CHAPTER 1

Pathogenesis of acute spinal cord injury and theoretical bases of neurological recovery

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Introduction

Experimental models and clinical observations of spinal cord injury (SCI) support the concepts of primary and secondary injury, in which the initial mechanical insult is succeeded by a series of deleterious events that promote progressive tissue damage and ischemia. Whereas the primary injury is fated by the circumstances of the trauma, the outcome of the secondary injury may be amenable to therapeutic modulation. This chapter, derived from a more detailed analysis,[1] reviews the pathogenetic determinants of these two phases of injury and summarizes the bases for interventions that may restore neurological function following SCI.

Pathogenesis

Models of SCI

Several experimental systems have been employed to investigate the pathophysiology of SCI and to test the effects of neuroprotective agents in the laboratory. Interest in such models dates as far back as the 2nd century AD, when Galen sectioned the spinal cord of monkeys and other animals in order to conduct studies on differential spinal lesions.[2] Current experimental paradigms involve neuronal cell cultures or anatomically intact segments of spinal cord subjected to various mechanical or ischemic insults such as weight drop, focal or circumferential extradural balloon compression, clip pressure, photochemical or thermal injury, distractional forces, or piston trauma.[3–10] The resultant injury can be assessed by histological examination (e.g. light or electron microscopy, special staining, and tracing methods), electrophysiological outcome measures (e.g. evoked potentials), or behavioral assessments (e.g. open field locomotion or postural stability on an inclined plane).[6,8,9,11]

Such studies are susceptible to a number of inherent flaws in experimental design that impair their ability to simulate human SCI. For instance, the weight drop method only mimics the trauma of initial impact and omits the force of persistent compression. Whereas most humans suffer anterior or circumferential

cord compression from fracture dislocations of a closed vertebral system, most animal models create posterior compression through an open laminectomy.[2] Animal models may not account for neurogenic shock or concomitant injuries that produce systemic hypoxia and hypotension, factors which are known to aggravate the extent of injury resulting from any given mechanical stress.[12] Also, these models often fail to analyze the effects of repetitive mechanical trauma to the spinal cord from an unstable fracture.[6] Furthermore, few animal studies examine the same range of injury severity that is encountered in human trials, in which patients with both complete and incomplete deficits are often randomized to the same treatment group.

Because of differences in drug metabolism, results in animal models often fail confirmation in human trials. Other variations in experimental methodology, such as the type of species being studied, may also play a role. Unlike human trials, animal studies all require the use of anesthesia, which may affect the response to the substance being tested. Conversely, in the clinical setting, humans receive myriad drugs besides the one being studied, and adverse pharmacological interactions may antagonize the efficacy of the agent in question. Furthermore, neuroprotective therapies are often administered in the laboratory more promptly after injury than may be feasible in clinical practice.

As a result of these discrepancies in drug kinetics, the inability to extrapolate the results of animal models to the human condition does not necessarily invalidate the potential utility of the agent being tested. However, these factors contribute to conflicting or irreproducible results in the literature and hinder attempts at constructing a unified theory of pathogenesis and treatment in SCI.[13]

Despite these limitations, laboratory models have proven relevant to human SCI. Developments in the fields of basic neuroscience, including studies of the cerebral cortex and spinal cord, support the theory that the central nervous system (CNS) responds to injury in an archetypal fashion, whether the inciting insult represents trauma, hypoxia, hypoglycemia, epilepsy, various toxins, neurodegenerative disorders, or other pathophysiological processes.[14–20] The concepts of primary and secondary injuries, first advanced over 80 years ago, have emerged as an explanation for this phenomenon of a rehearsed mechanism of neuronal death. According to this paradigm, the initial mechanical insult in SCI is succeeded by a series of deleterious events that promote progressive tissue damage, largely mediated by ischemia and aberrant calcium influx into neurons. While the primary injury is fated by the circumstances of the trauma, the outcome of the secondary injury may be amenable to therapeutic modulation.

Determinants of primary injury

SCI may follow many types of trauma to the cord itself or to the surrounding vertebral column, and the extent of subsequent damage depends on several biomechanical factors that may be unrelated to the degree of bony fracturing.[21,22] Distractional forces associated with flexion, extension, dislocation, or rotation can all result in stretching or shearing of the neural elements themselves or

spinal cord vasculature, and damage to either substrate could incur clinical deficit.[3,21,22] Other possible mechanical stresses include compression and contusion from bone fragments, ligaments, and hematoma within the spinal canal. These mechanisms may be responsible for cord injury even when the bony alignment appears normal at the time of admission. For instance, momentary dislocation may occur from ligamentous disruption, resulting in transitory cord compression or distraction. These distortions are substantially greater than what is depicted by initial radiographs, since soft tissue elasticity and postural influences tend to initiate spontaneous recoil, and muscle spasm tends to maintain the reduction by the time such radiographs are taken.

