terstitial tissue of the skin. In diabetes, the Maillard reaction may accelerate aging in these tissues and contribute to the earlier onset of cataracts and atherosclerosis.

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Opiate Antagonist Improves Neurologic Recovery After Spinal Injury

Abstract. *The opiate antagonist naloxone has been used to treat cats subjected to cervical spinal trauma. In contrast to saline-treated controls, naloxone treatment significantly improved the hypotension observed after cervical spinal injury. More critically, naloxone therapy significantly improved neurologic recovery. These findings implicate endorphins in the pathophysiology of spinal cord injury and indicate that narcotic antagonists may have a therapeutic role in this condition.*

Traumatic injuries to the spinal cord may cause neurologic impairment in two ways—by directly interrupting neuronal pathways and by initiating a series of pathophysiologic changes that lead to progressive ischemic damage to the spinal cord (*1*). There is experimental evidence that these ischemic changes are potentially reversible and result at least in part from a reduction in spinal cord blood flow (*2*). Under normal circumstances, the spinal cord, like the brain, can maintain relatively constant blood flow over a wide range of blood pressures; such autoregulation is impaired after injury (*3*). When this occurs, perfusion of the cord becomes more directly dependent on systemic blood pressure. Since significant hypotension often accompanies injuries of the cervical or upper thoracic spinal cord (*4*), this combined loss of autoregulation and decreased systemic blood pressure may potentiate ischemic changes observed after trauma to these regions. We have recently demonstrated that the opiate antagonist naloxone reverses the hypotension caused by transection of the cervical spinal cord, thereby implicating endorphins in the pathophysiology of spinal shock (*5*). If endorphin activation also contributes to the hypotension caused by cervical spinal injury, naloxone treatment should increase both systemic blood pressure and local spinal cord blood flow, thus limiting ischemic damage and improving neurologic function. The purpose of our studies, therefore, was to investigate the effects of parenterally administered naloxone on blood pressure and neurologic recovery after low cervical spinal injury.

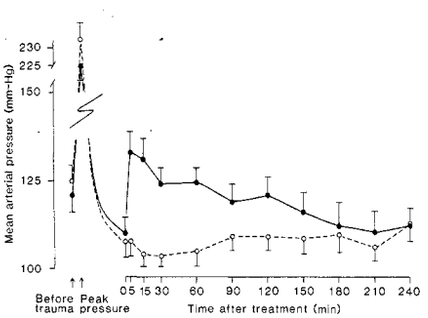

Fig. 1 Effects of naloxone (N = 9, filled circles) or saline (N = 13, open circles) treatment on mean arterial pressure after 500 g-cm trauma to the cervical spinal cord. Points represent averaged values ± standard errors of the mean.

Adult cats (2 to 3 kg) were anesthetized with intravenous pentobarbital (30 mg per kilogram of body weight), paralyzed with gallamine triethiodide, and placed on a ventilator. Blood pressure was continuously recorded on a Dynograph (Beckman) through the use of a femoral artery catheter connected to a pressure transducer (Statham). A femoral venous catheter permitted intravenous drug administration. A laminectomy was performed to expose spinal segments C_6 to T_1; with the dura intact, the C_7 spinal segment was traumatized by dropping a 20-g lead weight a distance of 25 cm (500 g-cm force) onto a 10-mm^2 plastic impact plate which had been contoured to match the curve of the spinal cord. This model, originally described by Allen (*6*), has been extensively used in studies of spinal cord injury (*7*). Pilot studies indicated that these injury variables would produce a moderately severe, reproducible spastic quadriparesis in untreated animals. Forty-five minutes after injury, animals were treated intravenously with equal volumes of either naloxone hydrochloride (N = 9, Endo Laboratories) or saline (N = 13). Blood pressure was recorded and drugs were administered continuously over a 4-hour treatment period with an infusion pump (Harvard, model 975); the naloxone dosage (a 2-mg bolus followed by 2 mg per kilogram per hour) was established from previous experiments (*8*, *9*). Blood pressure was recorded during the 4 hours of treatment, after which the catheters were removed. The laminectomy site was closed in layers and the animal was allowed to recover in its home cage. Neurologic function was evaluated at 24 hours, 1, 2, and 3 weeks by two neurologists who were unaware of treatment or blood pressure findings. Neurologic status was rated according to an established five-point scale based primarily on motor function (*10*). Forelimb and hindlimb scores were determined separately as follows: 0, absence of voluntary movement; 1, minimal voluntary movement;

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2, good voluntary movement, but inability to support; 3, ability to support weight, but unable to walk; 4, ability to walk, but with substantial spasticity, ataxia, or both; 5, normal function. The scale was modified to permit half-point scoring in order to describe neurologic function falling between points. After the 3-week neurologic examination, animals were killed with intravenous injections of pentobarbital.

