Spinal cord injury and plasticity: Opportunities and challenges

Karim Fouad a, *, Aleksandra Krajacic b, Wolfram Tetzlaff b

a University of Alberta, Canada
b ICORD (International Collaboration on Repair Discoveries), University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

There is still no effective treatment to promote functional recovery following spinal cord injury. However, promoting injury-induced adaptive changes (plasticity) within the central nervous system, associated with repair, promise new treatment strategies. Recent contributions from our group and current challenges of this relatively young field are discussed in this review.

© 2010 Elsevier Inc. All rights reserved.

1. Plasticity and its contribution to recovery

The challenge of assessing the functional implications of plasticity following any injury of the CNS is complicated by findings of adaptive changes in spared and injured circuitries within the entire nervous system. This is surprising as for many years it was believed that the central nervous system (CNS) is rigid and hard-wired and thus not able to self-repair. However, plasticity cannot be seen as a “repair mechanism” only, but might also contribute to unwanted effects. Since the complete molecular mechanisms of plasticity are not well understood, it is necessary to understand the principles and limitations of these adaptive mechanisms, which might open up new treatment avenues for injuries and diseases of the CNS. In this review we will discuss the authors’ current thoughts on the role of plasticity in motor recovery following SCI and the present challenges the field is facing.

1. Plasticity and its contribution to recovery

The challenge of assessing the functional implications of plasticity following any injury of the CNS is complicated by findings of adaptive changes in spared and injured circuitries within the entire CNS. Such changes not only occur at various anatomical areas but also at different physiological and molecular levels, basically wherever investigations have been performed. Areas where plasticity has been described following SCI include the sensory-motor cortex of humans [14,31,54] as well as of animals [20,36,42,75], the brainstem [33,73,74], and the spinal cord above and below level of an injury [2,3,5,16,19,36,38,45,91]. The broad range of mechanisms involved in plasticity include growth of new axonal branches.

Keywords:
Central nervous system
Plasticity
Spinal cord injury
Functional recovery
Rehabilitation

Contents

1. Plasticity and its contribution to recovery ................................................................. 337
2. Promoting plasticity to treat spinal cord injury ...................................................... 338
3. Rehabilitative training and plasticity ................................................................. 339
4. Plasticity and lesion severity .............................................................................. 340
5. The other side of the coin, plasticity and adverse effects ................................ 340
6. Conclusion ........................................................................................................ 340
Acknowledgements ............................................................................................. 340
References ........................................................................................................... 341
For example, strong correlation of plasticity with the time course cal reasons. Nevertheless, various studies argue that the recovery relesion experiments and pharmacological or electrophysiological latter is more convincing, and can theoretically be achieved with recovery, or to dissect out their contribution to recovery. While the aspects of plasticity are to correlate mechanisms of plasticity to recovery. For instance, strong correlation of plasticity with the time course of recovery was found in the study by Ballermann and Fouad where compensatory sprouting of spared reticulospinal tract fibers following thoracic hemisection coincided with locomotor recovery. Since the reticulospinal tract is involved in triggering locomotion using tonic descending signals to excite spinal locomotor networks, this study indicates a direct relation of plasticity and recovery. Similarly, a positive correlation of recovery of forelimb function and corticospinal tract (CST) sprouting was found following incomplete cervical injuries in rats. In addition, studies that have carried out sequential relesion of spared corticospinal tract fibers support the notion that sprouting of CST fibers is beneficial to functional recovery. For instance, Barea and Muir [5] performed a unilateral pyramidal tract lesion to confirm CST plasticity following an incomplete spinal cord injury, and found that recovered function and evoked potentials in the hindlimb were abolished by the second lesion. Similarly, after Kanagal and Muir [55] lesioned the dorsal funiculus six weeks following a dorsolateral funiculus (DLF) lesion in rats and found in a skilled fore-paw reaching task that the secondary lesions to dorsal funiculus increased the reaching deficits seen after initial DLF. According to Weidner et al. [91], complete lesion of the dorsal CST combined with the lesion of the ventral CST eliminated sprouting and functional recovery that was seen if only the dorsal CST was lesioned. Furthermore, functional recovery was abolished if dor sal CST lesions were followed 5 weeks later by ventral CST lesions. This suggests that a second lesion to the CNS is not only a great tool to relesion a fiber system of interest and to investigate its impact on recovery, but also to extend spinal injury and investigate plasticity beyond the lesion site. An important consideration of such a strategy is the timing of the second lesion as plasticity will take time to establish its effect. For example, adaptive changes in central pattern generating networks have been beautifully demonstrated by Rossignol and co-workers [39] where a hemisection of the spinal cord in cats was followed by a complete transection 64–80 days later. Animals that underwent the two surgeries were quickly retrained to step on a treadmill, in comparison to those receiving a full transection only. Another example is the staggered hemisection model, where two hemisections on different sides of the spinal cord are performed [18]. If one lesion is performed a few weeks before the other, mice quickly recover weight support and locomotion although all direct descending control to locomotor networks in the lumbar spinal cord is disrupted.