These forces may be operant not only acutely, at the moment of injury, but also chronically, secondary to persistent deformity. Mechanical instability can lead to further structural deformations, such as posttraumatic kyphosis or subluxation, which add additional compressive or distractive forces and result in worsening neurological deficit. Kyphosis, for instance, has been shown to cause tension within axonal tracts and constriction of intramedullary blood vessels.[3,21]

For any force applied to the neural elements, the extent of subsequent injury also depends on the relative dimensions of the spinal canal at that level. Whereas larger canals might provide a buffer for any given mechanical stress, stenotic canals lack such reserve. Thus, 53% of fractures of thoracic spine result in neurological injury compared with only 39–47% in the cervical region.[1,23] Similarly, one study revealed a much higher likelihood of complete injury resulting from lesions of the thoracic region (77.5%) than the cervical (60.4%) or thoracolumbar junction (64.7%) regions.[22] This discrepancy probably relates to the narrower canal of the thoracic spine, such that the degree of cord compression tends to be more severe for any given encroachment, as well as the relative paucity of blood flow to the thoracic cord.[21–23] Likewise, Eismont measured the midsagittal canal diameter in patients with fracture dislocations of the cervical spine and found that those with smaller canals were prone to more significant neurological injury, while larger canal diameters afforded a protective effect.[24] Other studies have shown that the relative stenosis incurred by cervical spondylitic disease predisposes to SCI following minor trauma, even in the absence of detectable bony injury.[3,22]

The anatomic location of injury in relation to the conus medullaris also seems to have some prognostic significance. Cauda equina injuries have a better prognosis for neurological recovery than comparable injuries to the spinal cord itself, since lower motor neurons are inherently more resistant to trauma, with fewer mechanisms of secondary injury and greater regenerative capacity than upper motor neurons and their tracts.

Determinants of secondary injury

In addition to local forces that potentially compromise spinal cord function, systemic pulmonary and cardiac factors that determine tissue oxygenation and perfusion can profoundly modulate the extent of injury resulting from

any given mechanical stress.[12] Taken together, these considerations of local and systemic influences imply that ischemia underlies much of the mechanism of posttraumatic SCI. While other pathological processes such as edema, intramedullary hemorrhage, axonal degeneration, or demyelination may also play a role, these all have an integral relationship with impaired cord perfusion and bioenergetic failure at the cellular level. Experimental models employing the basic mechanisms of both compression and distraction have confirmed that SCI is associated with long-lasting ischemia that parallels the force of the experimental insult and the severity of the clinical deficit.[3,9,10,25,26] The ischemia is worse in the gray matter and may extend focally for considerable distances rostral and caudal to the injured segment.[3,8,9,12,25,26] The impaired perfusion may be followed by a phase of "hyperemia" or "luxury perfusion" due to the reduction of perivascular pH from accumulation of acid metabolites such as lactate.[26] This tissue reperfusion may increase cellular damage by promoting the influx of free radicals and other toxic byproducts.[18]

The intrinsic mechanisms occurring during SCI have been well documented and are schematically diagrammed in Figure 1.1.[1] In the initial phase, petechial hemorrhages develop within the spinal cord substance due to rupture of postcapillary venules or sulcal arterioles, either from mechanical disruption by the inciting force itself or from intravascular coagulation due to fibrin and platelet thrombi leading to venous stasis and distension.[8,10,12,21,27] Leakage of proteinaceous fluid from the intrinsic vessels of the cord then leads to edema at the injury site and surrounding tissues.[8,26] Because the spinal cord is contained within a relatively inelastic pial membrane, edema produces increased interstitial pressure that may diminish local spinal cord blood flow.[2] Vasoactive substances released by injured cells, including endothelin released from damaged capillaries, and other mechanical, biochemical, or neurogenic mechanisms may also play a role in impairing cord perfusion.[8,12,26–28] Focal narrowing, disruption, aneurysmal dilation, or occlusion of sulcal arterioles and intramedullary capillaries have all been demonstrated with the use of microangiographic techniques and three-dimensional vascular corrosion casts.[27,28] These changes may represent the morphological correlates of microvascular spasm, thrombosis, and rupture that underlie regional impairments in spinal cord perfusion. This focal ischemia is compounded by hypotension or hypoxia, since autoregulation is lost in SCI and spinal cord blood flow passively follows alterations in systemic hemodynamics.[8,9,12,21,26]

