# Rat Models of Traumatic Spinal Cord Injury to Assess Motor Recovery

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## Abstract

Devastating motor, sensory, and autonomic dysfunctions render long-term personal hardships to the survivors of traumatic spinal cord injury (SCI). The suffering also extends to the survivors' families and friends, who endure emotional, physical, and financial burdens in providing for necessary surgeries, care, and rehabilitation. After the primary mechanical SCI, there is a complex secondary injury cascade that leads to the progressive death of otherwise potentially viable axons and cells and that impairs endogenous recovery processes. Investigations of possible cures and of ways to alleviate the hardships of traumatic SCI include those of interventions that attenuate or overcome the secondary injury cascade, enhance the endogenous repair mechanisms, regenerate axons, replace lost cells, and rehabilitate. These investigations have led to the creation of laboratory animal models of the different types of traumatic human SCI and components of the secondary injury cascade. However, no particular model completely addresses all aspects of traumatic SCI. In this article, we describe adult rat SCI models and the motor, and in some cases sensory and autonomic, deficits that each produces. Importantly, as researchers in this area move toward clinical trials to alleviate the hardships of traumatic SCI, there is a need for standardized small and large animal SCI models as well as quantitative behavioral and electrophysiological assessments of their outcomes so that investigators testing various interventions can directly compare their results and correlate them with the molecular, biochemical, and histological alterations.

**Key Words:** compression; contusion; demyelination; excitotoxicity; free radicals; inflammation; ischemia; laceration

## Introduction

Traumatic spinal cord injury (SCI[1]) in the United States happens to approximately 11,000 persons each year (Spinal Cord Injury Information Network, www.spinalcord.uab.edu). While the majority of these injuries occur to the cervical spinal cord, devastating motor, sensory, and autonomic dysfunctions below the injury render long-term hardships to the survivors of all levels of SCI—cervical, thoracic, lumbar, and sacral. The suffering also extends to survivors' families and friends, who endure emotional, physical, and financial burdens in providing for necessary surgeries, care, and rehabilitation.

Based on imaging and histology of injured human spinal cords, Bunge and colleagues classified each traumatic SCI as (1) a contusion evolving to cavity formation, (2) a massive compression, or (3) a laceration (Bunge et al. 1993, 1997). The most frequent contusion injuries are focal spinal cord compression and render both an intact glial limitans and pia surrounding varying extents of intact white and gray matter. Fluid-filled cavities or cysts evolve from the hemorrhage into the spinal cord parenchyma and where tissue has degenerated. In contrast, the glial limitans and pia are cut in massive compression and laceration injuries. Massive compression injuries occur over substantial lengths of the spinal cord and include maceration. Laceration injuries are focal and, similar to massive compression injuries, result in the formation over time of a connective tissue mass in the spinal cord.

After the primary mechanical SCI, there is a complex secondary injury cascade (Tator and Fehlings 1991) that leads to the progressive death of otherwise potentially viable axons and cells and that impairs endogenous recovery processes. Investigations of possible cures and ways to alleviate the hardships of traumatic SCI include those of interventions that attenuate or overcome the secondary injury cascade, enhance the endogenous repair mechanisms, regenerate axons, replace lost cells, and rehabilitate (Anderson et al. 2005a; Blight and Tuszynski 2006; Bradbury and McMahon 2006; Kleitman 2004; Rabchevsky and Smith 2001; Tator 2006; Thuret et al. 2006). These investigations

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[1]Abbreviations used in this article: BBB scale, Basso, Beattie, and Bresnahan open-field locomotor rating scale; EMG, electromyographic; IH, Infinite Horizon; MIER, magnetically evoked interenlargement response; OSU, Ohio State University; SCI, spinal cord injury; SSEP, somatosensory evoked potential; tcMMEP, transcranial magnetic motor evoked potential.

have led to the creation of laboratory animal models of traumatic human SCI.

