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Review Article

Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms

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✓ In patients with spinal cord injury, the primary or mechanical trauma seldom causes total transection, even though the functional loss may be complete. In addition, biochemical and pathological changes in the cord may worsen after injury. To explain these phenomena, the concept of the secondary injury has evolved for which numerous pathophysiological mechanisms have been postulated. This paper reviews the concept of secondary injury with special emphasis on vascular mechanisms. Evidence is presented to support the theory of secondary injury and the hypothesis that a key mechanism is posttraumatic ischemia with resultant infarction of the spinal cord. Evidence for the role of vascular mechanisms has been obtained from a variety of models of acute spinal cord injury in several species. Many different angiographic methods have been used for assessing microcirculation of the cord and for measuring spinal cord blood flow after trauma. With these techniques, the major systemic and local vascular effects of acute spinal cord injury have been identified and implicated in the etiology of secondary injury.

The systemic effects of acute spinal cord injury include hypotension and reduced cardiac output. The local effects include loss of autoregulation in the injured segment of the spinal cord and a marked reduction of the microcirculation in both gray and white matter, especially in hemorrhagic regions and in adjacent zones. The microcirculatory loss extends for a considerable distance proximal and distal to the site of injury. Many studies have shown a dose-dependent reduction of spinal cord blood flow varying with the severity of injury, and a reduction of spinal cord blood flow which worsens with time after injury. The functional deficits due to acute spinal cord injury have been measured electrophysiologically with techniques such as motor and somatosensory evoked potentials and have been found proportional to the degree of posttraumatic ischemia. The histological effects include early hemorrhagic necrosis leading to major infarction at the injury site.

These posttraumatic vascular effects can be treated. Systemic normotension can be restored with volume expansion or vasopressors, and spinal cord blood flow can be improved with dopamine, steroids, nimodipine, or volume expansion. The combination of nimodipine and volume expansion improves posttraumatic spinal cord blood flow and spinal cord function measured by evoked potentials. These results provide strong evidence that posttraumatic ischemia is an important secondary mechanism of injury, and that it can be counteracted.

KEY WORDS • **spinal cord injury** • **ischemia** • **vascular response** • **spinal cord blood flow**

In most countries, acute spinal cord injury occurs at an annual rate of 20 to 40 persons per million[85] and, although prevention programs have been initiated, there is no evidence that the incidence is declining. The main causes of spinal cord trauma are motor-vehicle accidents, sports and recreational activities, accidents at work, and falls at home.[122] Approximately half of the patients with spinal cord trauma have complete injuries of the spinal cord with no preservation of voluntary motor or sensory function below the level of the lesion, and almost two-thirds have levels in the cervical region. With the possible exception of methylprednisolone,[20] there is no effective means of restoring neurological function below the level of a complete lesion.[124] During the past 20 years, many investigators have studied the pathophysiological mechanisms of acute spinal cord injury with the aim of finding methods to restore neurological function. Each complete cord

injury costs society approximately $1.5 million for lifetime medical costs and lost earnings in addition to the great personal loss sustained by the victims and their families. Thus, great benefits would accrue from the discovery of effective treatments for spinal cord injury.

The purpose of this paper is to review the evidence supporting the theory that there is a secondary injury of the cord following the initial trauma. This theory has evolved from intense study in many laboratories of the pathophysiology of spinal cord trauma. Among the many possible mechanisms of secondary injury, there is much evidence to support posttraumatic ischemia, and this review will focus on this mechanism. The concept that posttraumatic ischemia is important in the pathophysiology of acute spinal cord injury is attractive since it is potentially treatable and reversible.

The Concept of Primary and Secondary Acute Spinal Cord Injury

It has been hypothesized that there are two mechanisms of damage to the spinal cord after acute spinal cord injury: the primary mechanical injury and a secondary injury due to one or more additional damaging processes initiated by the primary injury.[29,69,106,107] The concept of secondary injury was first postulated in 1911 by Allen,[4] when he found that myelotomy and removal of the posttraumatic hematomyelia resulted in improvement of neurological function in dogs subjected to experimental acute spinal cord injury. Allen[3] theorized that there was a noxious agent present in the hemorrhagic necrotic material that caused further damage to the spinal cord and that the injurious agent was a "biochemical factor." This was the first experimental evidence of posttraumatic autodestruction; since then, numerous other pathophysiological mechanisms have been postulated to explain the progressive posttraumatic destruction of spinal cord tissue (Table 1). Similar theories have been used to explain the progressive loss of neural tissue in other conditions such as head injury, ischemia, and subarachnoid hemorrhage.