Ischemia initiates a cascade of secondary pathogenetic mechanisms collectively known as excitotoxicity because of their dependence on endogenous excitatory amino acid (EAA).[15,20] Ischemia depletes the supply of adenosine triphosphate (ATP), leading to dysfunction of energy-dependent processes such as the sodium–potassium pump that preserves cellular homeostasis. Ionic species then move passively across the cell membrane according to concentration gradients previously maintained between the intracellular and extracellular spaces, leading to a net efflux of potassium and a large influx of sodium, chloride, and calcium into the cell. Acute cellular swelling results. Furthermore,

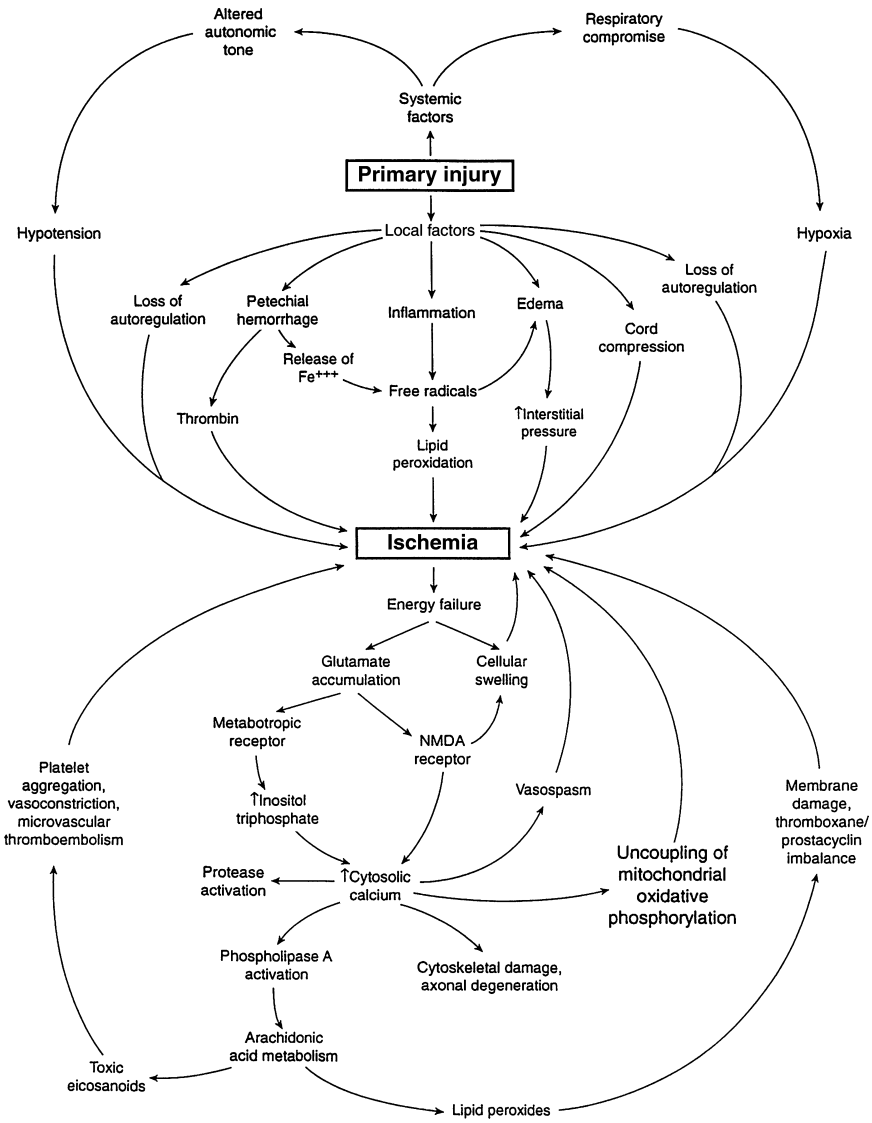

Figure 1.1 Schematic representation of key mechanisms, molecular species, and interrelationships underlying the pathogenesis of acute SCI. Principal pathways of secondary injury that converge upon ischemia are emphasized, while others have been omitted for simplicity. These pathogenetic determinants represent the logical targets for therapeutic modulation (reprinted with permission from Ref. [1]).