In this article, we describe adult rat SCI models and the motor, and in some cases sensory and autonomic, deficits that each produces. Rats have been chosen to study traumatic SCI not only because they are readily available but also because the morphological, biochemical, and functional changes that occur after SCI are similar to those seen in humans (Fleming et al. 2006; McTigue et al. 2000; Metz et al. 2000; Norenberg et al. 2004). The rats are always anesthetized for the SCI and other surgical procedures, after which they require specialized veterinary care, the extent of which depends on both the location and severity of the injury (Santos-Benito et al. 2006). Female rats are preferable because of the relative ease of manual bladder emptying after SCI, resulting in less frequent urinary tract infections.

## Assessments of Motor Deficits and Recovery in Adult Rats with SCI

A number of assessments of behavioral and electrophysiological function are available for adult rats (for reviews, see Basso 2004; Kesslak and Keirstead 2003; Nichols et al. 2005; Webb and Muir 2005). Importantly, most of these assessments evaluate the sensorimotor function rather than sensory or motor functions individually. Some are quantitative while others are not. We recommend the use of quantitative assessments even though they require training the rats to criterion. The completion of assessments before SCI helps in establishing baseline values for each rat. We, like others, also recommend a battery of assessments whenever appropriate. For information purposes, we briefly discuss commonly used quantitative and semiquantitative assessments for adult rat models of traumatic SCI. Detailed information about these assessments is available in the reviews indicated above and the references throughout this section.

### Behavior

Because rats prehend food with their mouths then manipulate it with their forepaws, pellet retrieval tests are useful to assess reach, grasp, and retrieval behaviors after cervical SCI (Anderson et al. 2005b; Nash et al. 2002; Onifer et al. 1997b; Schrimsher and Reier 1992; Weidner et al. 2001). Importantly, it is necessary to train the rats used in post-SCI studies to prehend with their paws. Use of the "Staircase Test" platform and chamber (Montoya et al. 1991) enables cervical spinal cord-injured rats to avoid having to support themselves on three dysfunctional limbs while reaching for, grasping, and retrieving pellets (Onifer et al. 1997b). Investigators have examined forelimb and forepaw usage for support during spontaneous vertical exploration in a cylinder after cervical SCI (Liu et al. 1999b; Soblosky et al. 2001; Webb and Muir 2004). There are also studies of forelimb grip strength in which the cervical-SCI rat is pulled away while grasping a bar (Anderson et al. 2005b; Onifer et al. 1997b). Other studies evaluate forelimb and hindlimb placing and footfalls while the rat walks or locomotes on a horizontal (Onifer et al. 2005; Pearse et al. 2005) or inclined (Li et al. 2003) grid, horizontal ladder (Soblosky et al. 2001; Webb and Muir 2003, 2004), beam (Jeffery and Blakemore 1997; Kim et al. 2001), or rope (Anderson et al. 2005b; Kim et al. 2001).

Many of the current models of SCI utilize the Basso, Beattie, and Bresnahan open-field locomotor rating scale (BBB scale[1]; Basso et al. 1995) to assess functional outcome. The BBB scale has a range from zero (no hindlimb movements) to 21 (normal coordinate gait), using paw placement, joint movement, and truncal stability as important factors in determining the level of functional recovery. Scores in the 0 to 7 range focus primarily on hip, knee, and ankle joint movement, the 8 to 13 range keys in on paw placement and coordination, and scores of 14 to 21 rely heavily on trunk stability, tail position, and paw placement. Tarlov and Klinger (1954) developed one of the original open-field behavior tests for SCI and it involved a rather simplistic observational assessment of the animal's locomotor ability. A modified version of the Tarlov scale (Gale et al. 1985) consisting of six levels of motor movement (from 0 for no hindlimb movement to 5 for normal walking) appears extensively in the literature (Haghighi et al. 2000; Voda et al. 2005). Other analyses of locomotion include footprint analysis (Cheng et al. 1997; Kunkel-Bagden et al. 1993), the CatWalk-assisted gait analysis (Gensel et al. 2006; Hamers et al. 2001; Hendriks et al. 2006), and kinematics (Broton et al. 1996; Collazos-Castro et al. 2006). Several studies correlate these data to electromyographic (EMG[1]) recordings made at the same time from electrodes implanted in limb muscles (Ballermann et al. 2006; Kaegi et al. 2002; Thota et al. 2005).

