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Synaptic Plasticity, Neurogenesis, and Functional Recovery after Spinal Cord Injury

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Abstract

Spinal cord injury research has greatly expanded in recent years, but our understanding of the mechanisms that underlie the functional recovery that can occur over the weeks and months following the initial injury, is far from complete. To grasp the scope of the problem, it is important to begin by defining the sensorimotor pathways that might be involved by a spinal injury. This is done in the rodent and nonhuman primate, which are two of the most commonly used animal models in basic and translational spinal injury research. Many of the better known experimentally induced models are then reviewed in terms of the pathways they involve and the reorganization and recovery that have been shown to follow. The better understood neuronal mechanisms mediating such post-injury plasticity, including dendritic spine growth and axonal sprouting, are then examined.

Keywords

spinal cord injury; reorganization; behavioral recovery; sensorimotor pathways; adult neurogenesis

Spinal cord injury affects more than 250,000 people in the United States, with more than 11,000 new cases reported annually. If people living with serious injuries to the spinal nerves are added to those suffering from central spinal injuries, the number may be closer to 400,000. Spinal injury research has greatly increased in recent years, but we still have much to learn. My intention here is to provide an overview of what is currently known about synaptic plasticity and functional recovery following different spinal cord injuries. I start with a brief review of the pathways that may be involved (or spared) by the injury, and define some of the features that distinguish primate and rodent spinal neuroanatomy, since these are the most commonly used animal models in basic and translational research. I then review what is known about experimentally induced spinal injuries that affect specific pathways of the cord. Finally, some of the better understood neuronal mechanisms mediating postinjury plasticity, such as dendritic spine growth and axonal sprouting, are examined. Adult neurogenesis is introduced as a possible addition to the list of mechanisms operating to bring about changes following spinal injury. This is a new field of inquiry in spinal injury research, but worth further study to determine its therapeutic potential.

Understanding the extent of an injury, and the time since its occurrence, is critical when trying to assess long-term reorganization and the potential for recovery of function. Clinical injuries are typically complicated, and the imaging techniques (e.g., magnetic resonance imaging) currently at our disposal cannot easily resolve the details of an injury or estimate the progression of that injury over time. For this reason, injuries classified as “complete” frequently have some sparing of sensorimotor fiber tracts, which may provide the basis for significant functional

improvement. One well documented and extreme example of this was apparent in the late Christopher Reeve, who regained sensation over the majority of his body surface, and the ability to move fingers and an arm, more than 5 years after an initial C1-2 complete cervical spinal injury (Corbetta and others 2002). This example may be unusual, but it underscores our current inability to accurately predict long-term recovery of sensorimotor function in people with chronic spinal injury. It also underscores the potential for functional improvements in patients with even a small amount of pathway sparing. Animal studies that allow us to investigate well-defined injury models under highly controlled conditions continue to be critical to our understanding of the mechanisms mediating functional recovery following spinal cord injury.

Functional Anatomy of the Spinal Cord

Figure 1 shows the major sensorimotor pathways of the cervical spinal cord in the macaque monkey and rat that are potentially involved following a spinal cord injury. This circuitry has been described extensively in the literature (Darian-Smith and others 1996; Willis and Coggeshall, 2004a, 2004b; Darian-Smith and Darian-Smith, 2004; Mountcastle, 2005, for reviews) and is only summarized here to aid the reader. There are important differences between the primate (including humans) and rodent spinal cord in terms of pathway organization. It is helpful to keep these differences in mind when interpreting data, particularly when rodent data are correlated with the clinical condition. For this reason, the rodent spinal neuroanatomy is also provided for comparison with that of the macaque monkey in Figure 1.

The primary somatosensory pathway comprises the afferent projections of the sensorimotor system, from peripheral receptors (e.g., mechanoreceptors, thermoreceptors, nociceptors, etc.) to the spinal cord, brainstem, thalamus, and cortex. When looking at hand function as an example, signals received by the mechanoreceptors of the skin, muscles, tendons, and joints of the hand are conveyed through the dorsal roots to the dorsal horn of the spinal cord and are transmitted to higher levels within the dorsal columns. Fibers in the dorsal column project to the cuneate nucleus in the ipsilateral medulla of the brainstem, and cross the midline (in the medial lemniscus) before terminating in the contralateral ventral posterolateral nucleus of the thalamus (i.e., VPLc in monkeys). The cell bodies of the spinothalamic neurons (transmitting pain and temperature information) originate in the cervical dorsal horn and cross the midline within one to two spinal segments before terminating primarily in the same thalamic nucleus. In primates, spinothalamic fibers also terminate in a more caudal thalamic nucleus (the anterior pulvinar) and rostrally in the posterior nucleus of the ventral lateral complex (VLp). Rodents (and even the cat), do not have an anterior somatosensory component to their thalamic pulvinar, which evolved exclusively in primates along with hand function. In primates, thalamocortical projections from the thalamic VPLc nucleus terminate within the primary somatosensory cortex (areas 3a, 3b, 1, and 2) in as many as four separate representations of the body map (Fig. 1C). Each body map is distinguishable as having a different peripheral neuronal input. In rodents (Fig. 1F), projections from the thalamic ventrobasal complex terminate in just one body map within the primary somatosensory cortex.