TABLE 1
Primary and secondary mechanisms of acute spinal cord injury

- *primary injury mechanisms*
  - acute compression
  - impact
  - missile
  - distraction
  - laceration
  - shear
- *secondary injury mechanisms*
  - vascular changes
    - loss of autoregulation
    - systemic hypotension (neurogenic shock)
    - hemorrhage
    - loss of microcirculation
    - reduction in blood flow
      - vasospasm
      - thrombosis
  - electrolyte changes
    - increased intracellular calcium
    - increased extracellular potassium
    - increased sodium permeability
  - biochemical changes
    - neurotransmitter accumulation
      - catecholamines (*e.g.*, noradrenaline, and dopamine)
      - excitotoxic amino acids (*e.g.*, glutamate)
    - arachidonic acid release
    - free-radical production
    - eicosanoid production
      - prostaglandins
    - lipid peroxidation
    - endogenous opioids
  - edema
  - loss of energy metabolism
    - decreased adenosine triphosphate production

Experimental Models of Primary and Secondary Acute Spinal Cord Injury

In patients with acute cord injury, it is well known that the mechanical injury rarely transects the cord completely, even when the injury is complete as defined above.[78] In the majority of human spinal cord injuries, the mechanism of the primary injury is acute compression or laceration of the spinal cord due to displacement of bone or disc into the spinal cord during fracture-dislocation or burst fracture of the spine.[121] Several experimental models have been developed to simulate the compression type of acute cord trauma (for a review see Fehlings and Tator[46]); the first of these was the weight-dropping technique in dogs introduced in 1911 by Allen.[4] Although many modifications and improvements of this model have been introduced,[116] it has major shortcomings, especially the lack of reproducibility. Other primary mechanisms of acute spinal cord injury in humans, such as acute distraction, have also been simulated by experimental models.[34] In 1978, our laboratory introduced the rat model of acute extradural clip compression of the cord which has proved to be very useful because both the force and duration of acute compression can be selected to create reproducible injuries of varying severity.[103] This model has been adopted by several other investigators and found to be reliable and inexpensive.[79,80] With these models, the pathophysiology of the secondary events accompanying acute cord injury have been extensively investigated in several laboratories.

Pathological Changes

After acute injury, the cord undergoes sequential pathological changes including hemorrhage, edema, axonal and neuronal necrosis, and demyelination followed by cyst formation and infarction (Fig. 1).[19,24,78,133] Allen[3] first described the evolution of these pathological changes in injured dogs. Within 15 minutes of acute injury, petechial hemorrhages occurred in the gray matter and edema of the white matter. During the first 2 hours, the hemorrhages in the gray matter increased and, by 4 hours, there were "numerous swollen axis

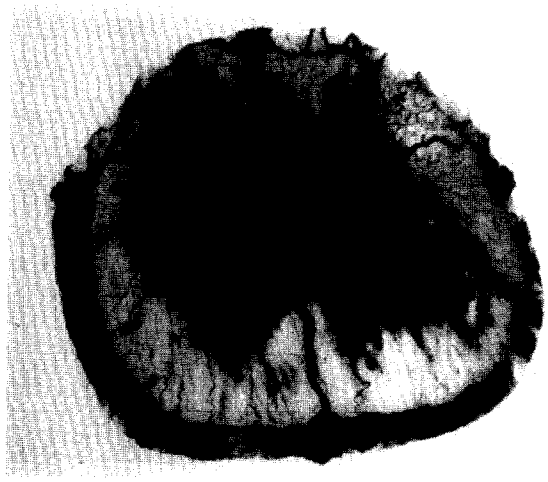

FIG. 1. Colloidal carbon angiogram 1 hour after severe clip compression injury of the spinal cord at the T-1 vertebral level in the rat. There is considerable hemorrhage in the gray matter and adjacent white matter. Much of the microcirculation in both the gray and white matter has not filled, although the anterior spinal artery and the anterior sulcal artery have filled.

cylinders." Ducker, *et al.*,[37] also showed that the pathological changes worsened with time so that by 6 days after injury, there was severe necrosis — a process which Nemecek[93] termed "autodestruction."

Dohrmann, *et al.*,[31] showed by electron microscopy that as early as 5 minutes after injury the muscular venules of the gray matter were distended by erythrocytes, but the axons appeared unchanged. Between 15 and 30 minutes posttrauma, small hemorrhages were seen with extravasation of erythrocytes into the perivascular spaces of postcapillary and muscular venules, and some axonal changes were now apparent. By 4 hours, there were disrupted myelin sheaths, some axonal degeneration, and ischemic endothelial injury. Griffiths and McCulloch[59] showed progressive axonal changes and the development of necrotic zones during the first few days after injury. The electron microscopic appearances of the axons following acute cord injury have been extensively studied by several workers, including Bresnahan[23] and Balentine.[11] Balentine has emphasized that trauma induces granular dissolution of the axoplasm and vesicular disruption of myelin, especially in the white matter.