Numerous studies have used the inclined plane to evaluate functional outcome in rats after SCI (Rivlin and Tator 1977). The device consists of a hinged board raised and lowered to different angles. The object is for the rat to maintain itself on the board for 5 seconds as the angle is gradually increased at 5° intervals. The assigned score is the maximum angle of the plane that the rat can maintain for 5 seconds without sliding off onto a padded surface. Uninjured rats achieve scores of approximately 80°.

### Electrophysiology

In both humans and animals with traumatic SCI, electrophysiology is a valuable tool for investigation of the neural substrates underlying deficits and functional recovery as revealed by behavioral testing. Terminal electrophysiology procedures can be useful in experimental animals (e.g., Massey et al. 2006), but it is much more advantageous to reproduce the procedure a number of times after SCI (Nashmi et al. 1997) and without anesthesia. The transcra-

nial magnetic motor evoked potential (tcMMEP[1]) procedure involves noninvasive magnetic stimulation at the unanesthetized rat's skull and the recording of evoked potentials with EMG electrodes temporarily inserted into hindlimb muscles (Fishback et al. 1995; Linden et al. 1999). While the tcMMEP procedure assesses supraspinal axon conduction, magnetically evoked interenlargement (MIER[1]) and somotosensory evoked potential (SSEP[1]) procedures are effective for the evaluation of propriospinal and sensory spinal axon conduction, respectively, in unanesthetized rats. The MIER procedure involves noninvasive magnetic stimulation at the rat's hip or knee and the recording of evoked potentials with EMG electrodes temporarily inserted into forelimb and masseter muscles (Beaumont et al. 2006). The SSEP procedure involves electrical stimulation of the paws with electrodes temporarily inserted into them, and the recording of evoked potentials from electrodes previously implanted in the cranium over the somatosensory cortex (Onifer et al. 2005). All three procedures take only a few minutes and cause only slight pain and distress and so are done in unanesthetized rats.

## Rat Models of Traumatic SCI

### Weight Drop

The first well-documented animal experimentation of SCI was that described by Allen (1911), which used a weight-drop technique on dogs. The approach was quite simple: A laminectomy was performed on the anesthetized animal, exposing the dorsal (posterior) surface of the spinal cord. A given weight was dropped from a known height, down a vented guide tube positioned perpendicular to the laminectomy site. As the weight struck the exposed spinal cord, either directly or through an impounder plate that rested on the exposed cord (and may have diffused the injury over a wider area), the underlying tissue was subjected to a dynamic compression. Depending on the weight and the height, different amounts of force were applied to the cord and resulted in varying degrees of SCI. The shape and diameter of the impounder surface were important variables in the injury outcome (Gerber and Corrie 1979; Koozekanani et al. 1976) as was the resistance encountered during the "free fall" (Dohrmann and Panjabi 1976; Dohrmann et al. 1978).

While Allen's original work utilized dogs, a weight-drop technique was later adapted for the anesthetized rat (Panjabi and Wrathall 1988; Wrathall et al. 1985). Because of the difference in size of the impactor tip, the technique was initially thought to be too unreliable in the rodent (Khan and Griebel 1983), with consistency observed only at the high severity end of the spectrum. Important variables that made the Wrathall model work were stabilization of the spinal column before the injury and a strain gauge, used to measure force, mounted on a "C" ring attached to an impounder resting on the exposed spinal cord dura. Many of the subsequent weight-drop models that were scaled down for producing cervical (Onifer et al. 1997b; Schrimsher and Reier 1992; Soblosky et al. 2001) or thoracic SCI in the rat offered limited information on the biomechanical properties of the injury, although they did allow for reproducibility and graded levels of functional outcome (Wrathall et al. 1985).