the altered composition of the extracellular and intracellular spaces leads to changes in membrane polarization that promote the release of EAA neurotransmitters such as glutamate and aspartate from synaptic vesicles. This release is compounded by impaired cellular uptake mechanisms in neurons and glia,

which depend on the presence of high-energy phosphates and are inactivated by the ATP depletion accompanying hypoxia.[14,29,30] As a result of these two mechanisms, the local concentration of glutamate in the extracellular space can increase by a factor of eight following an ischemic insult.[14,30]

Extracellular accumulation of glutamate may also occur through non-ischemic mechanisms. The intracellular glutamate concentration in brain tissue is approximately 10 mmol/l, while its extracellular concentration is normally only 0.6 μmol/l.[18] Excitotoxic damage to neurons can occur when the latter concentration reaches 2–5 μmol/l.[18] Thus, ambient glutamate concentrations are precariously close to those that can destroy neurons, and the injury of even a single cell from direct traumatic mechanisms could produce a local accumulation of glutamate that places neighboring cells at risk for excitotoxic damage.[18] Although the glutamate concentrations within the spinal cord are less well documented, they may approximate those found in the brain. Glutamate receptors have been demonstrated in both the dorsal and ventral horns, and many pathways mediating locomotion and nociception, including the corticospinal and rubrospinal tracts, appear to rely on EAA neurotransmitters.[31] Extracellular EAA concentrations within the spinal cord have been shown to reach toxic levels 15 min after experimental SCI.[31]

Glutamate may act upon several families of receptors, each with distinct pharmacological and electrophysiological properties.[18,20,29] These receptor classes are named for the agonist compounds that selectively activate them. Some of these receptors, such as the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate receptors, are collectively termed "ionotropic" because they comprise ligand-gated ion channels. Others are termed "metabotropic" and comprise transmembrane proteins coupled with changes in the concentration of intracellular second messengers such as cyclic nucleotides or phosphoinositol through GTP-binding proteins.

Although activation of the AMPA and kainate receptors results primarily in the influx of sodium from the extracellular space, some subtypes may be permeable to calcium as well. In contrast, the NMDA receptor principally mediates calcium entry. The NMDA receptor contains a binding site for glycine, which acts as an obligate co-agonist. Furthermore, at resting membrane potential, inward current through the NMDA receptor is prevented by voltage-dependent blockade of its ion channel by magnesium, even if the glutamate and glycine sites are occupied. However, the degree of this magnesium blockade is reduced as the neuron becomes depolarized. Thus, any process which impairs the neuron's ability to maintain its normal membrane potential, such as bioenergetic defects or simultaneous activation of the AMPA receptor, can lead to electrophysiological decoupling that causes additional calcium influx through the NMDA receptor, even in the face of ambient glutamate concentrations. Membrane depolarization also promotes calcium entry through activation of voltage-dependent calcium channels. Finally, glutamate can trigger the accumulation of intracellular calcium through activation of metabotropic receptors, leading to the metabolism of inositol phospholipids and mobilization

of intracellular calcium stores as well as inactivation of energy-dependent calcium transporters that pump cytosolic calcium across the cell membrane or sequester it within intracellular compartments such as the mitochondria and endoplasmic reticulum.[14,18–20,29]

These aberrant calcium fluxes trigger a myriad of calcium-dependent processes, such as activation of phospholipase A2, mobilization of free fatty acids, synthesis of toxic eicosanoids, generation of free radicals, further depletion of energy reserves through activation of calcium-dependent ATPase, covalent modification of receptor proteins, modification of the microtubular and neurofilament components of the cytoskeleton, impairment of mitochondrial oxidative phosphorylation, axonal degeneration, and activation of lytic enzymes such as proteases, phosphatases, and endonucleases.[14,18–20,25] This sustained elevation of cytosolic calcium concentration is postulated to be the final common pathway mediating cell death in many tissue types.[14–16,18–20]

