■ REVIEW ARTICLE

Repair in the central nervous system

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The subject of central nervous system damage includes a wide variety of problems, from the slow selective 'picking off' of characteristic sub-populations of neurons typical of neurodegenerative diseases, to the wholesale destruction of areas of brain and spinal cord seen in traumatic injury and stroke. Experimental repair strategies are diverse and the type of pathology dictates which approach will be appropriate. Damage may be to grey matter (loss of neurons), white matter (cutting of axons, leaving neurons otherwise intact, at least initially) or both. This review will consider four possible forms of treatment for repair of the human central nervous system.

Repair of grey matter is the goal in degenerative neurological conditions where, despite the loss of characteristic cell populations such as the dopaminergic cells of the substantia nigra in Parkinson's disease, the general architecture of the surrounding tissue is left intact. Repair strategies include the transplantation of embryonic neurons or neural stem cells into affected areas of the brain in the hope that they will survive, integrate, and form functionally-appropriate connections. Trauma is a far more destructive process than neurodegeneration: damaged areas of grey matter are effectively completely destroyed, and repair would involve feats of tissue engineering way beyond what current science is capable of. Realistically, therefore, treatment of traumatic central nervous system (CNS) injury is limited to repair of white matter, i.e., the promotion of axon regeneration. Attention has focused mainly on the spinal cord, for two reasons. First, many spinal cord injuries are essentially purely white matter problems; although a thoracic cord transection affects segmental grey matter as well as longitudinal white matter tracts, the loss of activity in a few intercostal muscles due to the former is of negligible importance compared with the paraplegia due to the latter. In contrast, head injury is almost always a combined grey/white problem. Second, there are good, reproducible animal models of spinal cord injury, including contusion and transection, which produce motor and sensory deficits that are measurable both behaviourally and electrophysiologically, and are analogous to those seen in human spinal cord injury. Head

injury in humans usually affects areas such as the frontal or temporal lobes and/or produces widespread diffuse injury, the main neurological deficits in survivors being in 'higher' functions such as memory and personality, which are difficult to model adequately in animals. Such lesions would also be much harder to generate experimentally in a reproducible way.

Besides white matter repair, there is a second important treatment strategy: the induction of neural plasticity. Plasticity is the ability of the CNS to 'rewire' itself by forming new neuronal connections. If this process could be promoted and optimised, a considerable improvement in disability might be brought about by making the best use of surviving (and regenerated) tissue. Stroke is another pathology that results in substantial or complete destruction of geographical regions of the brain, which at present cannot be directly repaired. This condition too could potentially benefit from treatments that induce plasticity and persuade perilesional brain areas to take over lost functions.

At present there are no treatments with clinically established efficacy that actively promote repair of the human CNS. Medical treatment focuses initially on stabilisation and prevention of further damage (thus, for example, unstable spines are fixed orthopaedically, and expanding intracranial or spinal blood clots are evacuated), and subsequently on rehabilitation and the provision of prosthetics and mechanical aids. However, basic science has made huge strides in recent years, and new treatments that promote axon regeneration, remyelination and plasticity will enter clinical practice, bringing significant

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changes in patient treatment. Some of these are approaching or are already in the early phases of clinical trials.

Pathology of injury to the central nervous system

Traumatic damage to the CNS occurs in two stages. The primary injury is the mechanical damage that occurs at the time of trauma. This is because of direct impact to CNS tissue, shock waves travelling through the tissue, or shearing forces generated by deceleration (the latter typically affecting the subcortical boundary between grey and white matter). Penetrating injuries producing laceration of CNS tissue are uncommon in the United Kingdom: most brain injuries are blunt, and result from the brain being shaken and impacting on the interior of an unbroken skull, and the most common spinal cord injury is contusion due to mechanisms such as fracture/dislocation rather than complete physical transection. Axons in the injured region may be severed and cells of all types mechanically destroyed. Damage to the microvasculature may lead to areas of ischaemic necrosis.

Secondary injury describes a variety of phenomena that follow over a period ranging from hours to weeks. Most seriously, injured CNS tissue is prone to oedema, and the consequent elevated intracranial pressure is a common and frequently fatal complication in the hours or days that follow a major head injury. Control of intracranial pressure by medical means (typically ventilation, head-up positioning to reduce impediment to venous return, and the use of osmotic diuretics), coupled with the use of inotropes to maintain cerebral perfusion pressure, is the mainstay of acute head injury management. Wide decompressive craniectomy in the event of failure of these simple measures is controversial, and evidence of improved long-term outcome has not yet been demonstrated, possibly because it prevents the immediate death of those patients with the most severe brain injuries. The procedure is the subject of an ongoing clinical trial.¹

Disintegration of the blood brain barrier after injury leads to ingress of macrophages from the bloodstream. Microglia from the surrounding tissue converge on the injury site. Perilesional astrocytes alter their phenotype and over several weeks form a 'glial scar' composed of astrocytes and a dense extracellular matrix.² Oligodendrocyte precursor cells, present throughout the mature CNS, proliferate³ in the surrounding tissue and synthesise several inhibitory substances.⁴ If the surface of the CNS is breached, meningeal cells enter and, together with astrocytes, form a further barrier on the damaged surface.⁵ The glial scar serves to wall off damaged areas, limiting the area affected by secondary damage, but unfortunately the extracellular matrix is rich in several molecules that are inhibitory to regeneration. Apoptosis, necrosis of devascularised tissue and persistent inflammation may lead to progressive cystic cavitation, a further barrier to axonal regrowth.