It is extremely important that an injury model have the capability of generating different degrees of injury severity and functional outcomes. If injuries are too moderate, spontaneous recovery occurs very rapidly and it is difficult to assess potential therapeutic outcomes. Injuries that are too severe result in extremely limited functional outcome and again can mask potentially useful therapeutic strategies. In an improvement over the Wrathall model, Khan and colleagues (1999) compared functional outcomes after injury in both rats and cats. While both species showed injury-related declines in behavioral and electrophysiological function, the time course of some spontaneous recovery was significantly shorter for the cats. As with earlier weight-drop models, little information concerning the biomechanical parameters of the SCI was available.

One of the most popular weight-drop models is the New York University (NYU)/MASCIS device. This rather sophisticated device was developed by Gruner (1992) and consists of dropping a 10-gram weight from 6.25, 12.5, 25, or 50 mm directly onto the exposed dorsal spinal cord dura. An electrical circuit determines cord surface before the injury, thus eliminating concerns about a preload injury, common with models that use an impounder plate. One of the major advantages to this model is the monitoring of injury parameters such as impact velocity and tissue displacement, providing a mechanism to eliminate injured animals that do not meet preestablished criteria. The device has greatly reduced the risk of multiple injuries because of drop-weight "bounce."

After the injury, all of the rats demonstrate a severe loss of locomotor activity. Basso and colleagues (Basso et al. 1996) used the BBB scale to describe graded locomotor outcomes following different thoracic injury severities with this device. With the exception of the 6.25-mm drop, all groups showed severe loss of locomotor movement in the hind legs. However, most of the groups showed spontaneous improvement over 3 to 4 weeks, after which locomotor ability reached a plateau. Investigators have reported graded motor deficits and recovery as found with grooming, paw preference, the CatWalk, and horizontal ladder tests, as well as kinematics and the BBB scale for rats following cervical or lumbar injury severities with this device (Collazos-Castro et al. 2005; Gensel et al. 2006; Magnuson et al. 2005).

### Aneurysm Clip Compression

As mentioned above, several research groups considered the rat too small for the weight-drop method originally designed by Allen. To overcome this problem and to more closely model the ventral (anterior) compression normally observed

in the human clinical condition, investigators effected SCI through sustained compression with specially modified Kerr-Lougheed aneurysm clips (Rivlin and Tator 1978). This model entails exposing the rat spinal cord and applying the aneurysm clip with one blade under the ventral surface of the cord and the other over the dorsal surface. The clip, calibrated for a known compression force, is rapidly released and allowed to compress the cord for a predetermined amount of time (e.g., 60 seconds) before release and removal. In the initial study, this type of injury resulted in a quite dramatic and sustained deficit as measured with an inclined plane task. Some investigators have applied compression force–calibrated aneurysm clips vertically (laterally) and assessed behavior outcome (von Euler et al. 1997a). In both cases, results indicated a high correlation of all neurological outcomes (BBB scale, inclined plane, beam walk) to the compression force.

## Calibrated Forceps Compression

As an alternative to the use of aneurysm clips that produce a very focal injury, Blight (1991) developed a moderate-severity injury technique in the guinea pig using modified forceps. This compression injury produced a considerably larger volume of tissue compression and displacement than the aneurysm clips, with the added advantage of a special spinal column stabilized support. A detailed study in the rat (Gruner et al. 1996) carefully monitored functional recovery using a modified Tarlov scale following a wide range of spinal cord compressions. The results demonstrated significant differences in the temporal pattern of the behavioral recovery when comparing the rat and the guinea pig. A delayed functional loss in the guinea pig was not observed in the rat, indicating possible significant species differences.