Another elegant approach to demonstrate meaningful post-injury rewiring of the CST was by Raineteau et al. where the reconnection of the lesioned CST (at the level of the pyramid) was examined using cortical micro-stimulation. Following this lesion the cortical stimulation in controls did not yield in evoked muscle potentials, however following a plasticity-promoting treatment the connection to the periphery was restored. By inhibiting synaptic transmission through the red nucleus using injections of the GABA_A agonist Muscimol in the same experiment, the rewiring was interrupted, thus demonstrating the functional relevance of plasticity.

Besides beneficial effects of plasticity on recovery, it is quite well known that adaptive changes within the CNS also can be maladaptive. For example, changes in pain pathways are involved in the post-injury development of neuropathic pain and allodynia. Not necessarily surprising is the finding that the mechanisms seen as beneficial in the motor system (including sprouting) are undesirable in pain pathways. Other adverse effects of plasticity following SCI include autonomic dysreflexia and spasticity, which will be discussed later in this review. It becomes clear that treatment effects in all systems, motor, sensory and autonomic have to be taken into account when applying plasticity-promoting treatments. In some cases it might be impossible to separate beneficial from harmful side effects. One good example of this particular phenomenon is the restoration of motoneuron excitability, following the injury-induced loss of descending neuromodulators, for example serotonin. Typically, the loss of serotonin results in flaccid paralysis and a spinal cord, where any spared descending input is rendered inefficient to initiate movements. We could recently show that recovery of motoneuron function over time occurs due to constitutively active serotonergic receptors (i.e., 5-HT2A [69]). Following a hemisection for example, this development of serotonin independence is essential for recovery of locomotion, but due to a lack of descending inhibitory control contributes to spasticity. Thus it is not surprising that spasticity has been discussed to contribute to recovery.

Another very recent finding provides yet another example where the CNS attempts to spontaneously recovery excitability following spinal cord injury: the reduction of post-synaptic inhibition by down-regulating the potassium-chloride co-transporter particularly in motoneurons [11]. Also this change in neuronal properties has been suggested to contribute to spasticity.

In summary, there is now a solid basis of studies demonstrating substantial plasticity at various levels and locations within the CNS following spinal cord injuries. These adaptations suggest that the CNS is attempting to restore neuronal function and recovery, and that plasticity following can generally be viewed as a repair mechanism. Understanding these naturally occurring adaptations presents itself as valuable opportunity to design new, functionally meaningful treatments for SCI.

### 2. Promoting plasticity to treat spinal cord injury

Detailed insight into the actual effects of plasticity and the dissection of these effects is of great importance when we attempt to promote plasticity. This appears especially important as over the last years promoting plasticity became a more and more promising treatment approach. Likely reasons are the growing knowledge about injury-induced plasticity and the notion that plasticity-promoting treatments exploit and enhance naturally occurring repair mechanisms, contrary to regenerative treatments that have to overcome multiple growth inhibitors in the lesion site of the adult mammalian CNS. Interestingly, many treatments that were originally designed to promote axonal regeneration were found to stimulate plasticity, and it is now suspected that their beneficial effect on recovery was primarily based on plasticity and not on moderately improved axonal regeneration. A good example is the Nogo-A neutralization which promoted substantial recovery following pyramidal tract lesions [74,84], while the effects on axonal regeneration were moderate. In contrast, the functional rewiring of the CST via the red nucleus and increased collateral sprouting
at the level of the brainstem and spinal cord offered a good link to the observed recovery. Also, the fast recovery observed following inactivation of the Rho-pathway, together with increased sprouting, indicated that the treatment effects on recovery were likely based on neuroprotection rather than increased plasticity [23].