Contusion of the cervical spinal cord produced a transient pressor response exceeding 100 mm-Hg and followed by a gradual decline of mean arterial pressure over the next 45 minutes to a value approximately 15 mm-Hg below pretrauma levels (Fig. 1). After treatment, arterial pressure continued to decline slightly in saline-treated animals over the first hour. By contrast, naloxone treatment significantly increased mean arterial pressure to a maximum between 5 and 15 minutes after treatment (Fig. 1). Significant differences in the mean arterial pressure between the groups continued over the first 2 hours after treatment (repeated measurement analysis of variance, $F(1, 20) = 7.37$, $P < .05$). Intergroup differences declined over hours 3 and 4 until the mean arterial pressure was identical when physiological monitoring was stopped (4 hours).

Neurologic recovery was also significantly better in naloxone-treated animals than in saline-treated controls at 1, 2, and 3 weeks (Fig. 2, A and B) (Wilcoxon matched-pairs signed-ranks test, $P < .05$). The differences in neurologic function between the groups were greatest at 1 week and were particularly noteworthy when the neurologic scores were translated into functional equivalents. For example, 1 week after trauma, the median saline-treated animal was able to support himself only with his forelimbs, whereas the median naloxone-treated animal walked well, with prominent spasticity only in the hindlimbs. Little further functional improvement was possible for the naloxone animals, and they continued to walk well at 3 weeks. In contrast, at 3 weeks, the median saline animal was unable to walk without support.

Our previous studies have implicated endorphins as pathophysiologic factors in endotoxin (*11*) and hypovolemic shock (*12*). In these experiments, intravenous naloxone rapidly reversed hypotension in both unanesthetized rats and pentobarbital-anesthetized dogs. We subsequently demonstrated that intravenous injections of naloxone reversed the hypotension caused by spinal cord transection in pentobarbital-anesthetized rats (*5, 9*) and cats (*8, 9*). Ethical considerations necessitated the use of anesthesia in the present experiments. The choice of pentobarbital was based on these earlier studies in which pentobarbital's cardiovascular effects could not be reversed by naloxone (*5, 9, 11*). The site of action of naloxone's cardiovascular effects in spinal injury appears to be at opiate receptors within the central nervous system, since intracerebroventricular naloxone stereospecifically improved blood pressure after spinal transection at doses that were without effect when administered intravenously (*5*).

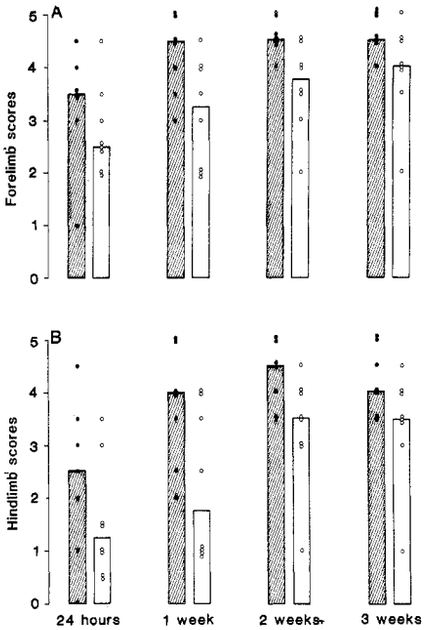

Fig. 2 Effects of naloxone ($N = 7$, filled circles) or saline ($N = 8$, open circles) treatment on neurologic recovery from cervical spinal trauma. Naloxone-treated animals had significantly better neurologic function than saline controls at 1, 2, and 3 weeks after injury (Wilcoxon matched-pairs signed-ranks test, $P < .05$). Values for individual animals are plotted; histograms represent median scores.

Since there is little human evidence of significant functional spinal cord regeneration, the therapy of spinal injury has focused on limiting secondary ischemic changes. Alpha-adrenergic blockers, hypothermia, and corticosteroid treatment have all been reported to improve functional recovery after spinal trauma (*10, 13, 14*). Of these treatments, large pharmacologic doses of corticosteroids have been most consistently shown to be efficacious (*14*). The beneficial effects of steroids have been attributed to their effects on membrane stabilization (*13, 14*). We have speculated that the efficacy of corticosteroids in shock (*11*) may relate to their well-established inhibition of pituitary endorphin release (*15*). Similarly, the beneficial effects of corticosteroids after spinal trauma may be due at least in part to their effects on endorphin systems.

Our findings demonstrate that naloxone treatment can significantly improve functional neurologic recovery after cervical spinal injury. Because naloxone also significantly elevates mean arterial pressure in the cat, we suggest that the beneficial effects of naloxone result from its ability to secondarily improve local spinal cord blood flow. Since naloxone blocks the opiate receptor, it has been used as a tool to infer endorphin activity (*16*). Thus, the beneficial effects of naloxone in this study implicate endorphins in the pathophysiology of spinal cord injury.

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