## Contusion

In an attempt to gain more control over the injury severity and more closely monitor biomechanical properties, several laboratories began to experiment with controlled pneumatic compression models (Anderson 1982; Kearney et al. 1988). One such model that used rats reported no indications of changes in functional outcome (Narayana et al. 1999). A report by Noyes (1987) described a new electromechanical spinal cord impactor, now known as the Ohio State University (OSU[1]) device. This model injures the spinal cord by means of a solenoid-controlled air cylinder mounted on a rigid frame with a tip that impacts the exposed dorsal spinal cord. The spinal column is firmly secured with no impounder plate on the exposed spinal cord. A companion study (Somerson and Stokes 1987) demonstrated the functional outcome following three different levels of injury using the Tarlov scale. Additional studies (Behrmann et al. 1992; Bresnahan et al. 1987) more carefully described functional recovery patterns in rats based on thoracic injury severity in terms of tissue displacement and post-trauma recovery time using the Tarlov scale, inclined plane task, grid walking, and footprint analysis. As with the weight-drop studies, functional deficits appeared immediately following the trauma and showed spontaneous recovery that plateaued around 2 to 3 weeks following injury. Reports describe graded motor deficits and recovery found with forelimb grip strength, inclined plane, and grid-walk tests as well as footprint analysis and the BBB scale for rats following different cervical injury severities with this device (Pearse et al. 2005). Although the lack of commercial availability of the OSU device limits its experimental usage by other laboratories, this sophisticated model provides excellent control over the biomechanical aspects of the injury (i.e., velocity, depth of compression, force) that can effectively dictate the severity of the injury.

A relatively new, commercially available kinetic contusion device uses force rather than tissue displacement to injure the rat spinal cord (Scheff et al. 2003). Similar to the OSU device, this model requires exposure of the dorsal surface of the spinal cord and the rigid stabilization of the spinal column. One of the unique features of this computerized device, first produced by Infinite Horizon (IH[1]), is the ability to inflict reproducible injuries without touching the spinal cord before the hit. Some experimenters believe that any device that touches the exposed spinal cord before a more severe compression could cause a priming injury and thus alter the intended injury outcome. The IH instrumentation senses the surface of the exposed spinal cord and continues to displace spinal tissue until it attains a predetermined force, at which point the impactor tip immediately withdraws. Initial behavioral and electrophysiological characterization studies used the BBB scale and the tcMMEP procedure to describe the loss and reacquisition of hindlimb function and motor axon conduction following a wide range of injury severities (Cao et al. 2005; Scheff et al. 2003). A subsequent paper, evaluating creatine as a neuroprotective agent, compared injury with the IH device to the NYU/MASCIS weight-drop model (Rabchevsky et al. 2003) and found that both models produced significant SCI and resulted in very similar functional recovery profiles. An advantage of the IH device is that it enables monitoring of various biomechanical parameters (i.e., velocity, force, tissue compression/displacement) and thus the early elimination from the study of animals that do not meet preset standards.

## Laceration

Of the many traumatic SCI models, the most frequently used methods of injury include complete transection, focal myelotomy (incision), dorsal or lateral hemisection, lateral overhemisection, resection, or aspiration lesions that definitively sever spinal cord axons of passage. Although these types of laceration injuries are not typically seen clinically, they can effectively disconnect both ascending and descending axonal pathways at designated levels of SCI. This ap-

proach allows the study of mechanisms that govern the inhibition or successful regeneration of axons across or around laceration injuries as well as of the resulting functional deficits and potential recovery. Importantly, the severity and level of SCI entirely dictate the applicability of quantitative assessments for impaired motor, sensory, and/or autonomic functions.

One of the many syndromes that occur after both complete and incomplete human SCI at thoracic level 6 (T6) or above is a condition called autonomic dysreflexia (Karlsson 1999; Rabchevsky 2006). The most common trigger of this arduous hypertensive disorder is painful distension of the bladder or bowel, which elicits massive discharge of uninhibited sympathetic neurons in the injured spinal cord disconnected from brainstem control. The inflation of a balloon catheter in the distal colon of unanesthetized rats induces autonomic dysreflexia 2 weeks after complete transection of the cervical (C) or high thoracic spinal cord (Cameron et al. 2006; Chau et al. 2000; Krassioukov et al. 2002; Krassioukov and Weaver 1995; Osborn et al. 1989, 1990). While there is no perception of noxious stimuli, the rats experience autonomic cardiopathophysiology that stems from post-traumatic intraspinal plasticity (Rabchevsky 2006).