Several investigators have shown that edema develops at the injury site and spreads into adjacent segments of the cord. By 24 to 48 hours after major trauma, the injury site is necrotic, especially the central zone previously occupied by hemorrhage.[123] Several days later, the hemorrhagic zone shows cavitation and the adjacent areas exhibit patchy necrosis, often with sharply defined margins. These progressive changes, consisting of cavitation and coagulative necrosis at the injury site and in adjacent areas,[133] have the pathological features of infarcts, and thus we have termed the process "posttraumatic infarction."[106,107]

The Vascular Mechanism of Secondary Injury

Acute spinal cord trauma causes numerous vascular changes which may be divided into systemic and local effects. Several investigators have shown that acute spinal cord injury causes immediate mechanical damage to the microvasculature of the cord followed by a secondary injury to these vessels; this combination produces spinal cord ischemia which may be progressive.[31,37,59,69]

Spinal Cord Microcirculation

Several angiographic methods have been used to study the microvasculature of the cord after experimental cord trauma,[45,52] and all have shown a major reduction in the microcirculation and lack of perfusion. In our laboratory, we used colloidal carbon angiography[132] with a colloidal carbon suspension perfused into the blood stream of rats at 15 minutes, 2 hours, or 24 hours after severe trauma. Serial 200-μm sections of the cord showed major areas with lack of filling of the arterioles, capillaries, and venules both at the injury site and for a considerable distance cephalad and caudad in the cord (Figs. 2 and 3). The ischemic zones encompassed a large portion of the gray matter and the surrounding white matter, and were especially severe in white matter areas adjacent to hemorrhages in the gray matter. The anatomical distribution and temporal sequence of the ischemic zones could not be entirely explained on the basis of mechanical damage to vessels caused by the primary injury, and therefore, we postulated a secondary injury to the microcirculation such as thrombosis or vasospasm of arterioles traversing the gray matter to supply the white matter. Lack of perfusion of the microcirculation at the injury site has also been demonstrated in the microangiographic studies of Fairholm and Turnbull[45] and Fried and Goodkin[52] in other models of cord trauma.

Vasospasm due to the accumulation of noradrenaline at the injury site was postulated many years ago by Osterholm and Mathews[95,96] as a possible mechanism of secondary injury. In our angiographic studies with colloidal carbon, the large vessels of the cord, such as the anterior spinal artery and the anterior sulcal arteries, almost always remained patent even after severe cord injury.[132] This feature should be kept in mind when considering the spinal cord blood flow (SCBF) changes described below.

Spinal Cord Blood Flow

Investigators have used a variety of methods to measure SCBF after acute cord trauma,[15,36,56,66,67,81,113,143] and almost all found a major reduction of blood flow in the spinal cord following severe injury. One of the most interesting findings has been the progressive worsening of posttraumatic ischemia during the first few hours

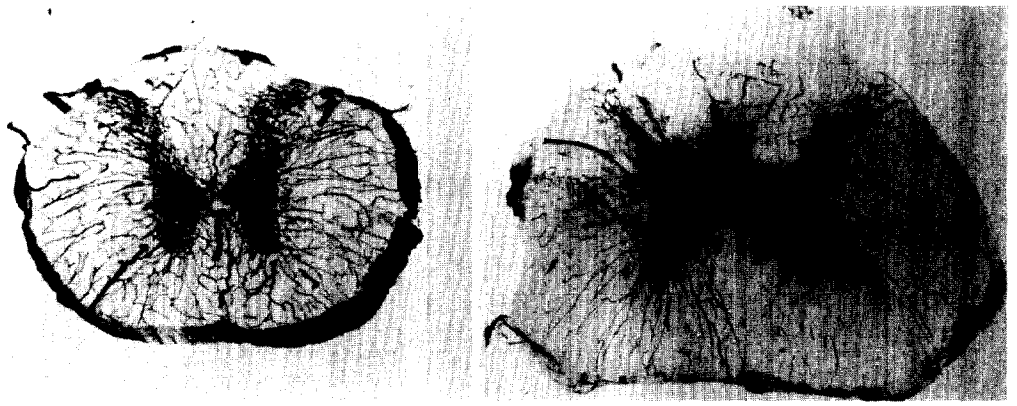

FIG. 2. *Left:* Colloidal carbon angiogram of a cross-section of the normal rat cord at the T-1 level. Note the extensive microcirculation, especially in the gray matter. *Right:* Colloidal carbon angiogram 2 hours after a moderately severe clip compression injury at T-1 in the rat. There is extensive hemorrhage in the gray matter. Large areas of white and gray matter show loss of the microcirculation.