Another experimental approach that was initially used to promote axonal regeneration is the digestion of proteoglycans associated with the perineuronal net and the glial scar formed at the lesion site [66]. In animal models of SCI, administration of the enzyme chondroitinase (cABC) promoted axonal regeneration and functional recovery [13,15,37,68,96]. Nevertheless, recent exciting reports on improved functional recovery are based on the ability of cABC to promote plasticity rather than axonal regeneration, supported by findings of a very fast recovery period (within 14–21 days; reviewed in [40]). There is a wealth of studies confirming the plasticity and recovery promoting effects of cABC following SCI, including recovery of motor and bladder function and enhanced plasticity of intact systems within the brainstem and spinal cord [7,13,41,66].

Also, the application of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT-3) were initially used to promote cell survival and axonal regeneration after SCI as well [10,12,44,53,57,78,81,94,95]. Now these growth factors are routinely used to promote plasticity in the spinal cord and brain [98]. Administration of BDNF to the cell bodies of lesioned CST fibers for example, enhanced collateral sprouting [49] which resulted in new intraspinal connections between CST and propriospinal pathways [87]. NT-3 exerts its effects on multiple levels, by enhancing sprouting of injured and spared fibers [81,97] and its application has influenced synaptic plasticity form afferents onto motoneurons [67]. It is noteworthy that BDNF and NT-3 are not only associated with plasticity in motor systems but also in the sensory system [76,83].

In conclusion, there are various pharmacological tools to promote plasticity in injured and spared circuitries of the spinal cord. Some of these approaches attempt to enhance naturally occurring plasticity, others achieve their goal by overcoming naturally occurring inhibition.

3. Rehabilitative training and plasticity

A well-established approach to promote plasticity and functional recovery following SCI without the administration of pharmacological agents is rehabilitative training. Despite the lack of pharmacological tools, training and exercise has profound effects on cellular and molecular function involved in plasticity [17,29,89]. This plasticity can be viewed as the interface between physical activity and recovery.

The probably best established and investigated training paradigm following SCI is treadmill training, which had been successfully translated from animal studies to the clinic. The seminal findings that stepping can be retrained in cats with complete spinal transection presented a dramatic demonstration of plasticity and activity-dependent recovery [4,21,63]. The observed plasticity was completely independent of descending input and occurred in the spinal cord. Subsequent studies examined training effects following incomplete lesions in mice [43], in cats [77] and in rats [34,35] as well as in humans [25,28,46,92].

An interesting finding resulting from the animal studies is the demonstration that spinal networks are not only able to adapt to training, but also that they can learn and retain information. When animals are allowed to recover from a hemisection before a subsequent complete transection, their ability to walk on a treadmill was significantly increased as compared to directly transected animals [6]. Similarly, mice with two staggered hemisections performed with a time interval allowing some recovery walked better than those receiving both lesions simultaneously [18]. Both, studies show that activity and training following injury can modify spinal networks in a functionally meaningful way. Besides spinal plasticity, locomotor training also influences descending tracts. This has been recently shown in patients [85] where treadmill training was shown to improve connectivity of spared corticospinal pathways. Treadmill training was also reported to positively influence other side effects of an injury, including neuropathic pain in animals [51] and muscle clonus in patients (as reviewed in [30]).

In conclusion, treadmill training appears to promote plasticity in an activity-dependent manner and might be necessary to “reprogram” spared circuitry by rebalancing changes in descending excitatory and inhibitory input as well as changes in the timing of these signals with the sensory feedback from muscle and cutaneous afferents. Surprisingly the functional benefits of treadmill training in rodents with incomplete lesions are frequently reported to be moderate to non-existent [34]. This can likely be explained by the fact that rats due to their low centre of gravity, but not cats or patients, can walk and thus constantly train themselves.