In both primates and rodents, additional pathways (e.g., spinoreticular, spinocerebellar, spinocervical) also transmit sensory information to higher levels, and higher levels of the pathway project feedback loops back to lower levels. For example, the somatosensory cortex projects directly to the cuneate nucleus, and to the dorsal horn of the cervical spinal cord, as part of the corticospinal tract. These pathways are continuously activated during the execution of fine manipulative tasks of the hand. The spinoreticular and spinomesencephalic tracts are mainly ipsilateral, terminate in the reticular complex and periaqueductal gray in the midbrain, respectively, and respond to noxious stimuli. The spinocerebellar pathways transmit signals

from muscle spindles and Golgi tendon organs, as well as cutaneous information (mainly of the lower body) to the cerebellar nuclei.

The descending motor pathways also differ in their organization between primates and rodents (Lemon 2008, for review). In primates, the corticospinal tract (CST) is the most functionally important control pathway in voluntary manual dexterity and is critical to the execution of fine, directed hand and finger movements. It originates from multiple regions of the motor and somatosensory cortex (Galea and Darian-Smith 1994), and 90% of fibers that project to the cervical cord descend in the contralateral dorsolateral CST. A further 8% of fibers project within the ipsilateral dorsolateral tract and ~2% form a bilateral ventral medial component. In the rat, the CST plays a less critical role in forepaw movement and relays mainly in the dorsomedial white matter in a position ventral to the dorsal columns (Brosamle and Schwab 1997; Courtine and others 2007). A much smaller number of fibers descend within the contralateral dorsolateral CST (between 5%–15%) and the ipsilateral ventral CST (<5%). The medial positioning of the CST in the rat is important when considering the effects of a dorsal transection or spinal contusion. In the monkey, sectioning the dorsomedial cord only blocks the major cutaneous mechanoreceptor pathway. In the rodent, the same injury will transect both the dorsal column and the CST pathways. In contusion injuries in the rat, the corticospinal pathway is likely to be significantly involved by the lesion, but this is not the case in a similar injury in the monkey or human.

Hominid forelimbs have not been used for weight-bearing synchronous locomotion for approximately 3 to 4 million years. Along with an expanding forebrain, primates evolved pathways that uniquely serve precision manual dexterity and hand eye coordination. With such an emphasis on hand function, primates also uniquely evolved corticospinal pathways that directly synapse with motor neurons innervating the hand and forelimb (corticomotoneuronal projections). In the cat and rodent, all corticospinal input to the cord synapses first on interneurons or networks of interneurons within the spinal intermediate zone (Porter and Lemon 1993; Lemon and Griffiths 2005). Rodents do not perform fractionated digit movements, have no opposing digits, and can perform only rudimentary sensorimotor tasks of grasping and holding with the forepaws.

In contrast to the CST in monkeys, the rubrospinal tract is relatively insignificant and almost nonexistent in the human. However, in rats the rubrospinal tract, which projects in the contralateral dorsolateral tract, plays a prominent role in voluntary forelimb movements. In an evolutionary sense, projections from the magnocellular red nucleus of the midbrain in the monkey have diminished relative to cats and rodents, and the parvocellular (small celled) component has enlarged to become a prominent feedback loop to the cortex via the inferior olive and lateral cerebellar hemispheres. The exact function of these prominent connections in the higher primates remains unclear.

The short and long propriospinal neurons (PSNs) may also be important following spinal injury. Long PSNs link forelimb and hindlimb activity during coordinated locomotion (e.g., walking or running). They originate in the cervical cord (C3-5), travel in the ventral and lateral columns, and terminate in the ventral horn of the lumbosacral enlargement. They are spared in midthoracic dorsal hemisection injuries and are able to bridge spinal segments above and below such a lesion. Long ascending PSNs have also recently been reported to project from lumbosacral segments to the contra- and ipsilateral (to a lesser extent) upper cervical cord in the rat (Dutton and others 2006), but it is not clear that a contralateral projection exists in the primate. Primates, including humans, also have long PSNs that connect their arms and legs and play a role in coordinating arm with leg swing during locomotion. However, there is no evidence in humans with midthoracic spinal cord injury that long PSNs contribute significantly to the recovery of locomotion after injury (Dietz, 2002). Short PSNs only connect the rostral

and caudal cervical cord (C3-4 and C6-T1) (Bareyre and others 2004). In the rodent, and the cat, which have no direct corticomotoneuronal (CM) connections, a substantial amount of corticospinal (CST) excitation reaches forelimb motor neurons via these cervical propriospinal projections. In contrast, in the macaque monkey and particularly in the human, where CST neurons innervate motor neurons directly, it seems that the propriospinal pathway plays little part in the transmission of cortical commands to motor neurons innervating the forelimb (Nakajima and others 2000).

The ventromedial brainstem pathways (i.e., the tectospinal tracts from the midbrain, and the vestibulospinal, reticulospinal, and bulbospinal pathways from the brainstem reticular formation) descend in the ventrolateral white matter and terminate in the ventromedial part of the intermediate zone. Many of these projections terminate bilaterally and are thought to be involved in the motor control of the postural muscles of the neck, trunk, and proximal limbs (Kuypers 1981). Their potential contributions to the recovery of central body and proximal limb movements following spinal injury have not been investigated.

From a behavioral and evolutionary standpoint, the rodent quadruped mainly uses its limbs for efficient locomotion through its external environment. Although the rodent's forelimbs and forepaws are used to reach and grasp, in locomotion they are moved stereotypically in a bilaterally synchronous gate with the hindlimbs. Even with a total transection of the thoracic cord, the hindlimbs can be trained to step, when the appropriate sensory feedback is applied to the hindpaws and the body weight supported. This demonstrates that the local spinal circuitry is capable of orchestrating coordinated limb movement, independent of cortical or brainstem control (i.e., a central pattern generator). In patients, a rudimentary stepping behavior can be learned with a technically complete spinal cord transection. However, although the therapies that simulate synchronous walking in such patients enable important collateral health benefits, these patients are not able to step without complete assistance. This is because the circuitry required for walking is particularly complex in humans and complicated further by the weight-bearing needs of the large human biped.