after trauma,[38,47,69,81] indicating that ischemia might be preventable if treated early. Our laboratory demonstrated severe decreases in posttraumatic SCBF with the ^{14}C-antipyrine autoradiographic technique in three different models of spinal trauma: the extradural cuff compression injury in monkeys;[106,107] the acute distraction injury in cats;[34] and the acute clip compression model in rats.[104] Although the autoradiographic method provided excellent anatomical information about local blood flow, it had the major shortcoming of permitting only one flow determination per animal. Accordingly, we used two other methods for measuring blood flow: radioactive microspheres and the hydrogen electrode technique. Both allow more than one flow measurement per animal and have been useful for testing agents to treat posttraumatic ischemia.

Using the microsphere technique, we confirmed the previous autoradiographic findings of posttraumatic ischemia of the cord,[130] but the technique required sampling of cord segments at least 1.5 cm long and allowed only two flow studies per animal. The injection of more microspheres to enable sampling of smaller segments or more than two flow studies per animal caused irreversible hemodynamic changes. The hydrogen electrode technique was not subject to these limitations and allowed repeated measurement of flow in small segments of the rat cord; indeed, this technique has been the most commonly used method for measuring SCBF.[66,67,113,143] With a microcomputer system for on-line determination of flow,[99] we consistently found that severe cord trauma caused profound and persistent ischemia of the cord.[60] After acute clip compression injury in the rat, ischemia began almost immediately, similar to the previous findings in monkeys after acute extradural cuff compression. In the rat, there was a direct linear dose-response relationship between

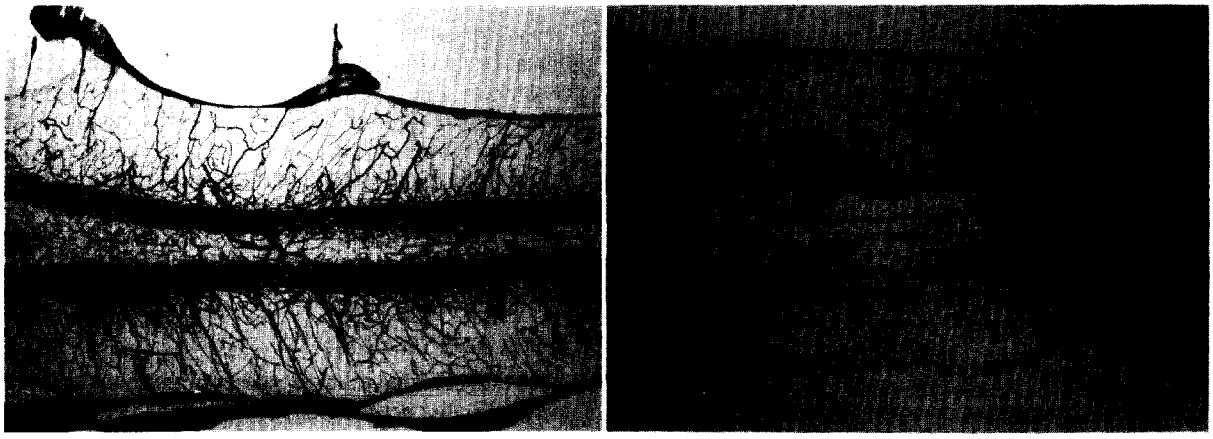

FIG. 3. *Left:* Colloidal carbon angiogram of a longitudinal section of the normal rat cord at the C7–T2 level. Note extensive microcirculation, especially in the gray matter. *Right:* Colloidal carbon angiogram 2 hours after a moderately severe clip compression injury at the T-1 level in the rat. There are scattered hemorrhages centrally with large ischemic zones in both the white and gray matter.

the severity of injury as represented by clip force and the ischemic response.[48,60] In addition, ischemia worsened during the first 3 hours if left untreated,[47] and persisted in the rats for at least 24 hours,[104] the longest interval studied in that species. In monkeys, the ischemia lasted for at least 24 hours after severe injury.[106]

In contrast, there has been the occasional report that spinal cord trauma with the weight-drop model can cause hyperemia in the white matter.[81] One possible reason is the known variability in the severity of injury with this model. We have never observed hyperemia after severe injury in any species, although we found hyperemia at the injury site in monkeys 24 hours after a mild injury,[106] and at sites adjacent to a mild injury in rats in experiments on autoregulation when the mean systemic arterial pressure was elevated to hypertensive levels.[63] Chehrazi, *et al.*,[27] found no reduction in SCBF in cats after cord injury produced by the weight-drop technique. It appears that some of the controversy regarding posttraumatic ischemia may be due to several factors, including variations in injury severity, sampling site in the cord, and arterial pressure.