More substantial rehabilitative effects were found in rodents following cervical SCI and reaching training [42]. Such training appeared to have amplified spontaneously occurring adaptations, including cortical map changes, collateral sprouting and the overall up-regulation of growth-associated proteins. As the effect of rehabilitative training and that of many pharmacological treatments is based on encouraging neuronal plasticity, it appears desirable to combine both approaches in order to maximize plasticity. Considering that during development new connections are removed or maintained depending on activity [93], it is expected that rehabilitative training and the consequent activation of newly formed, plasticity-induced connections is necessary to fine tune and maintain such connections. A beautiful example of such synergy has recently been demonstrated by Garcia-Alias et al. [41]. In rats with cervical SCI, the application of cABC alone resulted in only modest functional recovery, however when combined with training its potential became unleashed allowing for significant recovery in various reaching tasks. The finding by Garcia-Alias et al. [41] is encouraging, but also suggests that earlier studies on promising plasticity-promoting treatment candidates might have been dismissed prematurely. Maybe, just a small amount of rehabilitative training would have been needed to translate plasticity into recovery.

Taken together recent publications of experts in the field of rehabilitative training are.

4. Plasticity and lesion severity

Another criterion to be considered when judging the efficacy of plasticity-promoting treatments, including rehabilitative training approaches, is lesion severity. Intuitively, to be functionally relevant, plasticity-promoting treatments need a certain degree of spared “neuronal hardware” to work with. This appears quite obvious when considering the extreme example of a complete spinal transection. In this case circuitries below the level of the injury will likely respond to rehabilitative or pharmacological treatments (see treadmill training), however plasticity will fail to reestablish descending control of muscles below the level of the injury. Thus, functionally meaningful plasticity of descending systems depends on a certain degree of sparing. The question to be answered then is, what is the degree of sparing needed, and what models should be used to examine plasticity? Various studies in animal models have addressed the issue of necessary neuroanatomical substrates to allow for spontaneous recovery to occur [9,64,82]. It was suggested
that if as little as 10–15% of the spinal cord is spared, locomotor function can recover to a certain degree. However, not surprisingly the location of the sparing also is a decisive factor in this calculation [82].

Another challenge regarding the issue of lesion size is the choice of lesion model when studying plasticity or the efficacy of plasticity-promoting treatments. When using lesion models with small injuries, preserving a too much “neuronal hardware” will allow a substantial amount of spontaneous recovery/plasticity. In many cases this recovery is approaching pre-lesion performance, and thus, does not leave sufficient margin between untreated and treated animals to establish a statistically significant treatment effect. When admitting that until now there is no pharmacological treatment resulting in extensive recovery, the question of how many treatments were dismissed prematurely because of an unsuited lesion model has to be considered. The choice between a severe or mild lesion model might have simply prevented functional benefits of plasticity-promoting treatment effects. A representative example for this has been recently found following the activation of the TrkB receptor in rats with cervical SCI. Although no treatment effect on recovery was found for the paw with extensive deficits, the other paw with only minor deficits significantly improved its grasping ability (Fouad et al., unpublished). This suggests that the lesion severity on the one side was too extensive so that a plasticity-promoting agent could not promote meaningful recovery.

In conclusion, utilizing plasticity-promoting approaches in a too severe or too mild lesion model might underestimate or completely mask the potential of a treatment strategy. In other words, plasticity-promoting treatments will most likely show their biggest potential in animal models/patients with moderate lesions.

5. The other side of the coin, plasticity and adverse effects

Earlier in this review we mentioned neuropathic pain, that is based on injury-induced changes in the sensory system (reviewed in [65]), autonomic dysreflexia involving recurrent episodes of paroxysmal hypertension and associated bradycardia [90], and spasticity involving a wide array of post-injury changes [27]. All these side effects develop over time and thus are considered to be caused by changes in the nervous system. Consequently, approaches to pharmacologically promote plasticity will involve not only circuitries involved in motor function, but also sensory and autonomic function. Therefore, global approaches to promote plasticity within the entire CNS using for example intrathecal injection of growth factors have to be carefully examined and the side effects on autonomic and sensory function taken into account. Surprisingly, these considerations are frequently neglected.