Representational Maps

As in all sensory systems, the skin across the body surface and deeper fascia are represented in the somatosensory system in a topographic or "somatotopic" fashion. This means that inputs from adjacent body parts are generally located next to each other and this pattern is maintained at all levels of the neuraxis, from cord to cortex. The digit pads of the primate hand represent the sensory "fovea" of the somatosensory system and have a higher receptor density than elsewhere. In turn, input from the digits projects to a disproportionately large region of the subcortical structures and primary somatosensory cortex, and a greater part of the brain is devoted to processing this information. Representational maps can be obtained from any level of the pathway, using electrophysiological recording methods to plot receptive field maps across the skin and deeper tissues. Such maps have been used extensively as an indirect measure of cortical and subcortical circuit and synapse reorganization following a range of peripheral and central injuries (Kaas 2002; Kaas and others 2008), including dorsal root (Darian-Smith and Brown 2000) and central injuries to the spinal cord (Jain and others 1997/2000; Weng and others 2003).

Primary and Secondary Responses to Spinal Cord Injury

As with a traumatic injury anywhere in the CNS, a direct impact to the spinal cord initiates an injury response that unfolds as a series of cellular and molecular events in the subsequent hours, days, and weeks. Primary injury involves direct cell death and bleeding that is caused by the initial mechanical damage sustained. However, within hours, further tissue damage begins to occur around the injury core. This secondary damage involves a cascade of vascular,

biochemical, and cellular events. Vascular changes include inflammation and edema, ischemia, hypoxia, and a reduced spinal perfusion. At the biochemical level, there are excitotoxic changes, the release of proteases, and the formation of nitric oxide and free radicals. At the cellular level macrophages and neutrophils invade the injury site and there is apoptosis of oligodendrocytes and Wallerian degeneration. Microglia and astrocytes are activated, which results in glial scarring (Fawcett and Asher 1999).

Contusion injuries to the primate (monkey and human) and rat (but not mouse) spinal cord typically cause ischemia and a central necrotic region. Over several weeks, macrophages clear this region of tissue debris, leaving one or more fluid-filled cysts or cavitations encased in scar tissue (Fawcett and Asher 1999; Maier and Schwab 2006). The astroglial scar, regardless of whether it surrounds a cyst, is known to form a barrier to axonal growth and regenerative processes. A dorsal rhizotomy, which occurs just outside the cord, permanently severs axons projecting into the cord. If the dorsal root fascicles tear the cord at the dorsal root entry zone, then many of the central trauma responses described above will also apply to this injury. If, however, there is no tearing of the CNS, then necrosis and astroglial scarring do not occur centrally within the cord and many of the responses described above are minimal or even absent.

The period following spinal injury can also be described in terms of stages in neuronal reorganization at different levels of the affected sensorimotor pathway. In this scenario, during an acute phase (minutes to hours), there is an immediate loss of input to regions of the CNS beyond the injury site suddenly deprived of normal input. Immediately following a spinal injury that blocks sensory input, from part of the hand for example, there is a sudden quiescence or silencing of activity along the pathway where this input was once transmitted. This is particularly obvious as a “silent zone” in the representation of the hand in the body map in the somatosensory cortex. Along with this cessation of coherent activity there can be a rapid expansion of the representation of neighboring parts of the hand around the silent zone, which results from the disinhibition of these projections. This expansion can occur within minutes and may last for weeks to months. In a chronic second stage (lasting weeks to months), neurons spared by the lesion form new connections and there is a consolidation of the body map representations along the affected pathways. In a final stage that may occur over many years, there is a slow atrophy of neuronal populations that have chronically lost all of their input.

Neuronal Reorganization following Spinal Injury

Spinal injuries that damage the sensorimotor pathways are known to cause synaptic changes in neuronal circuitry, within the spinal cord and at higher levels, over the postinjury weeks and months. Even in the most commonly used rodent models, these changes are not well understood. Synaptic plasticity has been demonstrated most notably in terms of 1) changes in functional maps at the spinal and higher levels of the sensorimotor pathways, 2) structural changes to neurons, and 3) altered firing properties of spared neuron populations.

Behavioral Adaptation and Functional Map Changes

The following paragraphs summarize some of the known behavioral adaptations and functional map changes that occur following spinal injuries at multiple levels of the pathway. Only injuries affecting fibers central to the dorsal root ganglia (i.e., the dorsal roots) and beyond are described, inasmuch as these do not regenerate like peripheral nerves.

Spinal Rhizotomy—The study of the behavioral effects of a spinal dorsal root cut (or dorsal rhizotomy) began more than a century ago (Mott and Sherrington 1895), when it was shown that cutting roots C4-T1 completely blocked sensation and voluntary movement of the forelimb. In the modern era, Vierck (1982) also studied the behavioral effects of a dorsal

rhizotomy in the monkey (C3-T3) on forelimb reaching to points in space. Although he also observed an initially severe deficit, he observed that after many months of training there was a gradual recovery of some rudimentary directed limb movements. In more extreme dorsal rhizotomy studies in the macaque monkey, whereby roots C2-T4 were cut to deafferent the entire forelimb (Pons and others 1991; Jones and Pons 1998), limb sensorimotor function did not return in 20 years (Pons and others 1991; Woods and others 2000). There was, however, an extensive reorganization of the body map representations within the thalamus and cortex, such that the face was represented over an abnormally large region and abutted trunk representation (Jones and Pons 1998). In early studies in the cat, Basbaum and Wall (1976) also showed that when they cut dorsal roots supplying the hindlimb, initially deafferented spinal dorsal horn neurons altered in their response properties and developed novel receptive fields. Together these studies suggested a central neuronal plasticity, and some functional recovery with training, but the mechanisms responsible were not identified.