Unlike complete spinal cord transection injuries, the reproducibility of partial spinal cord laceration injuries is somewhat inconsistent. Such injuries include focal myelotomies at spinal level C4, with the subsequent use of a pellet retrieval test to examine the effects of damage to axon pathways in the dorsolateral and ventrolateral funiculi on forelimb reach, grasp, and retrieval behaviors (Schrimsher and Reier 1993). Unilateral SCI of distinct ascending and descending spinal pathways at similar levels is useful to investigate locomotor and sensory deficits as well as compensatory recovery using electromechanical assessments (Webb and Muir 2002, 2003, 2004). An alternative to unilateral SCI is more extensive dorsal-ventral and ventral-dorsal laceration SCI (Schucht et al. 2002). Among the behavioral tests utilized with these lesions are a forepaw usage task, the BBB scale, analyses of footslips during ladder or grid walking, quantitative kinetic measurements of ground reaction forces during locomotion, and Von Frey filament testing for tactile sensation. The recently created VibraKnife™ creates discrete myelotomies and dorsal hemisections of the midcervical spinal cord that elicit differential alterations in forelimb SSEPs and in upper extremity sensorimotor deficits (Onifer et al. 2005). After various discrete thoracic spinal cord hemisection injuries, use of the MIER procedure demonstrates differential alterations in ascending propriospinal axon pathway conduction that significantly correlate both with white matter sparing in the lateral funiculus and with hindlimb function assessed by the BBB scale (Beaumont et al. 2006).

Combinatorial injuries, consisting of a thoracic spinal cord dorsal hemisection and unilateral transection of a pyramidal tract, show that new intraspinal circuitry forms spontaneously in the injured spinal cord of adult rats (Bareyre et al. 2004). In particular, transected hindlimb corticospinal tract axons sprouted into the cervical spinal cord gray matter to contact long propriospinal neurons that bridged the lesion and extended processes to lumbar motoneurons. This created a new intraspinal circuit relaying supraspinal input to its original spinal targets. Electrophysiological and behavioral testing, as well as retrograde transynaptic tract tracing that revealed progressive changes in cortical representations over time, confirmed functionality.

Complete resection injuries and discrete hemisection aspiration lesions of the thoracic spinal cord have also been used to test various "bridge" interface approaches by grafting neural tissues, alone or in combination with biosynthetic guidance channels, to promote successful graft survival and axonal regeneration in the injured adult rat spinal cord (Aguayo et al. 1981; Bregman et al. 1993; Cheng et al. 1996; David and Aguayo 1981; Iannotti et al. 2003; Jakeman and Reier 1991; Reier et al. 1986; Xu et al. 1995, 1997, 1999). Outcome measures for such interventions include histological and axonal tract tracing methods to assess tissue integrity, cytoarchitecture and neural connectivity between graft and host, the combined behavior score, the modified Tarlov scale, and forelimb functional recovery tasks.

## Chemical-mediated SCI

Procedures involving a variety of chemical-mediated injuries throughout the adult rat spinal cord can be useful to model specific aspects of the secondary injury cascade that occur after the initial traumatic SCI and to address questions about spinal cord circuitry. In contrast to the previously described models, chemical-mediated SCI is a targeted approach that may not include all the components of traumatic SCI. The clinical relevance of findings from experiments that evaluate treatments in these models must take this into account.

Vascular damage occurs after traumatic SCI and results in hemorrhage, reduced blood flow, and ischemia (poor oxygen and nutrient supply) (Casella et al. 2002; Fleming et al. 2006; Loy et al. 2002a; Norenberg et al. 2004; Tator and Fehlings 1991). There is evidence that ischemia causes spinal cord damage and then dysfunction in both humans and rats after occlusion of the descending thoracoabdominal aorta (for review, Black and Cambria 2006; Zhang et al. 2000). It is also possible to produce ischemia in the rat spinal cord by combining intravenous injection of the photosensitive dyes rose bengal (Watson et al. 1986) or erythrosin B (Cameron et al. 1990; Hao et al. 1991) with irradiation of the exposed vertebrae to produce vascular thrombosis. An alternative is to bathe the dura-covered spinal cord with rose bengal then use irradiation (Garcia-Alias et al. 2003; Verdu et al. 2003). Irradiation duration is an effective way to grade the ensuing motor behavioral and axon conduction deficits (Cameron et al. 1990; Garcia-Alias et al. 2003; Prado et al. 1987; Wiesenfeld-Hallin et al. 1993)

