EDITORIAL

Acute spinal cord injury (SCI), which predominantly occurs in younger individuals, represents one of the most devastating events that can occur in a person's life. The vast majority of SCIs, whether they completely or incompletely interrupt the flow of neurophysiological impulses to and from the brain, result in life-changing disabilities that require major adjustments on the part of the individual and their family members and friends. However, a primary impetus for research aimed at lessening post-SCI damage to the injured spinal segment and improving neurological recovery is derived from the fact that most SCIs do not involve actual physical transection of the cord, but rather a contusive, compressive, and/or stretch injury that initially leaves the spinal cord anatomy largely intact. However, within the first minutes, hours, and days after this type of blunt SCI, a complex cascade of pathophysiological events occurs, which leads to secondary injury to the spinal cord tissue that is responsible for most of the post-SCI neuropathology and permanent loss of function.

For the past 4 decades, many of the molecular mechanisms involved in this secondary injury cascade have been revealed, along with the discovery of pharmacological or other therapies that target one or more secondary injury events, preserve spinal cord tissue, and improve neurological recovery in animal models of SCI. Based on this "neuroprotective" strategy, the first and only treatment to date that has demonstrated a significant improvement in neurological recovery, in a multicenter, randomized, placebo-controlled clinical trial in human SCI, has been high-dose methylprednisolone (MP) (National Acute Spinal Cord Injury Study II) [1–3]. This landmark trial was inspired by the multiple studies carried out in the 1980s by Hall, Braughler, Anderson, and Means in cat SCI models. They documented the ability of high-dose MP, intravenously administered, to protect the contused or compressed spinal cord, together with the inhibition of oxygen free radical-induced lipid peroxidation (see review by Hall and Springer [4]). Although, the National Acute Spinal Cord Injury Study II trial and its interpretation have been repeatedly critiqued since its publication in the early 1990s [1–3] and the risk-to-benefit ratio of high-dose MP treatment has been questioned, the fact remains that it represents the only available acute neuroprotective treatment for SCI, and its modest level of protective efficacy has continued to inspire the search for safer and more effective acute treatment approaches. In that regard, this issue of *Neurotherapeutics* contains multiple articles that review promising neuroprotective mechanistic avenues, some of which are moving toward clinical translation.

Based on the strong validation of the role of free radicals in secondary injury by high-dose MP, newer antioxidant approaches are discussed by Hall [5]. This is followed by a presentation by McEwen, Sullivan, Rabchevsky, and Springer [6] detailing the increasingly appreciated involvement of mitochondrial dysfunction and novel mechanisms for pharmacologically augmenting the resistance of the injured spinal cord mitochondrion to post-traumatic failure. A major consequence of free radical production and mitochondrial failure is the exacerbation of intracellular calcium overload that can trigger various damaging events, among which is the activation of cysteine proteases (e.g., calpain, caspase 3), which are key players in necrotic and apoptotic neuronal degeneration. Ray, Samantatray, Smith, Matzelle, Das, and Banik [7] review the neuroprotective effects of cysteine protease inhibiting agents in SCI models.

In recent years, the complex involvement of post-SCI humoral and cellular inflammatory processes in both secondary injury and repair has become one of the hottest research topics in the SCI field. Accordingly, 4 reviews are devoted to the role of posttraumatic spinal cord inflammation. The first review is by Hawthorne and Popovich [8] who present the latest concepts concerning the activation of resident microglia and the influx of blood borne myeloid cells, their interactions with various chemokines and cytokines, and their detrimental and reparative roles. A second review is by Pajoohesh-Ganji and Byrnes [9] who focus on chronic SCI and novel inflammatory factors that have both detrimental and beneficial effects, and may also be targets for therapeutic approaches. A third review is by Zhang, Chang, Hansen, Basso, and Noble-Hausselein [10] who consider the role of matrix metalloproteinase activation, its role in blood–spinal cord barrier disruption, leukocyte infiltration, and apoptotic neuronal degeneration. This third review also describes the ongoing discovery of novel and selective matrix metalloproteinase inhibiting compounds for acute treatment of SCI. The fourth review, largely an inflammation-directed article, by Wu, Stoica, and Faden [11] presents the role of aberrant cell cycle activation in post-traumatic spinal cellular death mechanisms and microglial and astrocytic

activation, and the neuroprotective effects of prototypical pharmacological cell cycle inhibitors.

Additionally, Fassbender, Whittemore, and Hagg [12] discuss the emerging role that acute microvascular pathophysiology plays in spinal cord dysfunction, as well as a reactive angiogenic response. These authors also describe both pharmacological and genetic experimental approaches aimed at rescuing and stabilizing the microvasculature.

One of the most imminently promising approaches to achieving neuroprotective effects in the injured spinal cord is the induction of therapeutic hypothermia (i.e., moderate lowering of the body, and hence spinal cord temperatures, to ~33°C). Dietrich, Levi, Wang, and Green [13] review their extensive studies in which they have documented the multiple secondary injury mechanisms that are inhibited by hypothermia, and the beneficial effects on neurological recovery in rodent SCI models. These authors also detail early studies suggesting a similar benefit in SCI patients, which is inspiring more in-depth clinical trials. Indeed, a probable advantage of therapeutic hypothermia may be its ability to simultaneously blunt multiple secondary injury mechanisms compared to most pharmacological approaches that only antagonize a single secondary injury target.