Effect of Acute Spinal Cord Trauma on Spinal Cord Autoregulation

The normal cord is capable of autoregulation with blood flow remaining constant over a wide range of arterial pressure. Several investigators have shown impairment of autoregulation in the spinal cord after injury by the weight-drop technique.[82,114,141] Our laboratory examined the relationships among arterial pressure, SCBF, and injury severity in rats subjected to either a 2.3- or 53.0-gm clip compression injury with stepwise reduction or elevation of blood pressure by phlebotomy or intravenous adrenaline, respectively.[63] We confirmed that autoregulation was markedly affected by trauma. Indeed, after severe trauma, systemic hypotension caused a further decline in SCBF. The severely injured spinal cord could not maintain its blood flow in the presence of systemic hypotension. Furthermore, elevation of posttraumatic mean systemic arterial pressure to more than 160 mm Hg did not significantly improve SCBF at the injury site and caused marked hyperemia at adjacent sites.[63]

Cardiovascular and Hemodynamic Effects of Acute Spinal Cord Trauma

Acute cord trauma can cause neurogenic shock,[120] and numerous studies have shown posttraumatic hypotension following experimental acute spinal cord injury.[2,25,33,55,101,125] In the rat model, we found that cord injury at T-1 caused a brief rise in arterial pressure followed by a persistent decline in arterial pressure and cardiac output.[60] With additional measurements of heart rate, total peripheral resistance, and central venous pressure, the major cardiovascular and hemodynamic effects of acute cord injury leading to neurogenic shock could be precisely defined. Posttraumatic hypotension and diminished cardiac output were found to be due to a combination of decreased sympathetic tone and myocardial effects.[60]

Posttraumatic Spinal Cord Ischemia and Changes in Axonal Conduction

To characterize the posttraumatic changes in axonal function in the motor and somatosensory tracts of the cord and to correlate these changes with SCBF, the relationships among the severity of cord injury, motor and somatosensory evoked potentials, and SCBF were recently examined in our laboratory.[48] A linear relationship ($r = -0.89$) was found between the severity of cord injury and the reduction in blood flow at the injury site, and linear discriminant analysis revealed that the motor and somatosensory evoked potentials were significantly related to the severity of cord injury. Furthermore, the reduction in amplitude of the evoked potentials was significantly correlated with the reduction in posttraumatic blood flow. Multiple regression analysis revealed that both the severity of cord injury and the degree of posttraumatic ischemia were significantly related to posttraumatic axonal dysfunction. The reduction in axonal conduction in the motor and somatosensory tracts of the cord was significantly correlated with the reduction in posttraumatic blood flow.[48] Thus, these studies provide quantitative evidence linking posttraumatic ischemia to axonal dysfunction following acute cord trauma.

The Cause of Posttraumatic Ischemia

In spite of extensive investigations in many laboratories, the exact cause of posttraumatic ischemia remains unknown. Eludication of the etiology of posttraumatic ischemia would be of major importance for improving the treatment of cord injury. Numerous theories have been postulated to explain posttraumatic ischemia. Vasospasm may be due to mechanical damage or to the release of a vasoactive amine[35,95,96] or other vasoconstrictor. Acute cord injury may cause direct endothelial damage or swelling.[6,31,49] As described above, numerous studies have shown early and extensive hemorrhages, especially in the gray matter. We found that these hemorrhages were associated with zones of ischemia of the white matter in the distribution of the vessels coursing through the hemorrhagic gray matter[132] and, thus, hemorrhage may promote ischemia. Other studies have suggested that the ischemia may result from thrombosis or platelet aggregation[93] due to an agent such as thromboxane A_2.[30]

It has also been postulated that excitotoxic amino acids may be involved in the secondary vascular injury. Although the mechanisms underlying the sensitivity of neurons to ischemic insults are unknown, glutamate (a neurotransmitter and excitatory amino acid) has been implicated.[76,137] For example, it has been hypothesized that glutamate receptor activation may play a key role in the development of ischemic damage in cerebral