Potentiating factors in this sequence of events include increased phospholipase activity, either from direct mechanical stimulation or from mobilization of calcium, resulting in the liberation of free arachidonic acid from membrane phospholipids.[25,32] This substrate is rapidly metabolized by cyclo-oxygenase to prostanoids such as thromboxane and prostacyclin. Thromboxane stimulates platelet adherence to endothelium, intravascular platelet aggregation, microvascular occlusion, vascular stasis, microvascular thromboembolism, and vasoconstriction; prostacyclin has the opposite effects on the microcirculation. Other byproducts of the cyclo-oxygenase pathway include free radicals such as lipid peroxides. These latter molecules selectively inhibit prostacyclin production, and the resultant thromboxane–prostacyclin imbalance contributes to an environment favoring thromboembolism and a tendency toward further ischemia.[25,32]

In addition to altering the ratio between thromboxane and prostacyclin production, lipid peroxides interact with polyunsaturated fatty acid components of the cell membrane to cause a chain reaction of phospholipid peroxidation that compromises the structural and functional integrity of the cell membrane and, ultimately, produces cell death.[25,33] Free radicals may also directly damage the nervous tissue's vascular integrity, cellular proteins, and nucleic acids. Besides cyclo-oxygenase, other enzymatic sources of free radicals include xanthine oxidase, which catalyzes production of the superoxide anion and hydrogen peroxide in response to CNS ischemia.[34] Because this enzyme is located primarily in the endothelial cells, the oxygen-derived free radicals induced by the xanthine oxidase system act primarily at the capillary level, altering vascular permeability and worsening posttraumatic edema.[34] Reactive iron species contained within the hemoglobin of extravasated blood may also act as a catalyst of free radical formation and lipid peroxidation reactions.[2] The subsequent release of these substances into the local environment as the cellular and vascular barriers disintegrate can impair neighboring cells and result in progression of deficit.

One limitation of this paradigm is that the excitotoxic model cannot directly account for injury to the white matter and glial elements of the CNS. Although

ischemic damage is commonly observed in this tissue, most studies have failed to demonstrate that axons, myelin, astrocytes, and oligodendrocytes are endowed with NMDA receptors or are vulnerable to glutamate administration.[29] However, the concept of a "bad neighborhood" resulting from the local accumulation of lytic enzymes, free radicals, and other toxic factors derived from glutamate-mediated injury in adjacent neuronal tissue may explain the pervasive effects of focal CNS ischemia.[15,25] Furthermore, some studies suggest that periaxonal astrocytes may express certain subtypes of the AMPA and kainate receptors on their surface, thus implicating these cells in glutaminergic white matter injury.[35]

In the ensuing phases of SCI, inflammation and demyelination prevail. Two waves of peripheral leukocytic influx occur. In the early peak, neutrophils predominate, and their lytic enzymes may further damage vascular, neuronal, and glial cell populations.[2] Later, macrophages participate in the phagocytosis of hemorrhagic and necrotic tissue. Both phases of inflammation have been implicated in the demyelination of spared axons, which starts within the first 24 h after injury and increases over the next several days.[2] Well-demarcated areas of cavitation within the gray and white matter, extensive Wallerian degeneration, and scarring represent the final stages of histopathological evolution.[2] Although this scar is predominantly comprised of astroctyes and other glia, fibroblasts also make a significant contribution.

Theoretical bases of neurological recovery

Although the propensity for neurological improvement following both complete and incomplete SCI has been verified by experimental models and clinical observations, the biological basis of such recovery remains enigmatic. As Tator has suggested, functional restoration probably involves a combination of several different processes acting upon numerous anatomical substrates, including nerve roots at the level of injury, gray and white matter, and spinal cord vasculature.[11] Neural regeneration, the regrowth of lesioned neural elements with the restoration of functional synaptic connections, may account for late recovery occurring months to years after injury.

Root recovery

Several studies have confirmed that the peripheral nervous system is more resistant to injury and has a greater capacity for repair than the CNS.[2,11] This resilience is manifested by the frequency with which improved nerve root function is detected among patients with acute SCI. Re-establishment of segmental function at the site of injury, reflecting recovery in one or more nerve roots at that level, may restore innervation to particular muscle groups, organs or dermatomes, although motor roots generally have increased vulnerability to injury and decreased capacity for recovery than sensory roots.[11] Root recovery is expected in both complete and incomplete lesions in 66–90% of patients.[36] However, the greatest proportion of total neurological recovery occurs caudal

to the level of injury, reflecting improvements in the function of long spinal tracts themselves.