The majority of nontransecting human SCIs involve the fracture of one of more spinal vertebrae, which can result in bony fragments or dislocated vertebrae that inflict an ongoing compressive insult to the injured spinal cord. Recently, it has been appreciated that the resulting compression of the injured spinal cord can produce an additional ischemic insult to the mechanically injured spinal cord. Moreover, the interruption of spinal cord blood flow will prevent the intravascular delivery of neuroprotective agents to the damaged tissue. There is increasing recognition that this situation represents a critical care emergency. Accordingly, Fehlings and Wilson [14] review the emergence of a more aggressive surgical approach, which by itself may improve outcomes in SCI patients, as well as increasing the chance for acute neuroprotective agents and hypothermia to manifest their maximal degree of protective efficacy.

Even in the absence of acute neuroprotective interventions, it is well known that in most human SCIs many spinal axons survive the primary and secondary injury events. In fact, some retain their normal ultrastructure and myelination, allowing them to conduct impulses in a normal fashion. However, many axons that survive have lost much or all of their myelination, precluding their ability to sustain normal salutatory conduction. The important studies by Blight [15, 16] in the early 1980s revealed the fact that hind limb motor functional recovery after contusive SCI in cats is dependent on the number of normally myelinated axons that survive the injury and thereby are able to conduct impulses with a normal velocity. Thus, the loss of spinal axons and/or their myelination due to acute secondary injury or delayed apoptotic degeneration of the myelin-producing oligodendrocytes is the critical impediment to neurological recovery. Given this fact, this issue of *Neurotherapeutics* also deals with what can be done to reconstruct the damaged neural circuitry and restore or improve function? One approach for preventing the harmful effects of demyelination to axons and their function is by oligodendrocyte protection, as well as replacement with endogenous and/or transplanted oligodendrocyte progenitor cells, which is described in the article by Almad, Sahinkaya, and McTigue [17].

Motor, sensory, and autonomic functions can spontaneously return or recover to varying extents depending on lesion severity. The article by Onifer, Smith, and Fouad [18] indicates that the underlying mechanisms known to be responsible for these functional changes are collectively referred to as plasticity. This ranges from the properties of spared neuronal circuitries being altered to synaptic rearrangements. Additionally, it has been recognized that since experimental results were reported in the 1950s by McCouch, Austin, Liu, and Liu [19], both spared and lesioned axons throughout the animal and human neuraxis can undergo collateral sprouting. Importantly, not all plasticity is beneficial. Pain, autonomic dysreflexia, and spasticity can occur after spinal cord injury both spontaneously and as a result of treatments. The article by Rabchevsky and Kitzman, presented on [20], describes the latter of these debilitating secondary complications and the potential of pharmacological agents to alleviate them individually or both by targeting a common stimulatory pathway. On the other hand, facilitatory approaches can enhance plasticity and lead to improved function. Onifer, Smith, and Fouad [18] discuss the pros and cons of some activity-based, pharmacological, and gene-delivery approaches that are currently being investigated.

Despite previous advances in emergency medicine, including the use of high-dose MP, and the ongoing discovery and development of safer and more effective neuroprotective strategies, the numbers of chronic SCI cases increases. In many cases, promoting long-distance axon regeneration will be necessary to restore and improve function. The potential for injured axons in the spinal cord to regenerate was first suggested from experiments by Santiago Ramón y Cajal as well as others in the early to mid-1900s. Using neuroanatomical tracing techniques, this was unequivocally demonstrated in the 1980s by Aguayo and colleagues [21–23]. In their studies, grafted peripheral nerve segments were used to provide an axon growth permissive environment and to avoid the nonpermissive spinal cord. Since then, these peripheral nerve graft findings have been extended, as described in the article by Côté, Amin, Tom, and Houle, [24]. Moreover, a variety of other axon growth

permissive environments have been identified, including peripheral nerve Schwann cells, olfactory ensheathing glia, fetal tissue, stem cells, precursor cells, progenitor cells, marrow stromal cells, and reactive macrophages used alone, combined, and in biomaterials. Two extremely important issues that have arisen from experimental studies, and in some cases, clinical studies of these tissues and cells are 1) the modest axon growth into the permissive environments, and 2) the unwillingness of regenerated axons to exit them and re-enter the spinal cord. Côté, Amin, Tom, and Houle, in their article [24], discuss an approach that they found to be successful for dealing with the latter issue. This involves digesting inhibitory chondroitin sulfate proteoglycans that are present at the end of the peripheral nerve graft, and within the glial scar, with chondroitinase ABC (ChABC). More regenerated axons exit the peripheral nerve graft and form functional synapses when ChABC is placed at an appropriate target. Importantly, this approach also promotes functional axon collateral and regenerative sprouting, as described in the article by Onifer, Smith, and Fouad [18]. Although there are other impediments to axon regeneration in the injured spinal cord environment and intrinsic to the axons themselves, the glial scar can also be attenuated with cell cycle inhibitors and matrix metalloproteinases inhibitors, which is discussed in the articles by Wu, Stoica, and Faden, as well as by Zhang, Chang, Hansen, Basso, and Noble-Haeusslein [10, 11] respectively.

Tremendous experimental strides have been made in the last 4 decades toward the development of cures for traumatic SCI. Clinical trials have occurred and are ongoing, as well as being planned. Although this issue of *Neurotherapeutics* covers many topics relevant to the treatment of acute and chronic SCI, it is important to note that the included reviews do not comprehensively deal with all of the neuroprotective, neurorestorative, and neurorehabilitative strategies that are under investigation. However, the included articles will hopefully give the reader an idea of the richness of SCI therapeutic research and the likelihood that new and probably combinatorial treatment approaches will be entered into clinical translation in the not too distant future.

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