as well as white and gray matter pathology (Bunge et al. 1994; Hao et al. 1991; Olby and Blakemore 1996; Prado et al. 1987; Verdu et al. 2003; von Euler et al. 1997b; Watson et al. 1986) in these models of spinal cord ischemia. Intrathecal delivery (Hokfelt et al. 1989; Salzman et al. 1996; Westmark et al. 1995) and minimally traumatic spinal cord gray matter injection (Benton et al. 2005) of the vasoconstrictor endothelin can also produce ischemia that leads to locomotor deficits (Salzman et al. 1996). Spinal cord gray matter injection of the nonspecific nitric oxide synthase inhibitor N-nitro-L-arginine methyl ester additionally causes neuron degeneration, possibly by vasoconstriction due to reduced levels of nitric oxide (Dora et al. 1998; Yezierski et al. 1996).

Excitatory amino acid concentrations rapidly rise to toxic levels after traumatic SCI (Liu et al. 1991) and the resultant excitotoxicity plays a major role in white and gray matter pathology (for a review, Park et al. 2004). Models of excitotoxic rat oligodendrocyte and neuron death as well as of evoked potential conduction block involve administering glutamate, glutamate and aspartate, N-methyl-D-aspartate (NMDA), or kainate, an agonist of the AMPA/kainate glutamate receptor, through microdialysis fibers implanted in the spinal cord (Liu 1994; Liu et al. 1999a; Xu et al. 2004). Intrathecal delivery of kainate also results in both oligodendrocyte and neuron death (Nottingham and Springer 2003; Sun et al. 2006). Topical application of kainate or NMDA to the dorsal spinal cord causes excitotoxic neuron death (Ikonomidou et al. 1996), whereas microinjections of kainate or quisqualic acid, an agonist of the AMPA-metabotropic receptor, into gray matter produces spinal cord gray matter degeneration (Hadi et al. 2000; Magnuson et al. 1999; Nothias and Peschanski 1990; Onifer et al. 1997a; Pisharodi and Nauta 1985; Yezierski et al. 1993). Combining spinal cord gray matter injection of kainate with the proinflammatory cytokine tumor necrosis factor-α, at doses where these chemicals are not toxic, also causes gray matter degeneration (Hermann et al. 2001). Importantly, discrete excitotoxicity in cervical (Pisharodi and Nauta 1985) or lower (but not mid-) thoracic and upper lumbar (Hadi et al. 2000; Magnuson et al. 1999) spinal gray matter selectively damages neurons critical to adult rat forelimb or hindlimb function, respectively, but not long-tract motor axon conduction. Hindlimb locomotor deficits can also result after intrathecal delivery of kainate at the lumbar spinal cord (Sun et al. 2006).

Free radical, peroxynitrite, and calpain-induced damage to lipids and proteins occurs after traumatic SCI (for a review, Hall 2001). Models of this effect include the administration of the herbicide paraquat, a superoxide generator (Liu et al. 1995), hydrogen peroxide and $FeCl_2$ (Liu 1993), or S- or 3-morpholinosydnonimine, peroxynitrite donors (Bao et al. 2003; Bao and Liu 2002) through microdialysis fibers in rat spinal cord gray matter to generate superoxide, hydroxyl radical, and peroxynitrite. These oxidants destroy neurons, block motor axon conduction, and impair open-field locomotion, hindlimb function, and inclined plane stability when generated in lumbar spinal cord gray matter (Bao and Liu 2002; Liu 1994).

Inflammation occurs after traumatic SCI and is a cause of secondary degeneration (Fleming et al. 2006; Keane et al. 2006). Microinjection of zymosan, a yeast particulate that activates resident microglia/macrophages, into the rat spinal cord white and gray matter causes inflammation that leads to a pathology similar to that seen after traumatic SCI and open-field locomotion dysfunction (Popovich et al. 2002). Phospholipase $A_2$ is a family of enzymes that generate precursors of inflammatory mediators involved in spinal cord inflammatory disease (Kalyvas and David 2004). Microinjection of phospholipase $A_2$ into the rat thoracic spinal cord ventrolateral white matter produces a dose-dependent hemorrhage, inflammatory cell infiltration, demyelination, gray and white matter degeneration, and deficits in open-field locomotion and motor axon conduction (Liu et al. 2006).