Preventing global treatment effects could be achieved by focusing pharmacological treatments on specific cell populations or locations, for example, by treating cell bodies of neurons [49], or by local application of growth factors, for example by using viral vectors [59]. But even when only a specific cell group is targeted, promoting plasticity can result in unspecific connections, as we found that lesioned CST fibers formerly innervating the lumbar enlargement grow collaterals towards cervical motoneuron pools when stimulated with BDNF [87]. The application of plasticity-promoting drugs can also have a wide range of unwanted side effects. The neurotrophin BDNF, for example, is acting as an excitatory on various populations of neurons [24,80,86], and application to the brain or activation of its TrkB receptor can cause seizures [1] and possibly uncontrollable muscle contractions and spasticity. Thus, although plasticity-promoting drugs appear to promote naturally occurring repair mechanism, the unspecific and frequently wide spread action should be considered carefully before brating their success. Another unknown factor is the effect of treatment-induced growth of serotonergic fibers and their effect on neuronal excitability. Over the last years it became quite obvious that it is especially the serotonergic fibers that respond to growth promoting treatments [72,88], but the effect of this enhanced growth on spasticity has so far been neglected.

Since plasticity-promoting drugs potentially promote adverse effects, rehabilitative training can be considered to be the safest therapy to promote neuronal plasticity. If anything it was reported that training following SCI has positive effects on pain and spasticity. In patients treadmill training has been reported to reduce clonus in patients and in rats it to reduce allodynia [51]. Nevertheless, rehabilitative training can also create side effects. For example, training a specific task can result in recovery in that task, but can interfere with the recovery in other, untrained tasks. This phenomenon has been found independently in SCI cats that were trained to walk or stand [22], or rats with cervical SCI that were trained in a reaching task but also had to cross a horizontal ladder [41,42]. In all cases, animals did perform worse in the untrained task when compared to completely untrained controls.

In order to explain this effect on untrained tasks one could speculate that following injury there is a certain amount of “spared neuronal hardware” available that can be used to adapt to the new situation. If training starts immediately after injury, the trained task will make use of the spared hardware and thus can excel at the cost of an untrained task. If training is delayed, we found that the effects on untrained task is reduced [58] suggesting that spontaneous recovery, during which a wide array of motor systems is utilized in a balanced fashion, will make use of spared hardware, so that delayed training might be slightly less effective, however would not have a monopoly on spared circuitry.

It is surprising that there is only limited knowledge on the best strategy for rehabilitative training following SCI. This is especially true for the training onset, where only in few occasions it has been reported that training with an early onset is more efficient than in a chronic situation following injury [71,79]. Unraveling the mechanism determining the efficacy of rehabilitative training will be a challenge for the future. A likely factor involved is cyclic adenosine monophosphate, which has been reported to continuously decline after SCI [58,72].

In summary there are still many questions unresolved when it comes to the ideal timing and design of rehabilitative training following SCI including whether broad or focused training is more beneficial, when training should begin and whether training effects can be undone. The latter is however fairly likely, as patients who cannot independently continue to use the trained function tend to lose the training benefits over time [48].

6. Conclusion

In conclusion, plasticity is still an insufficiently explored contributor to functional recovery following SCI, which depends on the amount of spared neuronal hardware, lesion location, and activity during rehabilitation. More and more sophisticated mechanisms to restore neuronal function are being discovered, however they also appear to be frequently related to undesirable effects as spasticity. Thus, careful and systematic consideration of lesion models and functional readouts will be necessary to judge the strategies designed to promote this promising treatment avenue in the future.

Acknowledgements

We would like to thank the International Spinal Research Trust for their support. KF was also supported by the Alberta Heritage Foundation for Medical Research.
References


学霸图书馆
www.xuebalib.com

本文献由 “学霸图书馆-文献云下载” 收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，
提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。
图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具