In more recent studies in our laboratory, we examined the acute, chronic, and longer term effects of a much smaller cervical dorsal rhizotomy in the macaque monkey. In these experiments, dorsal rhizotomies only involved cutting rootlets innervating the first two or three digits of one hand. When we assessed the performance of a precision grasp task that required cutaneous and proprioceptive feedback (Darian-Smith and Ciferri 2005), we observed significant recovery of function. Monkeys were divided into two groups and trained in a precision grip task to retrieve a target object held in a clamp (Fig. 2C). Group 1 animals received a dorsal rhizotomy to deafferent the thumb and index fingers, and group 2 received a slightly larger lesion that deafferented the middle finger and thenar eminence (Fig. 2A, B). The percentage of successful retrievals, the strategy of digit opposition, and the duration of digit contact with the object prior to retrieval (contact time) were all assessed pre- and postoperatively. All monkeys had a severe functional deficit in the hand during the first postoperative week. Group 1 monkeys recovered their ability to retrieve the object in >80% of trials over the first six to eight weeks, and group 2 monkeys with the larger lesion also regained function in the impaired hand over several months. The data from one such monkey are illustrated in Figure 2. As this example illustrates, recovery was sometimes dramatic, but was never complete. Monkeys quickly adopted alternate strategies for grasping the target, and used or recruited digits that were incompletely deafferented. Hand representations mapped in the contralateral somatosensory cortex (Darian-Smith and Brown 2000), and in the cuneate nucleus (Darian-Smith and Ciferri 2006), showed a partial reactivation and a close correspondence between the “hand” maps and the extent of digit use (Darian-Smith and Ciferri 2005). For example, the hand map shown at 29 weeks after rhizotomy in the cuneate nucleus in Figure 3 shows only one receptive field on the thumb (electrode penetration 8). Behaviorally, this monkey regained function in the index and middle fingers, with only minimal use of its thumb. The cortical map correspondingly showed a greatly reduced input from the thumb but a near complete reactivation of the surrounding finger representations (Darian-Smith and Ciferri 2006).

These studies showed that the sparing of even small numbers of somatosensory fibers (<5%) can lead to functional map changes and quite dramatic behavioral recovery during the early postoperative months. Additional parallel structural changes (e.g., sprouting of spared axon terminals within the cord) were also evident, and our work on this is discussed later.

Dorsal Column Transection—A number of studies have examined the behavioral effects of dorsal column lesions on hand function, but many of the reported findings are inconsistent (Kaas and others 2008). Descriptions of deficits for supposedly similar lesions have ranged from subtle and insignificant (Leonard and others 1992) to chronic and debilitating (Glendinning and others 1992). Unfortunately, this stems (at least in part) from a lack of lesion reconstruction in many studies, which has made it difficult to correlate the specifics of the

injury with behavioral changes. Vierck and Cooper (1998), who did make the link, showed that a cervical dorsal spinal column transection initially impaired the monkey's ability to discriminate textures, or specifically, the frequency or duration of tactile stimulation. Some, but not all, monkeys recovered texture discrimination capabilities over several months of testing, and it was proposed that those that did recover learned to use alternate cues and pathways to assess and discriminate textures. Humans with lesions including the dorsal columns (Nathan and others 1986) also reportedly show a loss of temporal and spatial discriminative ability.

What changes occur within the somatosensory pathways following a dorsal column lesion? One study that looked at systemwide responses in owl monkeys following a C3-4 cervical dorsal column lesion (Jain and others 2000) showed that when the dorsal columns were completely transected, the spared spinothalamic pathway was unable to reactivate the cortical map, and face inputs expanded to utilize the neighboring silent forelimb cortex. When even a tiny part of the dorsal column was spared, this input was able to reactivate the hand map and expand to fill the corresponding cortex. An anatomical analysis showed that preserved inputs from the face could sprout over many months from the trigeminal nucleus in the medulla into the denervated cuneate nucleus (Jain and others 2000). This implied that the spinothalamic pathway played little role in the cortical reorganization, although this issue remains controversial (Wall and others 2002), and the spinothalamic pathway may play more of a compensatory role in the human (Nathan and others 1986).

Hemisection and Corticospinal Tract Injuries—Behavioral deficits and postoperative recovery have also been studied following a spinal hemisection. Hemisections in the macaque, as in the human, also involve the dorsal column in addition to the corticospinal tracts and other ascending and descending pathways on the lesion side of the cord. In a series of experiments (Darian-Smith and others 1996; Galea and Darian-Smith, 1997), Galea and Darian-Smith found that near-complete hemisection lesions at spinal segments C3-4 resulted in a severe hemiparesis immediately postoperatively. However, monkeys consistently regained the ability to pick up objects with the impaired hand within one month of the lesion. At three postoperative months, they could use their hand and digits even more effectively in a reach-grasp-retrieval task, although recovery was never fully complete. Long-term deficits included a less direct reaching trajectory, a less precise preshaping of the hand during the reach component of the task, and a residual weakness of the opposing digits. The somatosensory component of the task was also clearly impaired, and sensory maps of the arm and hand representation in the primary somatosensory cortex, which were deprived of their normal input, were reorganized. The hand map was reduced in size and cutaneous receptive fields were unusually large. It was proposed that the preexisting “crossover” corticospinal projections within the cervical spinal cord contributed to the observed behavioral recovery. More recent investigations that have examined the behavioral recovery of cervical hemisections in rhesus macaques, and the anatomical bases for these changes, support these findings (Rosenzweig and others 2009).