tissue. In ischemic-hypoxic models of brain damage, the excitotoxic effect of glutamate has been documented extensively both *in vivo* and *in vitro*.[91,105,135] The mechanism of this neurotoxicity involves an early intracellular accumulation of sodium-producing cytotoxic edema and a delayed destruction of neurons associated with an elevated concentration of intracellular calcium. The latter in turn causes activation of calcium-dependent proteases and further damage. Cerebral ischemia causes a massive increase in the extracellular concentration of glutamate.[14] There are several types of excitatory amino acid receptors, although one type of postsynaptic receptor, the N-methyl-D-aspartate (NMDA) receptor, putatively mediates the neurotoxic effects of glutamate in cerebral ischemia. The systemic administration of NMDA receptor antagonists such as MK-801[138] has been shown to attenuate brain damage in several species.[39,115] Blockers of the NMDA receptor and its ionic channels by agents such as ketamine, phencyclidine, and MK-801 prevent the entry of calcium into the cell. Thus, NMDA receptors have become an appropriate target for therapy of cerebral ischemia. In acute cord trauma, there may be similar mechanisms of toxicity that are activated by posttraumatic ischemia. Indeed, it was recently reported that MK-801 improved the outcome of rats with acute spinal cord injury as shown by improved function on the inclined plane.[44]

Although unlikely, it is possible that posttraumatic ischemia is an epiphenomenon of injury and is only an indirect response to one of the other cellular or molecular sequelae of injury. Indeed, Young[140] has postulated that posttraumatic ischemia may have a protective effect by limiting the diffusion of calcium ions into the lesion site where the elevation of intracellular calcium is known to exert a damaging effect. The immediate onset, the dose-dependent severity of reduction, and the progressive and persistent time course of posttraumatic ischemia provide strong evidence that ischemia is a direct and damaging response to trauma. Importantly, there is also evidence outlined below that treatment of the ischemia restores cord function.[47]

Treatment of the Secondary Vascular Effects of Acute Spinal Cord Injury

Several investigators have attempted to treat acute cord trauma by counteracting or preventing the systemic or local vascular effects. For example, it has been hypothesized that treatment of posttraumatic hypotension or ischemia might improve functional outcome.[32,123,124] However, until recently, there was no proof that correction of the secondary vascular effects restored neurological function. For example, we showed that whole-blood transfusion or dopamine administration improved posttraumatic SCBF in rats,[32] but there was no improvement in spinal cord function as assessed by the inclined plane test. The experimental strategies that have been used to prevent or ameliorate the vascular effects of acute cord trauma are described below.

Opiate Antagonists

Faden, *et al.*,[41,42] showed that naloxone (a nonselective opiate antagonist) improved posttraumatic hypotension, SCBF, and clinical recovery after weight-drop injury in cats and rats; similar findings, except for reversal of posttraumatic hypotension, were reported by Young, *et al.*[50,143] For these reasons, we evaluated naloxone treatment in rats injured by clip compression and found no improvement in SCBF, arterial pressure, cardiac output,[129] or neurological function as assessed by the inclined plane test.[128] Other groups have also reported negative results with naloxone in experimental cord injury.[17,18,65] Faden and Jacobs[40] subsequently focused their efforts on selective kappa opiate receptor blockers.

Calcium Channel Blockers

As noted above, there is evidence that calcium ions play a key role in the pathogenesis of neural injury after trauma or ischemia.[67,73,145] Indeed, intracellular calcium influx has been termed the final common pathway of toxic cell death in the nervous system.[28,108] For example, disruption of cell membranes due to trauma, depolarization of calcium channels due to ischemia,[75] and excitotoxin-mediated activation of calcium channels[89,90] are associated with an intracellular shift of calcium ions. The latter has been shown to promote contraction of vascular smooth muscle resulting in vasospasm and ischemia,[67,75] to impair mitochondrial function,[136] to activate neutral proteases which disrupt microtubular and neurofilament proteins,[12,13,67] to promote axonal degeneration,[109-111] and to activate the synthesis of toxic eicosanoids.[67,87] Several studies have examined the changes in calcium ions after acute spinal cord trauma, and support the role of calcium ions in the pathophysiology of acute cord injury. For example, Happel, *et al.*,[70] showed a twofold increase at 2 hours and a fivefold increase by 5 hours in the total tissue calcium in contused spinal cord. Young, *et al.*,[146] and Stokes, *et al.*,[118] showed marked and persistent decreases in the extracellular concentration of calcium within 2 to 5 minutes of acute cord injury. Young and Koreh[145] and Kwo, *et al.*,[86] using atomic absorption spectroscopy, reported large increases in total tissue calcium at the site of cord injury and postulated a sequestration of calcium ions by inorganic phosphates. Furthermore, perfusion of solutions containing high concentrations of calcium ions onto the spinal cord provokes histopathological and biochemical changes similar to those seen with trauma.[13]

