Promoting anatomical plasticity and recovery of function after traumatic injury to the central or peripheral nervous system

Traumatic brain or spinal cord injury (SCI) has devastating consequences for patients, and can lead to life-long disability. However, even in the most serious cases, there is normally some recovery of function. For example, 73% of patients who initially present with complete paralysis but sacral sensory sparing recover some motor function within a year (Marino et al., 1999). The mechanisms of this recovery are still poorly understood and are likely to include the following: reduction of local ischaemia, oedema and inflammation; recovery from spinal shock of traumatized but undamaged pathways; remyelination of demyelinated axons; functional synaptic plasticity allowing spared pathways to take over the lost functions; and anatomical plasticity leading to new, and functionally effective, circuitry. In the past few years it has become apparent that the last of these possibilities, anatomical plasticity, may play a significant role. Although the CNS is not able to regenerate a major pathway such as the corticospinal tract, there is accumulating evidence that some pathways are able to sprout locally to establish novel circuits that restore a limited degree of function. The key question is, can such plasticity be promoted to enable patients to recover complex functions such as fine hand control? This exciting possibility is addressed by two papers in this issue of *Brain* from James Fawcett and colleagues at the Cambridge Centre for Brain Repair (Galtrey et al., 2007; Smith et al., 2007).

After injury to a pathway such as the corticospinal tract, axons normally die back a short distance but then initiate a regenerative response which is unsuccessful and confined to local sprouts at the injury site (Kerschensteiner et al., 2005). However recent studies have demonstrated that both damaged and undamaged pathways distant from the injury site can sprout to establish functional connections (Raineteau et al., 1998). Sprouting by intact rubrospinal pathways into denervated areas is increased below the injury site (Raineteau et al., 2001). A similar reorganization of motor pathways takes place when anti-Nogo-A is given after unilateral ablation of the motor cortex. The intact corticospinal tract sprouts into the contralateral denervated red nucleus and pons (Wenk et al., 1999) and electrical..
stimulation of the intact cortex promotes movement of the ipsilateral lesion-impaired forelimb (Emerick et al., 2003). The article in this issue of Brain by Smith and colleagues (Smith et al., 2007) provides another example of such anatomical plasticity, but with a different injury model and a different pharmacological agent (the purine nucleoside, inosine). Inosine has previously been shown to promote anatomical sprouting by intact corticospinal and corticobulbar projections after a cortical infarct or corticospinal tract lesion (Benowitz et al., 1999; Benowitz et al., 2002; Chen et al., 2002). Smith and colleagues now show that inosine also promotes anatomical sprouting and recovery of function after traumatic brain injury. In a rodent impact injury model, a 2-week intraventricular infusion of inosine led to a more rapid and complete recovery of skilled forelimb use, which was accompanied by sprouting of corticobulbar and corticospinal projections across the midline into denervated areas. The exact mechanism of action of inosine is unknown, but it has recently been shown to activate a protein kinase (Mst3b) that is also activated by NGF and BDNF and that regulates axonal outgrowth (Irwin et al., 2006).

The second article in this issue of Brain also addresses the question of whether anatomical plasticity can be harnessed to promote recovery of precise motor function, but in the context of peripheral nervous system (PNS) injury (Galtrey et al., 2007). Although regeneration in the PNS is very efficient, functional recovery is often only partial. For example, satisfactory sensory recovery following median or ulnar nerve injuries is achieved in only 43% of patients, and satisfactory motor recovery in only 52% (Ruijs et al., 2005). The main reason for this appears to be misdirected re-innervation, i.e. motor and sensory axons reconnecting to inappropriate targets, and a consequent scrambling of the cortical somatosensory map (Lundborg, 2000). Various attempts have been made to improve the accuracy of reinnervation by treating the PNS injury site with factors that either promote and direct regeneration, or reduce polyinnervation. However they have had only limited success (e.g. Angelov et al., 2005). Galtrey and colleagues now show that treatment of the spinal cord with an agent that is known to promote anatomical plasticity (ChABC) can compensate for poor PNS regeneration. In a rodent injury model, they examined the effect on skilled forelimb use of various types of injury and repair to the median and ulnar nerves, including either crush, cut and correct repair, or cut and incorrect repair (median to ulnar, ulnar to median). As would be expected, skilled forelimb use and grip strength recovered best after crush injury, and were worst after incorrect repair. However ChABC injected into the cervical cord 4 weeks after surgery led to an improved recovery of skilled forelimb use after correct repair, and improved recovery of grip strength after incorrect repair. The authors demonstrate that the ChABC treatment promotes sprouting in the spinal cord (possibly due to digestion of perineuronal nets), but otherwise did not examine the mechanism responsible for functional recovery. However, they propose that rewiring of spinal circuits may compensate for misdirected peripheral re-innervation by motor and sensory neurons.

These results show that recovery of fine motor function after traumatic brain or peripheral nerve injury can be promoted by enhancing anatomical sprouting in the CNS. However, several key questions remain to be answered, some of which are critical for translation to the clinic. First, since the agents in question have effects not only on anatomical plasticity but also on axonal regeneration and possibly also cell survival (see e.g. Hasko et al., 2004), there is the problem of determining which particular effect is responsible for the functional improvements. Secondly, it is still not clear what exactly the triggers are for anatomical sprouting and which systems are susceptible. For example, the extent of sprouting appears highly dependent on the type of injury (compare Bareyre et al., 2004; Vavrek et al., 2006) and the particular anatomical system (Oudega et al., 2000; MacDermid et al., 2004). In the case of ChABC, application to the intact spinal cord has no effect (Barritt et al., 2006) but with peripheral nerve injury (which involves no direct injury to the spinal cord) it is effective (Galtrey et al., 2007). Most studies have examined acute effects and little is known about the extent to which delayed treatment is effective (Li and Strittmatter, 2003). Thirdly, and most crucially, not all sprouting is beneficial. In addition to sprouting that appears to be anatomically appropriate, aberrant sprouting has been reported (Barritt et al., 2006). In the case of primary afferents, such sprouting may give rise to neuropathic pain (Hofstetter et al., 2005; Barritt et al., 2006). It would be disastrous if a plasticity-promoting treatment made a patient worse. We currently know very little about how to direct anatomical plasticity to beneficial ends. However one study indicates that a process of pruning takes place, whereby functionally beneficial pathways are consolidated and ‘inappropriate’ ones lost over time (Bareyre et al., 2004). If this is the case, the solution may be to combine a pharmacological treatment with physiotherapy. Smith and colleagues suggest that in patients ‘the most effective use of plasticity-inducing treatments will be to open a window during which intensive rehabilitation can drive plasticity in useful directions’ (Smith et al., 2007). This is a very exciting possibility, and likely to be a very fruitful area for further investigation.

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