and may be the reason for the slight but nonsignificant elevation of NE content after 2 hours of pretreatment. It also produces an increase of NE from sympathetic neurons into the circulation. Reduction of DOPA-induced increase of the hind limb flexor reflex in rats with spinal trauma by phenoxybenzamine may indicate that this agent blocks the NE receptors of effector neurons in the spinal cord. The usual pharmacological dose is 1 mg/kg in man. Rapid injections can result in a marked reduction of systemic blood pressure.

The NE and CA hypothesis of spinal cord injury concludes that there is an adrenergic component that has etiological significance in the pathogenesis of HN and transverse myelopathy. Osterholm and Mathews' demonstration of a fourfold increase of NE concentration at 1 hour posttrauma with a return to normal by 4 hours was believed to be responsible for progressive HN because of the potent vasoconstrictive activity on the microvasculature. The clinical improvement in three of four injured cats treated with AMT and the marked decrease in HN observed histopathologically in cats treated with various sympatholytic agents, including AMT, reserpine, and phenoxybenzamine, were considered to substantiate the NE hypothesis. Subsequent studies by other laboratories have not confirmed the finding of elevated NE levels at the site of spinal cord injury. Another catecholamine, DA, has been shown to be elevated at the injury site. Hedeman, et al., believe that its increase may be causally related to the ischemic hypoxia and paralysis of the lower extremities following spinal cord injury in dogs by induction of intraparenchymal vasoconstriction through an alpha adrenergic mechanism. Studies that demonstrated neurological improvement in dogs pretreated with phenoxybenzamine were believed to support this hypothesis.

This study demonstrates the efficacy of AMT and reserpine in reducing the concentration of NE in the nontraumatized cat spinal cord. However, AMT does not significantly alter NE levels within the 4 hours following its administration, the time at which Osterholm demonstrated the increase of NE levels. Because of its intermediate step in the biosynthetic pathway of NE, DA levels previously demonstrated to be less than 0.020 μg/gm in the cat spinal cord would also be expected to be reduced by AMT treatment. Reserpine may lower DA by preventing its uptake into storage granules, thereby making it more susceptible to enzymatic degradation by monoamine oxidase. According to the NE and CA hypothesis of spinal cord injury, experimental animals pretreated with these two agents 24 hours before trauma should have a reduction of HN that can be observed histopathologically. Our pathological studies in pretreated traumatized animals failed to demonstrate this but instead displayed the same or slightly greater gray and white matter hemorrhages posttrauma as compared to controls. There appeared to be a greater correlation of HN with the degree of blood pressure posttrauma than with the cord levels of NE.

The results in animals pretreated with phenoxybenzamine appear to support the etiological significance of blood pressure as a contributing factor in the degree of hemorrhagic involvement. Although there was no significant alteration of NE at the T-5 segmental cord level in pretreated animals, there was a marked decrease in gray and white matter hemorrhages posttrauma as compared to controls. There appeared to be a greater correlation of HN with the degree of blood pressure posttrauma than with the cord levels of NE.

Neuronal changes as early as 1 hour after trauma have been described in the human cerebral cortex, and in the primate spinal cord. These changes are similar to those we found in the cat spinal cord. With the exception of visualization of more neuronal bodies in those preparations that had fewer hemorrhages, the degree of damage appeared the same regardless of the cord level of NE. Axonal swelling, an increase in periaxonal spaces, and disruption of myelin sheaths were
observed throughout the white matter. Axon- 
al changes and myelin sheath disruption 
have been described in the injured primate 
spinal cord 1 hour following trauma. These 
early findings in this model of experimental 
spinal cord trauma indicate that tissue NE 
levels are not significant in the pathogenesis 
of neuronal and axonal changes at 1 hour 
posttrauma.

Summary

Alpha methyl tyrosine and reserpine have 
been demonstrated to be effective in reducing 
NE levels in the nontraumatized cat spinal 
cord while phenoxybenzamine has not. 
Animals pretreated with AMT or reserpine 
did not display any reduction of hemorrhagic 
 involvement of the gray or white matter 1 
hour following trauma when compared to 
controls, but those treated with phenoxyben- 
zamine did. There was a greater correlation 
of the degree of hemorrhages in the gray and 
white matter in the traumatized preparations 
to the systemic blood pressure than with cord 
levels of NE. Neuronal and axonal damage 
were evident regardless of the agent used. 
This study does not support histopatho- 
logically the hypothesis that elevated NE or 
CA levels are etiologically significant in the 
pathogenesis of posttraumatic progressive 
HN of experimental spinal cord trauma.

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