Resolution of cord ischemia

Surrounding the zone of irreparable ischemic damage is a penumbra of hypoxic tissue, whose cells may remain viable, even while lacking the capacity to maintain normal neuronal function. This tissue may be marginally supported by collateral circulation. If the ischemia exceeds a critical level, or persists beyond a certain threshold of time, irreversible damage will ensue and the zone of infarction will extend. If, however, blood flow can be restored before the onset of permanent injury, normal physiological function may be re-established.

Salvage of the ischemic penumbra can result from both medical and surgical interventions. Autopsy reports have shown that in most cases of SCI, including complete injuries, the cord remains anatomically intact.[2,9] Furthermore, animal studies of SCI suggest that preservation of a small proportion of spinal axons can support neurological recovery.[2,10,37] In a rat model, for instance, persistence of only 12% of the normal number of axons following clip compression injury conferred substantial maintenance of inclined plane performance and open field walking.[5] Thus, any manipulation that increases the fraction of functional axons traversing the injury site above this threshold, or that enhances the response of lower motor neurons to the attenuated input from those axons, can have a significant impact on neurological recovery.[10,37] Alternatively, since injured vasculature of the CNS tends to lose its autoregulatory response to hypertension, spinal cord blood flow could be increased passively by improving systemic hemodynamic parameters or selective infusion of CNS vasodilators.[8,12,26]

The central gray matter of the spinal cord is inherently more susceptible to trauma because it has higher metabolic activity and because it contains neuronal bodies whose machinery for biomolecular repair may be directly damaged. In contrast, the circumferential white matter tracts at the site of injury have a lower metabolic rate and have intact cell bodies that are distant from the locus of injury.[37] Thus, delayed pharmacological and physiological interventions are more likely to restore function to the white matter elements of the cord. Metabolic factors may also underlie the fact that motor tracts have increased vulnerability to injury and decreased propensity for recovery than sensory ones.[11]

Resolution of other injury events

Abnormalities of membrane polarization and excitability may accompany acute SCI. These changes in ionic equilibrium could result from the leakage of potassium into the interstitial fluid or from alterations in sodium permeability across the axolemma.[38,39] Such electrolyte shifts might underlie the early neuronal dysfunction associated with spinal shock and may account for the immediate inability to conduct action potentials across the injury segment.[38,39]

With time, however, restoration of the normal sodium and potassium gradients may re-establish impulse conduction in the long tracts and produce features of clinical recovery.[11] Spontaneous resolution of other processes, such as intramedullary hemorrhage, edema, and inflammation, are also likely to improve neurological outcome.[11]

Neural plasticity

Neural regeneration, the regrowth of lesioned neural elements with restoration of functional synaptic connections, has been the topic of intense experimentation over the past decade. Although the inability of injured CNS tissue to regenerate was traditionally considered an inviolable "law of nature," it now appears that many therapeutic interventions can promote the crucial aspects of neurite outgrowth, guidance, target recognition, and synaptic stabilization.[2] Current knowledge concerning the theoretical foundations of inducing regeneration following SCI and the practical limitations to its implementation have been reviewed elsewhere.[2,11] The reparative process depends on a complex interplay of cellular elements, extracellular matrix (ECM) components, paracrine hormones, and other factors.

Cellular elements

Following SCI, Schwann cells of peripheral nerve origin can migrate along the dorsal and ventral spinal roots and invade the cord parenchyma.[2,40,41] There, they may proliferate and foster many mechanisms of neuronal regeneration, including remyelination of CNS axons, which has been shown to restore action potential conduction through lesioned central pathways.[2,11,35,40–43] In addition, they may produce various neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor.[43] Finally, they play an important role in axonal guidance.[44] The versatility of these salutary properties forms the rationale for various attempts at transplanting Schwann cell populations into sites of CNS injury. In 1911, fibers of the cerebral cortex were found to grow along the denervated Schwann cell bands of peripheral nerve grafts.[2] More recently, transplantation of peripheral nerve segments into the injured spinal cord have provided bridges along which CNS axons can extend for up to several centimeters.[45,46] Purified Schwann cell implants, injected as suspensions or as guidance channels supported by a semipermeable membrane, have served as similar substrates for regenerating CNS fibers following spinal cord transection.[2,44]