Calcium channel blockers have been studied extensively in the brain where they produce dilation of cerebral vessels and an increase in cerebral blood flow in normal and pathological states including cerebrovascular disease.[5,10,53,92,94,117,126,134] Since the vascular physiology of the spinal cord and brain are similar with respect to autoregulation, the blood-central nervous system barrier, and CO_2 reactivity,[57,58,63] it has been

postulated that calcium channel blockers may be helpful in overcoming posttraumatic ischemia of the cord. Our laboratory was the first to report the effects on SCBF of nimodipine, one of the dihydropyridine group of calcium channel blockers.[62] This agent was chosen because of its known selective action on the cerebral vasculature.[72,117] Indeed, there are several recent positive reports on the use of this drug in cerebral ischemia due to vasospasm following subarachnoid hemorrhage.[97,98]

In normal rats, we measured SCBF, arterial pressure, and cardiac output during intravenous infusion of nimodipine at doses ranging from 0.001 to 1.0 mg/kg. The optimum dose, 0.05 mg/kg, produced a 40% increase in blood flow with only a 25% reduction in mean arterial pressure; larger doses caused more marked systemic hypotension.[62] This optimum dose was then administered to rats with clip compression injury;[61] however, due to the hypotension caused by both cord trauma and nimodipine, it was necessary to administer either whole blood, angiotensin, or adrenaline to counteract the hypotension and maintain the posttraumatic mean arterial pressure at 100 to 120 mm Hg. The combination of nimodipine and adrenaline was the most effective treatment and produced an increase in posttraumatic blood flow. In this experiment, the pressor agent was administered first, followed by nimodipine. In a subsequent study, nimodipine and adrenaline were administered simultaneously and produced a 60% increase in posttraumatic blood flow, whereas adrenaline alone failed to improve blood flow.[64] It is noteworthy that the combination of nimodipine and adrenaline did not significantly increase the amount of intramedullary hemorrhage at the injury site as determined by image analysis. Thus, nimodipine increased posttraumatic SCBF if the arterial pressure was maintained. Other investigators have studied nimodipine in experimental cord injury, including Faden, *et al.*,[43] in an ischemic model in rabbits and Ford and Malm[51] in a modified weight-drop model in cats; both groups found that nimodipine did not decrease the extent of pathological damage or improve clinical recovery. Neither group measured SCBF, and therefore it is not known if they used an optimum dose of nimodipine. Holtz, *et al.*,[74] gave nimodipine to rats for 4 hours after acute cord compression and found no change in SCBF or inclined plane test function 4 days after injury. It may be that the effect of nimodipine had dissipated by the time of measurement. Black, *et al.*,[16] gave nicardipine, another dihydropyridine calcium channel antagonist, to rats injured by the weight-drop technique and found no improvement in behavioral function, but blood flow was not measured.

Our most recent experiment with nimodipine was designed to determine whether an increase in posttraumatic blood flow would improve axonal function as measured by motor and somatosensory evoked potentials.[47] In this study, systemic hypotension was counteracted with dextran; this agent has previously been shown to increase posttraumatic SCBF, cardiac output, and arterial pressure and to produce hypervolemic hemodilution.[131] The combination of nimodipine and dextran, but not dextran alone, produced significant elevation of posttraumatic SCBF and improved axonal function as measured by the evoked potentials. Moreover, the improvement in axonal function was highly correlated with the improvement in blood flow. It is not known if the improved function was due entirely to the blockage of voltage-sensitive calcium channels by nimodipine[112] and subsequent vasodilation,[61,117] or whether there may also have been a direct cytoprotective effect because nimodipine has been found to promote functional and metabolic recovery after experimental cerebral ischemia.[54,88,117,144] Thus, there is now evidence that an increase in SCBF after acute cord injury is associated with improved function of injured axons. It should be noted that treatment was administered for only 1 hour, beginning 30 minutes after injury, and that the beneficial effects had almost completely disappeared within 1 hour of cessation of treatment; these findings may explain the negative findings of Holtz, *et al.*,[74] noted above. Additional studies are under way to determine if the benefits can be maintained by continuing treatment.

Hypervolemic or isovolemic hemodilution produced by agents such as dextran has been used in other ischemic conditions of the nervous system.[84,139] Unfortunately, although hemodilution has been reported to reduce infarct size, it may produce unwanted side effects such as edema,[119] especially when the blood-brain barrier is disrupted.[77] In our experiments we did not specifically assess this possibility; this should be examined in subsequent studies of hemodilution in experimental spinal cord injury.

Steroids

There is evidence that large doses of glucocorticoid steroids improve posttraumatic SCBF and microvascular perfusion[8,68,142] as well as clinical neurological recovery[9] after experimental spinal cord injury. In addition, a recent randomized controlled study in patients showed that high doses of methylprednisolone given within the first 8 hours of acute cord injury improved neurological function.[20] The positive result of this study supports the importance of secondary injury mechanisms in patients with acute spinal cord injury. However, the improvement noted was modest and the study has been criticized on several accounts including the short follow-up period. Further examination of the role of methylprednisolone in acute spinal cord injury is essential.