Rodent models of corticospinal tract injury that demonstrate behavioral recovery (Bareyre and others 2004; Ballerman and Fouad 2006) also demonstrate limited sprouting of spared corticospinal or corticobulbar fibers within the cord that form new connections and alternate transmission streams from the cortex to appropriate targets in the cord (Maier and Schwab 2006; Hagg 2006; Fouad and Tse 2008).

Mechanisms Mediating Functional Recovery/Circuit Remodeling

Structural Reorganization

Inasmuch as the regeneration of cut axons following injury has been shown to be extremely limited in the adult CNS, any spontaneous recovery of sensorimotor function observed

following spinal injury must result from structural remodeling of spared axons and/or dendrites within the damaged systems. Such remodeling can and does occur at more than one level of the neuraxis, from the spinal cord to the brainstem to the thalamus and sensorimotor cortex (Raineteau and Schwab 2001; Hickmott and Ethell 2006, for reviews).

Dendritic Changes—Dendritic spines are known to be synaptic target sites, so spine density and structural changes indirectly measure synapse remodeling. There is considerable evidence of dendritic plasticity in the CNS in response to environmental enrichment (Kolb and Whishaw 1998), hibernation (von der Ohe and others 2007), sensorimotor learning (Chang and Greenough 1982; Greenough and others 1985), and cortical damage or peripheral injury (Jones and Schallert 1992, 1994), and spinal cord injury is no exception. Following a spinal overhemisection in the rat, for example, Kim and colleagues (2006) observed changes in the density and morphology of dendritic spines in pyramidal neurons in the contralateral motor cortex. This group (Kim and others 2008) also showed that the structural modifications observed postoperatively (i.e., increased spine density and spine maturation) could be promoted in an enriched environment, following the transplant of embryonic spinal tissue and the administration of the neurotrophin NT-3 into the hemisectioned site.

Axonal Sprouting—Although there is little evidence in the literature for spontaneous axon regeneration following central spinal cord injury, ample evidence exists for axonal sprouting as a means of synaptic adaptation or compensation following such an injury. It is worth noting the distinction between regeneration and sprouting as these refer to different processes. Axon regeneration is the regrowth of transected axons at their cut tip, whereas sprouting, by comparison, involves the growth of collateral branches from fibers spared by the injury. As mentioned above, central spinal injuries typically result in the formation of an astroglial scar that presents a strong physical and chemical barrier to axonal regeneration. Axonal sprouting, however, can occur around a glial scar as well as distant (rostral or caudal) to the injury site in multiple distributed tracts, and this process appears to be critical for the strengthening of existing connections and the facilitation of new alternate functionally relevant connections (Aoki and others 1986; Li and Raisman 1995; Galea and Darian-Smith 1997b; Fouad and others 2001; Weidner and others 2001; Bareyre and others 2004; Darian-Smith 2004; Ballermann and Fouad 2006; Hagg 2006; Fouad and Tse 2008). For example, after making a thoracic lesion of the adult rat corticospinal tract, Bareyre and colleagues (2004) showed that spared corticospinal axons sprouted at the cervical level to form new connections with long propriospinal neurons. These new connections provided an alternate route to hindlimb motor neurons that correlated with behavioral recovery. In another example, Ballermann and Fouad (2006) made a lateral thoracic spinal hemisection in adult rats and reported sprouting in the reticulospinal tract, which also correlated with behavioral recovery. Most reports of injury-induced axonal sprouting come from work in the rat, but unpublished and indirect evidence in the nonhuman primate indicate that sprouting within the cord following central injury is not species dependent.

Axonal sprouting has also been demonstrated after a cervical dorsal root lesion (see Fig. 4) in the monkey. Dorsal root lesions differ from peripheral nerve lesions in that they occur between the dorsal root ganglia and the dorsal root entry zone. Such injuries are permanent and do not result in regeneration. During the first few months after such a lesion, spared nerve fibers that enter the cord adjacent to the lesion sprout locally within the spinal dorsal horn within the deprived region (Darian-Smith 2004), presumably to form new connections with second-order neurons that permanently lose their original input from the hand. The fibers that are spared are few in number (<5%) and initially functionally silent, as has been shown behaviorally and electrophysiologically (Darian-Smith and Ciferri 2005, 2006). This suggests that the induced sprouting of these fibers within the cord acts to increase synaptic connections and to strengthen the transmitted signal from the deprived hand to higher levels of the pathway over the postlesion period.

Ultrastructural Examination of Changes following SCI—Although the basic ultrastructure of the spinal cord has been described in some detail (Ralston 1979; Ralston and Ralston 1979, 1985) and has been investigated following peripheral nerve transection (Knyihar-Csillik and others 1987; Woolf and others 1995; Havton and Kellerth 2001), relatively few studies have examined ultrastructural changes following injuries to either the dorsal roots (Darian-Smith C, Hopkins S, and Ralston HJR, unpublished data, 2009; see next section) or central spinal pathways (Tai and others 1997; Linda and others 2000). From these, it is clear that degenerative and regenerative changes in local spinal neuronal populations are extremely dynamic during the early postinjury weeks and months. However, these studies do not yet provide a cohesive and predictable description of the detailed synaptic changes that take place.