The proliferative, migratory, and regenerative capacities of ependymal cells have also been recognized. These properties underlie much of the spontaneous repair following traumatic SCI in lower animals.[11] In the newt, for instance, ependymal cells proliferate in the stump of an amputated tail and form a scaffold that directs the growth of regenerating central fibers while in the rat, invagination of proliferating sheets of ependymal cells by growing axons after spinal cord transection provides morphological evidence for a similar

neurotrophic role in mammals.[41,47] Recently, a self-renewing population of mitotically active, multipotent neural stem cells has been recovered from the central canal of the adult mammalian spinal cord.[48] While such progenitors may impede regenerative attempts by contributing to the glial scar, Tator and others have speculated about their therapeutic potential as well, either through stem cell transplantation or application of exogenous growth factors that promote neuronal differentiation.[11,48,49]

Although the proliferative potential of oligodendrocytes remains uncertain, it is clear that surviving cells extend new cytoplasmic processes that can remyelinate adjacent axons.[40] Because this process is typically incomplete, future strategies that enhance recruitment, expansion, and migration of the quiescent oligodendroglial population may play a significant role in therapeutic attempts at inducing neural regeneration.[2]

The lesion scar representing the final stage of histopathological evolution following SCI has historically been regarded as an impermeable barrier to neurite outgrowth. More recent evidence suggests that astrocytes, which comprise the predominant cellular elements of this scar, may engender aspects of regeneration as well.[2,44] Membrane proteins, ECM components, and soluble factors expressed by the astrocyte all contribute to the complexity of these growth-promoting and growth-inhibitory effects, and the biochemical composition of the lesion scar awaits further characterization. In general, attempts at manipulating the lesion scar, such as the injection of pyrogens or collagenase or the use of spinal cord irradiation to reduce scar formation, have only achieved limited success in enhancing neural regeneration.[2]

ECM components

Several molecules normally found in the ECM contribute to a local microenvironment favoring neurite elongation and guidance. Fibroblasts, Schwann cells, and macrophages that migrate to sites of cord injury, as well as astrocytes residing within the glial scar, can all deposit various components of the ECM.[2] Schwann cells, for instance, synthesize and secrete laminin, which is known to modulate neurite outgrowth, as well as heparan sulfate proteoglycans, type IV collagen, and other components of the basal lamina associated with the peripheral axon–myelin unit.[43,44] This cell's ability to ensheathe and myelinate axons is entirely dependent on deposition of the basal lamina, and if the latter process is interrupted by conditions preventing the formation of ECM components (e.g. ascorbic acid deficiency, which impairs collagen production), myelination will not occur.[43] Conversely, neural regeneration could theoretically be enhanced by interventions which induce the formation of these crucial ECM proteins.

Paracrine and humoral factors

In newborn rats, rubrospinal and corticospinal neurons undergo massive cell death following axotomy, but injections of BDNF or neurotrophin-3 (NT-3) can largely counteract this event.[2] Similarly, the collateral sprouting response of transected corticospinal tract fibers in adult rats can be significantly enhanced

by soluble factors elaborated by embryonic spinal cord grafts or local application of NT-3.[2,50] Likewise, topical administration of NGF to corticospinal tract axons following spinal cord transection in adult rats partially restores the pattern of regenerative behavior typical of newborn animals, characterized by the induction of axonal sprouting and elongation.[51]

These experiments provide compelling evidence for the existence of endogenous trophic factors that can promote neurite regeneration. In addition, much attention has been focused toward identifying the nonpermissive factors that ordinarily impede this process. It appears that CNS myelin and oligodendrocytes are associated with a number of potent growth-inhibitory factors, including membrane-bound proteins, glycolipids such as galactocerebroside, and glycosaminoglycans.[2] Monoclonal antibodies directed against some of these molecules can neutralize the inhibitory effects and facilitate the elongation and sprouting of transected axons which otherwise would not regenerate.[2,50]

The complementary actions of these two treatment approaches suggest that future therapeutic strategies may combine the use of neurotrophic factors with antibodies against CNS myelin-associated neurite growth inhibitors.[50,51] However, these high molecular weight proteins are unlikely to cross the blood–CNS barrier after systemic administration. Furthermore, they may only demonstrate efficacy after prolonged administration.[11] For these reasons, intrathecal delivery or direct parenchymal injection is typically required.[11] A phase 1 clinical trial was undertaken to study the pharmacokinetics of intrathecal ciliary neurotrophic factor in four patients suffering from amyotrophic lateral sclerosis. Although a therapeutic benefit could not be demonstrated, the study confirmed the feasibility of chronic intrathecal administration of recombinant neurotrophic factors through the use of a drug pump, suggesting potential applicability for future SCI therapies as well.[52]

