Pharmacologic Management of Acute Spinal Cord Injury

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KEYWORDS

• Spinal cord injury • Secondary injury • Neuroprotective agent • Neuroregenerative agent
• Methylprednisolone • Central nervous system

KEY POINTS

- The recognition of delayed, progressive damage to the spinal cord after injury, termed secondary injury, provides a rationale for therapeutic intervention.
- Methylprednisolone is the most extensively studied therapeutic agent for acute spinal cord injury, and it remains a treatment option despite controversy.
- Numerous neuroprotective or regeneration-stimulating agents are in human trials and hold great promise for improving neurologic recovery after acute spinal cord injury.

INTRODUCTION

Spinal cord injury (SCI) has a global incidence of 10.4 to 83.0 cases per million per year, with most cases resulting in incomplete injury and permanent disability.[1,2] After the initial SCI, a complex pathophysiological process involving multiple molecular mechanisms ensues, which causes further damage for months and even years after the initial injury. The notion of inhibiting this secondary injury provides the possibility of neuroprotection and, to this end, numerous therapeutic targets have been identified. Moreover, we have learned of various inhibitors of central nervous system (CNS) regeneration that might be targeted therapeutically to improve recovery from SCI. This review discusses various historical and contemporary medical treatments investigated in humans for the treatment of acute SCI.

MECHANISMS OF SPINAL CORD INJURY

Two stages of SCI first conceptualized by Allen[3] in 1911 are now recognized, although this paradigm was not generally accepted by the scientific community until recently. *Primary injury* refers to the initial traumatic impact to the spinal cord resulting in neuronal damage (**Table 1**).[4,5] Injury to neurons can involve shear, laceration, contusion, and compression, and there can be acute stretch of neurons, glia, and spinal cord vasculature. Full anatomic disruption (or transection) rarely occurs in SCI; approximately 50% of patient cases show complete injury and 50% show incomplete injury, although the ratio can greatly vary depending on the study evaluated.[2,6] Trauma to the spinal cord can occur from the force of the trauma along with disruption of bone, muscle, or ligaments with associated cord contusion. *Secondary injury* involves the delayed progression of injury occurring weeks to months after initial trauma and is defined by complex and highly interrelated molecular processes that progressively damage CNS tissue.[1,7,8] *Secondary insults* are distinct from secondary injury and represent systemic events resulting in insufficient nutrient supply to the spinal cord.[9] These events

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Table 1
Summary of injury mechanisms in spinal cord injury

Category	Timing	Mechanism
Primary injury	Seconds	Compression, laceration, distraction, shearing, contusion, transection, stretching
Secondary injury	Seconds-minutes	Hemorrhage, decreased adenosine triphosphate, increased lactate
	Hours	Vasogenic and cytotoxic edema, microvessel vasospasm, thrombosis, ionic excitotoxicity, loss of Na/K gradient, release of neurotoxic opioids, inflammatory cascade, lipid peroxidation, glutamatergic excitotoxicity, oxidative stress
	Days/weeks	Microglial stimulation, gliosis, macrophage activation, apoptosis

most commonly include hypotension and hypoxia.

Secondary injury involves a complex interrelated signaling cascade and tissue changes causing continued damage long after the primary injury has ceased. These injurious cascades can theoretically be targeted by pharmacologic therapies, but there has been little success with this to date.[1,2] The timing of the various types of secondary injury after SCI can vary (see **Table 1**). Cellular insults involve vasospasm, localized ischemia, oxidative stress, reperfusion injury, and ischemia during compromise of spinal cord vasculature.[10] Ischemia involves insufficient oxygen supply to meet metabolic demands. Diminished production of adenosine triphosphate (ATP) causes dysfunction of energy-dependent sodium-potassium channels resulting in cytotoxic intracellular edema and ion-mediated cell damage. Intracellular acidosis also results in cellular enzymatic dysfunction, including diminished DNA repair. Elevation of intracellular calcium levels can cause myelin dysfunction,[11] as well as the inactivation of beneficial antioxidant enzymes and activation of those that are injurious to the cell, such as calpain, caspases, and nitric oxide synthase. This can ultimately lead to cell death through apoptosis.[12] Mitochondrial dysfunction also can be triggered by elevated intracellular calcium, and this causes increased mitochondrial permeability through mitochondrial permeability transition pores. This generates free radicals, which cause oxidative stress, and it impairs the ability of mitochondria to generate ATP.[13] Neuroinflammatory cascades and immune dysregulation also follow SCI.[14] Upregulation of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukins, and interferons, can induce aberrant cell signaling. Immune cells, such as microglia, T cells, neutrophils, and monocytes, can invade the injured area following SCI. Spinal cord inflammation is a challenging therapeutic target, as it can both improve and inhibit recovery. For instance, the inflammatory response can clear myelin debris, which inhibits axonal regrowth, but it can also produce injurious free radicals.

A large body of recent research has improved understanding of the mechanisms governing impediments to SCI recovery and regeneration.[1,2] Targeting these inhibitors to regrowth following SCI is a promising therapeutic approach for SCI. Cells from the CNS have long been known to show diminished capacity for regeneration compared with those of the peripheral nerves. In a landmark study, however, axons from the CNS demonstrated the ability to grow through peripheral nerve grafts. This demonstrates that the CNS has greater capacity for regeneration than previously believed.[15–19] As CNS axons have demonstrated an ability to regenerate, this implies that the CNS environment inhibits this inherent regenerative capacity. This premise inspired work from Schwab and others, which led to the identification of molecules inhibiting regeneration in the CNS, including Nogo,[19] myelin-associated glycoprotein (MAG),[20] oligodendrocyte myelin glycoprotein (OMgp),[21] semaphorin 4D,[22] ephrin B3,[23] repulsive guidance molecule,[24] chondroitin sulfate proteoglycans (CSPGs),[24] and Netrin-1.[25] The family of myelin-associated inhibitor (MAI) proteins includes 3 classic members, including Nogo-A, MAG,[20] and OMgp.[21,26] These bind to shared receptors, namely Nogo-66 receptor-1 (NgR1) and paired immunoglobulin-like receptor B (PirB), to regulate cytoskeletal dynamics and inhibit growth.[27] Downstream molecules inhibiting axonal growth, including RhoA and its effector kinase, ROCK, also have been discovered to impact nerve regeneration.[28] In addition, glial scarring after injury can serve as a physical barrier to