Changes to the Spinal GABAergic Circuitry following SCI

Deafferentation injuries alter the normal balance of excitatory and inhibitory circuitry within the dorsal horn. GABA is the most ubiquitous of the inhibitory neurotransmitters in the superficial spinal cord, and consequently it has received greatest attention. Rat studies have shown that GABA-immunoreactive (GABA-ir) neurons are evenly distributed in the superficial laminae of the spinal dorsal horn and comprise ~33% of the overall neuron population (Todd and Sullivan 1990; Todd and Lochhead 1990; Castro-Lopez and others 1993). The main actions of GABAergic neurons in the spinal cord are the presynaptic inhibition of primary afferent terminals and the postsynaptic inhibition of dorsal horn neurons (including interneurons, sensory projection neurons, and motor neurons in the ventral horn).

Studies that have examined GABAergic circuitry following peripheral injury typically report a reduction of inhibitory mechanisms (Castro-Lopes and others 1993; Ibuki and others 1997; Ralston and others 1997; Eaton and others 1998; Moore and others 2002; Somers and Clemente 2002), and it has been proposed that reduced GABA inhibition decreases the modulation of incoming noxious signals. This is thought to result in an abnormally intense transmission and perception of the stimulus as neuropathic pain. Central lesions also result in a reduction of GABAergic elements (Ralston and others 1997).

We have recently been examining synaptic alterations at the ultrastructural level in the monkey spinal cord following a dorsal rhizotomy (Darian-Smith C, Hopkins S, and Ralston HJR, unpublished data, 2008). Such injuries do not cause demonstrable neuropathic pain in the macaque, but they do produce an initially severe deficit in hand function, which then recovers remarkably over the first postlesion months (Darian-Smith and Ciferri 2005). The focus of our analysis was on synaptic profiles within the superficial laminae I-III of the dorsal horn, inasmuch as these layers are known to receive the major mechanoreceptor and nociceptor inputs from the affected digits (Darian-Smith, 2007,2008; Willis and Coggeshall 2004a, 2004b). In contrast to the effects of peripheral and central lesions, we observed a significant increase in the GABAergic circuitry in the dorsal horn on the side of the lesion compared with the normal side (Fig. 5). The reduced C-type profiles on the side of the lesion reflect the loss of primary afferents and were expected. An absence of pain-related symptoms in our animals, and an elevated GABAergic neuronal population within the superficial dorsal horn, is consistent with the view that reduced inhibition in the dorsal horn plays a role in neuropathic pain (see Yeziarski 2006; Ralston and others 1997) but offers little in the way of an explanation for the increase. Even a basic understanding of the inhibitory/excitatory balance within the spinal cord awaits further study.

Neurogenesis following CNS Injury

Mammalian adult neurogenesis is known to occur under normal conditions in what are coined “neurogenic” regions of the brain. These include the subventricular zone, hippocampus,

olfactory bulb, and possibly regions of the neocortex although the latter remains controversial. Neurogenesis can also be induced in broader regions of the CNS in adult mammals in response to certain types of injury or disease (Magavi and Macklis 2000; Arvidsson and others 2002; Nakatomi and others 2002; Parent and others 2002; Chi and others 2006; Ohori and others 2006; Vessal and others 2007; Hou and others 2008), although the details of where it occurs and how it can best be induced remain unclear. Its presence in response to injury and disease raises the exciting possibility that certain parts of the CNS switch on endogenous neurogenesis in response to certain pathologies, and incorporate new neurons into the functional architecture of cell-depleted and circuit-challenged regions of the brain. Recent studies in the normal dentate gyrus (Toni and others 2008) and ischemic striatum (Hou and others 2008) are starting to provide direct evidence that neurons formed during adult neurogenesis have a fully functioning physiology, neuronal morphology, and synaptic phenotype at the ultrastructural level (Toni and others 2008). Work is now needed to determine whether the neurons produced following injury or disease likewise form functional, long-lived cells that are integrated into the neuronal circuitry.

Spinal Neurogenesis—Emerging literature across a number of species indicates that under normal circumstances, the adult spinal cord is non-neurogenic (Horner and others 2000; Yang and others 2006; Vessal and others 2007). However, recent studies show that neurogenesis can be induced in the spinal cord following certain types of injury and disease. In examples of disease states, Chi and colleagues (2006) observed neurogenesis in the spinal cord after motor neuron degeneration in amyotrophic lateral sclerosis mice, and Danilov and colleagues (2006) observed new spinal neurons in a rodent model of multiple sclerosis.