Rationale for therapeutic intervention

Comprehension of the pathogenetic determinants of SCI, the theoretical bases of neurological recovery, and the principles of neural regeneration establish the foundation for rational therapy. Emerging concepts of the CNS response to injury have engendered much interest in the potential for mitigating secondary damage and restoring neurological function through both pharmacological and surgical interventions.[1]

Pharmacological strategies

The molecular events outlined above that represent logical targets for pharmacological modulation include glutamate accumulation, aberrant calcium fluxes, free radical formation, lipid peroxidation, and generation of arachidonic acid metabolites. Because of the complexity of these processes, numerous strategies have been devised. Although many therapeutic agents show promise in animal models, only methylprednisolone has been proven in large,

randomized, double-blinded human studies to enhance the functional recovery of neural elements following acute SCI.[1]

It has been demonstrated that pharmacological agents must be given within a narrow window of opportunity in order to be effective. In fact, it has been proposed that paramedical personnel administers a bolus of methylprednisolone to suspected SCI victims in the field, but the clinical utility of this practice remains unproven.

The cascade of events that lead to impaired spinal cord perfusion is complex, and the diversity of molecular species that converge upon cord ischemia suggests that future therapies must consist of various combinations of these agents, each directed toward counteracting a different aspect of pathogenesis. Detailed preclinical studies must precede such therapy, because of potential drug interactions that may undermine the efficacy of already proven strategies. For instance, gangliosides have been shown to block some of the neuroprotective effects of methylprednisolone; similarly, the combination of naloxone and methylprednisolone increased mortality in some spinal-injured animals.[53,54]

The effects of glucocorticoids, lazeroids, gangliosides, opiate antagonists, calcium channel blockers, glutamate receptor antagonists, antioxidants, free radical scavengers, and other pharmacological agents in both animal models and human trials are summarized in the next chapter and elsewhere.[1]

Operative strategies

In vitro studies, animal models, and clinical outcome analyses of SCI have all failed to yield incontrovertible guidelines that define the role of surgery in the comprehensive management of the cord-injured patient. As a result, there is no consensus regarding the necessity, timing, nature, or approach of operative intervention. Intuitive hunches and anecdotal accounts have not been consistently corroborated by scientific studies, and individual or institutional preferences abound. Because of numerous methodological limitations, including ethical concerns about withholding potentially beneficial treatments to victims of SCI, it has not been feasible to subject such theories to prospective, randomized, controlled trials. Thus, the majority of the extant literature consists of retrospective analyses of unrandomized case series. The benefits of surgical intervention as opposed to natural history are difficult to discern from these papers.[55]

Historically, neurosurgical treatment of SCI has been confined to the mechanical elements of decompressing or stabilizing the vertebral column that surrounds the damaged cord. The controversies pertaining to these interventions are scrutinized in subsequent chapters of this book.

Recent advances in molecular and cell biology, however, suggest possible roles for surgical manipulation of the cord itself. For instance, neural transplantation has been employed as a strategy to modulate the milieu of the injured cord and enhance its endogenous reparative potential. Tissue sources for transplantation have included peripheral nerve grafts, dorsal root ganglia,

Schwann cells, olfactory ensheathing cells, adrenal tissue, and fetal spinal cord tissue.[56–58]

The exact mechanisms by which transplanted tissue may induce functional recovery remain unknown. Neural grafts may act as a bridge or scaffold for the passage of host axons that regrow and find appropriate targets caudal to the lesion. Alternatively, transplanted neurons may integrate into the host spinal cord and establish new synaptic connections, thereby restoring intraspinal circuitry or acting as a relay between supraspinal pathways and intrinsic central pattern generators within the caudal stump. Remyelination of anatomically intact, but functionally disrupted axons may enhance action potential conduction across the lesion. Lastly, the graft may elaborate neuroprotective factors that mitigate against axonal retraction and promote the survival or regeneration of host neuronal tissue.

Conclusions

The concepts of primary and secondary injury are well established and have broad implications for the treatment of acute SCI. The notion of SCI as a momentary, irreversible event has been supplanted by that of a dynamic and complex process amenable to therapeutic manipulation at each stage. Whereas the optimal timing of surgical interventions such as decompression remains a matter of debate, it appears that the pharmacological strategies aimed at mitigating secondary injury must be implemented within a narrow window of opportunity after trauma. The theoretical efficacy of these therapies warrants cautious optimism about the prognosis of acute SCI, and it is no longer tenable to consider it an ailment "not to be treated (see preface)".

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