It has been postulated that the cytoprotective mechanism of action of steroids is inhibition of lipid peroxidation rather than glucocorticoid receptor activation. Thus, it has been hypothesized that other agents such as nonglucocorticoid 21-aminosteroid U74006F, a potent inhibitor of lipid peroxidation,[22] can duplicate or improve upon this action. Recently, Hall[66] showed that

U74006F was effective in reversing posttraumatic spinal cord ischemia in cats after a weight-drop injury.

Elevation of Systemic Pressure

Since the injured spinal cord loses its ability for autoregulation, the systemic hypotension resulting from acute cord injury should be treated to prevent worsening of posttraumatic ischemia. The aim of treating posttraumatic hypotension should be restoration of mean arterial pressure to normotensive levels only, to avoid the possibility of enhancing intramedullary hemorrhage by hypertension and hyperemia.[1,100,102] As noted above, restoration of normotension alone is insufficient to restore posttraumatic SCBF and function.[47,61,64] Additional measures are also required that theoretically could include measures to expand blood volume to counteract the decline in cardiac output or could improve local microcirculation in the cord by counteracting effects such as vasospasm.

Posttraumatic SCBF has been improved by a variety of agents including blood transfusion and dopamine,[32] and the combinations of adrenaline and nimodipine[64] or dextran and nimodipine,[47] with the latter combination also producing functional improvement. It is noteworthy that Hardy, *et al.*,[71] were able to restore somatosensory evoked potentials in cats by producing systemic hypertension with noradrenaline, and similar results were reported by Brodkey, *et al.*,[26] with restoration of normotension. However, the injury model involved static compression without impact.

Other Mechanisms of Secondary Injury

In addition to posttraumatic ischemia, there are several other possible mechanisms of secondary injury including spreading edema,[127] changes in energy metabolism,[7] catecholamine release,[95,96] the production of eicosanoids, arachidonic acid, free radicals, and lipid peroxidation,[21] and the release of excitotoxic amino acids[76,105] (Table 1). Some of these have been discussed above because they have been implicated in the vascular mechanism of secondary injury, but each may cause damage independent of any effects on the blood vessels of the cord. Conversely, one or more of these by-products of trauma may increase the autodestruction by worsening the ischemia initiated by another cause. For example, release of vasoactive eicosanoids from damaged cell membranes at the injury site may account for the progressive worsening of posttraumatic ischemia.

It should be noted that some studies of acute cord injury induced by weight-dropping have not found evidence of posttraumatic ischemia, and therefore do not support the vascular theory.[27,81] Kobrine, *et al.*,[83] found that impulse conduction in the long tracts of the normal cord was "rather resistant to the effects of ischemia," which would diminish the importance of posttraumatic ischemia. However, there is strong evidence that injured axons are much less tolerant to ischemia than are normal axons.[48]

Conclusions

There is a great deal of experimental evidence that the spinal cord suffers a secondary injury following primary mechanical trauma. Of the several postulated mechanisms of secondary injury, the vascular theory has considerable supporting evidence based on biochemical, pathological, angiographic, blood flow, and therapeutic studies. Not all studies support the vascular theory, and variations in injury models, animal species, and experimental design may contribute to some of the conflicting opinions.

The proven vascular changes following acute cord trauma include local effects such as direct disruption of small vessels and hemorrhage, loss of the microcirculation (possibly due to vasospasm), and failure of autoregulation; the systemic effects include hypotension and diminished cardiac output. Posttraumatic ischemia of the cord shows a direct linear dose-response relationship with the severity of injury, is progressive during the first few hours after trauma, and persists for at least 24 hours. Posttraumatic hypotension may be especially damaging after acute spinal cord trauma because of the loss of autoregulation in the cord.

It is suggested that treatment of the secondary vascular injury should be directed toward the local circulatory effects in the cord and the systemic neurogenic shock. Posttraumatic ischemia of the cord should be treated in order to prevent posttraumatic infarction. There are several experimental treatments that have counteracted posttraumatic ischemia of the cord and neurogenic shock. One of the most effective treatments has been the combination of the calcium channel blocker nimodipine and the volume expander dextran, which has resulted in recovery of neurological function. Other effective experimental treatments have included steroids and opiate antagonists.

The exact mechanism of posttraumatic ischemia of the spinal cord is unknown. Further work should be done to elucidate the pathophysiology of this mechanism of secondary injury since knowledge of the exact mechanism would facilitate the discovery of more effective methods of restoring SCBF and improving neurological function in patients with acute spinal cord trauma.

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