Neurogenesis can also occur in the cord in response to specific kinds of spinal injury. When there is direct trauma to the spinal cord (e.g., a contusion injury or hemisection), massive gliosis is observed throughout the “lesion zone” (the region deprived of input), which results in the formation of a glial scar (Fitch and Silver 2008). Activated astrocytes within the scar release factors that block axonal sprouting and other regenerative processes (Silver and Miller 2004; Feeney and Stys 2005; Klusman and Schwab 2005; Barkho and others 2006). Thus, studies that have investigated neurogenesis following a hemisection (Yang and others 2006) or dorsal column lesion (Vessal and others 2007) observe massive gliosis but no neurogenesis. But what happens when the injury occurs outside the cord and when gliosis and scarring is minimal or absent? We recently set out to investigate this (Vessal and others 2007) in a series of experiments in both rats and monkeys. Dorsal roots innervating several digits of the hand in the monkey were cut, which resulted in a corresponding loss of sensory input to the thumb, index, and middle fingers. As has been described (above) this resulted in a severe initial deficit in manual dexterity (Nagano 1998; Darian-Smith and Ciferri 2005) followed by significant neuronal reorganization and behavioral recovery (Darian-Smith 2004; Darian-Smith and Ciferri 2005, 2006). Bromodeoxyuridine (BrdU), which is an analogue of thymidine and incorporated into dividing cells during part of the division cycle, was injected into monkeys two to three weeks after they had received a dorsal rhizotomy. Monkeys were then killed six to eight weeks later (Fig. 6). In rats with equivalent lesions, BrdU was injected one week postoperatively and the animals killed 4 weeks later. Rats with a central dorsal column lesion were also analyzed to provide a direct central injury comparison with dorsal root lesion animals. In both sets of experiments and in both species, neurogenesis was observed within the dorsal horn in the “lesion zone” of the spinal cord in the form of cells colabeled for BrdU and a series of mature neuronal markers. Neurogenesis was not observed in rats with central dorsal column lesions, which is consistent with other reports following central spinal injuries. Total number estimates of new neurons within the region of the cord affected by the injury were substantial, averaging more than 3400 in the spinal gray matter within the 3 monkeys examined. Inasmuch as BrdU is incorporated into dividing cells during a very brief period (~2 h) following injection (Cameron and McKay 2001), these numbers represent only a tiny portion of the total produced.

If even a small number of these newly born neurons survive and integrate into the local circuitry (and this is not currently known), the numbers would be sufficient to influence local circuitry reorganization.

Interestingly, the spinal cord is not the only site of induced neurogenesis following a spinal dorsal root lesion. An investigation just completed in our laboratory now indicates that neurogenesis is also induced in the corresponding reorganized sensorimotor cortex (Vessal M, Darian-Smith C, unpublished data, 2009). This has not been shown previously and indicates that at least following a dorsal root injury, neurogenesis can be induced at more than one site along the projection pathway. In our study in the adult monkey, it is occurring in primary somatosensory cortex, many synapses away from the injury site. If these newly formed neurons can be shown to survive and to incorporate themselves functionally into the neuronal circuitry over the longer term, they may prove to be important in the development of therapies that optimize systemwide recovery following spinal injuries.

Regenerative Treatments that Promote Plasticity following Spinal Cord Injury

The limited capacity for axonal growth in the adult CNS owes much to inhibitory factors that are upregulated or released following injury (e.g., Nogo-A, chondroitin sulphate proteoglycans, semaphorin 3A, Ephrin/EphA4, etc.). Relatively little is yet understood about these proteins and the adaptive and maladaptive roles each may play following injury. However, the progress that has been made holds considerable promise for the development of therapies that enable far more extensive and beneficial axonal sprouting and circuit remodeling than is presently possible. One of the most extensively studied of these proteins is the myelin-associated growth inhibitory protein Nogo-A. It has been demonstrated that neutralizing this factor results in the disinhibition of corticospinal axon terminals around the glial scar. Work on Nogo-A neutralization (Schwab 2004; Barritt and others 2006; Buchli and others 2007; Rossignol and others 2007; Walmsley and Mir 2007; Gonzenbach and Schwab 2008) has produced sufficiently promising results that clinical trials are currently under way.

Considerable work has also focused on chondroitin sulfate proteoglycans (CSPGs), which form much of the extracellular matrix surrounding neurons in the adult CNS. The CSPGs are a heterogeneous group of molecules found in what are known as perineuronal nets, which surround neurons in the mature CNS, and are thought to be involved in the regulation of activity-dependent synaptic plasticity (Pizzorusso and others 2002). Following spinal injuries that produce glial activation, CSPG expression is increased at the injury site as well as at denervated secondary sites such as the dorsal column nucleus neurons (Asher and others 2000; Silver and Miller 2004; Massey and others 2008). This increase in CSPG expression is thought to block axonal growth at the injury site. However, when the enzyme chondroitinase ABC is applied following injury, CSPG expression is blocked and the perineuronal nets break down. The application of chondroitinase-ABC following spinal injury has now been shown to promote regenerative sprouting of sensory and motor pathways (Barrit and others 2006; Fawcett, 2006; Yiu and He 2006; Galtrey and others 2007; Kwok and others 2008) and is accompanied by functional recovery (Bradbury and others 2002; Caggiano and others 2005; Houle and others 2006).

Therapeutic approaches such as these, possibly in combination with each other or additional treatments (e.g., using growth factors, etc.) have the potential to augment axonal sprouting and to promote postinjury synaptic changes that can optimize functional recovery in patients over the long term.

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C6 in the Macaque and Human

C6 in the Rat

Figure 1.

(A, D) Terminal distributions for the different primary afferent subpopulations terminating in the dorsal horn (left side), and the major ascending (color), and descending (gray scale) tracts involved in the transmission of sensorimotor information within the cord (right side). (A–C) Monkey neuroanatomy and (D–F) the equivalent for the rat. (B, E) Major sensorimotor ascending and descending pathways of the cervical spinal cord. (C, F) Some of the organizational features of the primary somatosensory cortex, and in the case of the rat (F), there is only a single body map. In the macaque (C), there are four different somatosensory regions, each with a separate hand (and body) representation. Some other major species differences are evident in, for example, the location of the major corticospinal tract (medial and ventral to the dorsal columns in the rat, and dorsolateral in the macaque and human). (Adapted from Darian-Smith 2008 with permission from Elsevier.)

Figure 2.