Oligodendrocyte degeneration and demyelination are hallmarks of traumatic SCI (Guest et al. 2005). Intraspinal microinjection of the following cause rat oligodendrocyte death and demyelination: lysolecithin or L-apha-lysophosphatidyl choline (a major component of oxidized low-density lipoproteins that has inflammatory properties) alone and after x-irradiation to prevent remyelination (Blakemore and Patterson 1978); ethidium bromide (an intercalating gliotoxin) alone (Graca and Blakemore 1986; Yajima and Suzuki 1979) and after x-irradiation (Blakemore and Crang 1989); complement proteins plus antibodies to galactocerebroside alone and after x-irradiation (Keirstead and Blakemore 1997); and an antibody to myelin oligodendrocyte glycoprotein and complement (Perez-Bouza et al. 2005). Importantly, chemical-mediated oligodendrocyte degeneration and demyelination in discrete rat spinal cord axon pathways can produce hindlimb and motor axon conduction deficits. For example, ethidium bromide injected into the cervical spinal cord dorsal funiculus produces hindlimb deficits during beam walking (Jeffery and Blakemore 1997). Photon irradiation of the thoracic spinal cord after injection of ethidium bromide into either the ventral or ventrolateral funiculus impairs open-field locomotion (Loy et al. 2002b). Moreover, oligodendrocyte degeneration and demyelination of the ventral white matter, of both the ventrolateral and dorsolateral funiculus, and of both the ventrolateral and dorsal funiculus results in greater open-field locomotion dysfunction (Loy et al. 2002b,c). Motor axon conduction deficits through the ventrolateral funiculus also result from ethidium bromide injection into the thoracic spinal cord ventrolateral funiculus and photon irradiation (Loy et al. 2002c). Intrathecal administration of cholera toxin B-subunit conjugated to saporin at the lumbar cord causes oligodendrocyte death, demyelination, and locomotion deficits (Jasmin et al. 2000).

Syringomyelia, a clinical syndrome that can occur after traumatic SCI (Wirth et al. 2001), is characterized by fluid-filled cavity formation, then enlargement with delayed and then progressively deteriorating function (for a review, see Brodbelt and Stoodley 2003). Modeling of syringomyelia

entails injection of a suspension of kaolin into the rat cisterna magna to produce hydrocephalus (Kashiwaguchi et al. 1989), into the spinal cord subarachnoid space to create arachnoiditis (Tatara 1992), or into the spinal cord dorsal columns (Stoodley et al. 1999) and central gray matter (Milhorat et al. 1993) to occlude the central canal. Microinjection of quisqualic acid in the spinal cord gray matter alone (Schwartz et al. 1999) and combined with a kaolin suspension injection into the spinal cord subarachnoid space (Yang et al. 2001) is another way to produce cavities. These models result in inflammation, demyelination, neuron loss, and both gray and white matter degeneration (Lee et al. 2005; Milhorat et al. 1993; Tatara 1992; Yezierski et al. 1993).

## Conclusions

No particular animal model of traumatic human SCI completely addresses all of its aspects, although the use of multiple paradigms has greatly advanced our understanding of the pathophysiology following spinal cord trauma. Importantly, as investigators in this area move toward clinical trials, there is clearly a need for standardized small and large, especially nonhuman primate (Courtine et al. 2007), animal models of SCI to enable testing of various interventions and to directly compare results. Equally important is the need to standardize behavioral and electrophysiological outcome measures for the different injury models because inappropriate assessment of functional deficits and recovery adds to the complexity of correlating their results with molecular, biochemical, and histological alterations. Bringing these concepts to a consensus among neuroscientists who use different models and assessments, based on preference or availability, may prove to be one of the biggest challenges to overcome in the search for ways to cure traumatic SCI in humans and to alleviate its hardships.

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