(A–C) Data from a monkey (M3) that received a dorsal rhizotomy that removed input initially from the thumb, index, and middle fingers. (A) Monkey's cortical receptive field map 22 weeks following the rhizotomy. The photograph and cortical map illustrate the sites of microelectrode penetrations caudal to the central sulcus (CS) in the somatosensory cortex. The cortical field of each digit representation is outlined and color coded and a silent cortical zone resulting from the deafferentation of the digits is identified by the unfilled circles. Note the partial reemergence of input from the index and middle fingers and the corresponding partial recovery of the use of these digits in C. Scale bar = 2 mm. (B) Success rates (y axis) for target retrievals over the postinjury weeks (x axis). This monkey did not successfully retrieve the target for the first 7 weeks but then began to regain function in its first three digits. Although the distal pads of the thumb and index finger were not used again to contact and retrieve the object, this monkey recovered a remarkable amount of function in the thumb, index, and middle digits, after an initial delay. (C) Four frame sequences showing the predominant manual stratagems used after lesion in the same monkey. Column 1 shows the normal prelesion precision grip stratagem executed by opposing the distal pads of the thumb and index finger. Column 2 shows the impaired hand at one week following the lesion; there was a complete loss of the ability to sense and respond to the clamp or target. The hand was held "paddle" style, and all attempts to remove the object failed. Columns 3 and 4 show successful but abnormal and alternate stratagems (opposition of the thumb and middle finger) adopted by the 11th week (shown here in the 13th week) and used and improved over the remaining assessment period. (From Darian-Smith and Ciferri 2005 with permission.)

Figure 3.

Somatotopic maps of the representation of the hand in the cuneate nucleus in a monkey that received rhizotomies similar to the animal in Figure 2, which blocked input from digits D1–D3. Receptive fields (RFs) were significantly reorganized within the nucleus on the side of the lesion at 29 weeks following the dorsal root lesion, and input from the thumb was virtually absent (only 1 RF in track 8). A core unresponsive region was also consistently found on the side of the lesion in a region corresponding to D1–D3 representation on the normal side. This matched behavioral recovery over the postinjury period in which thumb use was limited, and cortical maps in which thumb representation was also greatly reduced. Scale bar = 1 mm. (From Darian-Smith and Ciferri 2006 with permission.)

Figure 4.

(A) A series of sections taken through the cervical spinal dorsal horn of a macaque monkey showing the distributions of terminals of primary afferents labeled with cholera toxin subunit B conjugated to horseradish peroxidase injected bilaterally into the thumb and index finger in a monkey with a postoperative survival period of 16 weeks. The rostrocaudal extent of the lesion is shown by the oblique black bar on the left of a series of transverse sections of the cervical spinal cord. The six enlarged cross-sections illustrate the distributions of labeled terminals within the dorsal horn in C6 and C7. Labeling in the dorsal horn now occurred throughout the lesion zone in the left hemicord, defined by the distribution of label in the right normal hemicord. Inset shows a distribution map superimposed on an adjacent section (Luxol Fast Blue). Note the myelin sparse degeneration zone within the dorsal column and the presence of terminal labeling within superficial and deep laminae of the spinal dorsal horn. Gray shading through the section stack outlines the rostrocaudal extent of labeling within the dorsal horn on each side of the cord. Roman numerals show the approximate location of the different laminae within the dorsal horn. Scale bar = 2.5 mm. (B) Distribution territory histograms of terminal labeling within the spinal dorsal horn in each of the monkeys used in the analysis. Each bar gives the volume estimate for any one section. Gray indicates distribution territory histograms on the control side; black indicates distributions on the side of the lesion. Dashed pale gray lines indicate lesion positioning and rostrocaudal extent. All short-term comparisons were statistically significant and long-term insignificant. P.O., postoperative. (From Darian-Smith 2004 with permission.)

Figure 5.

(A) Count profiles of two synaptic elements through the superficial laminae of the dorsal horn in two monkeys. Counts shown are mean values for all sections through segments C5-7, normalized so that numbers are presented per 100 μm^2 . Data on the side of the lesion (blue diamond) are directly compared with data on the nonlesioned side (filled squares), and paired sample *t*-tests used to determine the statistical differences of elemental profiles on the two sides of the cord. *P* values and distribution profiles are given for each data set and indicate a similar profile distribution pattern across the two monkeys. These data show that primary afferent terminals decrease dramatically (C type) whereas inhibitory profiles increase significantly (F-GABA-ir) on the side of the lesion during the early months following a cervical dorsal root lesion. (B) Electron micrograph of GABAergic terminals (colloidal gold immunolabeling) within the deprived (left) and "normal" (right) dorsal horn in a monkey that received a cervical dorsal rhizotomy four months earlier. In the left image, inhibitory terminals synapse with dendrites, D, and the synapse shown in the right image is axosomatic.

Figure 6.

(A) Examples of cells within the dorsal horn in the lesion zone of a monkey that had received a cervical dorsal rhizotomy five weeks previously, colabeled with the cell division marker 5-bromo-2-deoxyuridine (BrdU) and either the neuronal markers, neuron-specific nuclear protein (NeuN), or GABA. The location of these colabeled neurons is shown top right. Orthogonal images and a spectral intensity profile show mark colabeling. (B) A histogram showing total numbers of 5-bromo-2-deoxyuridine/neuron-specific nuclear protein (BrdU/NeuN)-colabeled cells through cervical segments C5-8 in the monkey, estimated using the fractionator method (West and others 1991) for each half (R, rostral; C, caudal) cervical segment. Counts were significantly higher in the dorsal horn on the side of the lesion compared with the contralateral “control” side. (C) Examples of cells immunopositive for neuronal markers and BrdU in a rat that also received a dorsal root lesion. (From Vessal and others 2007 with permission.)