Stroke generally causes a more precisely defined geographical area of destruction. Life-threatening swelling is uncommon, but secondary injury may occur in the 'ischaemic penumbra' at the watershed with adjacent vascular territories.

Axon regeneration

Why axons in the central nervous system do not regenerate. It was observed long ago that severed axons in the CNS do not have the ability to regrow any significant distance,⁶ and the prevailing belief was that they were essentially incapable of doing so. In 1980, it was shown that lengths of peripheral nerve implanted in spinal cord lesions could support the regeneration of CNS axons over several centimetres,^{7,8} but also that the axons would not grow out of the far end of the graft back into the CNS. Thus the failure of axons in the CNS to regenerate is largely due to the non-permissive nature of the environment they inhabit. If these inhibitory cues can be identified and removed, or if suitable growth-promoting agents can be added, then axons might be persuaded to regrow through the injury site. Several growth inhibitors have been identified which are either components of the extracellular matrix present in the glial scar² or molecules associated with CNS myelin.⁹

Inhibition by components of the glial scar. Key classes of inhibitory molecules are 1) chondroitin sulphate proteoglycans; 2) ephrins; and 3) semaphorins, all of which are upregulated following injury. Chondroitin sulphate proteoglycans are components of the CNS extracellular matrix; the precise mechanism by which they cause growth inhibition is not known, but the fact that they do so is well established.^{10,11} Ephrins and their Eph receptors are a family of membrane proteins that are involved in axon guidance during development, but are also present in the CNS in adulthood. Binding of ephrins on one cell to their receptors on another activates bidirectional signalling pathways that in neurons lead to the collapse of the growth cone.¹² Upregulation of Eph-B3 receptors has been demonstrated in both astrocytes and neurons following spinal cord injury in the rat.¹³ Semaphorins are a large family of membrane-bound and secreted proteins that are also involved in axon guidance during development. Upregulated production of Sema-3A by the meningeal cells that migrate in to form the lesion core¹⁴ is again inhibitory to axonal growth.

Inhibition by myelin-associated molecules. Cultured neurons grow readily on substrates of myelin extracted from peripheral nerve, but not on beds of mature oligodendrocytes or isolated CNS myelin.¹⁵ In animals where myelination is prevented by neonatal irradiation there is a degree of spontaneous regeneration of lesioned corticospinal tract axons.¹⁶ The proteins Nogo-A^{17,18} and myelin-associated glycoprotein have been identified as mediators of the growth-suppressive effects of CNS myelin. In addition, oligodendrocytes secrete the inhibitory protein tenascin R.

Treatments in or approaching clinical trials

Four potential treatments have been successful in promoting axonal regeneration and behavioural recovery in a range of spinal cord injury and other damage models. Two of these, antibodies against Nogo-A and a Rho inhibitor, are currently in the early stages of trials for the treatment of

Fig. 1

Diagram showing mechanisms of treatment to promote axonal regeneration.

spinal cord injury. Chondroitinase and olfactory glial cell implants should reach trials soon (Fig. 1).

Anti-Nogo. Several monoclonal antibodies directed against Nogo-A neutralise the inhibitory properties of myelin both *in vitro*¹⁹ and *in vivo*,^{20,21} and have improved locomotor recovery after spinal cord injury in the rat.^{22,23} Progressing to a primate model, enhanced axon regeneration and neurological function have been demonstrated in the corticospinal tract of the monkey after thoracic spinal cord injury.²⁴ A humanised version of the antibody (ATI355), infused into the injury site via a cannula, is undergoing phase I human trials under the aegis of the European Multicentre Study about Spinal Cord Injury.²⁵

Rho inhibition. Many of the inhibitory signals described above (ephrins, Nogo) converge on the intracellular molecule Rho-A, which is a key mediator of actin depolymerisation and hence inhibition of axonal elongation. Blocking Rho-A might in theory negate a whole set of inhibitory influences. Enzymatic inactivation of Rho-A, or blockade of its downstream target Rho kinase, has been shown to promote axonal regeneration in the optic nerve of the adult rat²⁶ and regeneration of corticospinal tract axons after spinal cord injury in mice, with consequent improvement in locomotor function.²⁷ The Rho inhibitor cethrin is administered as a gel to the injury site at acute decompression of the traumatised spinal cord. In phase I human trials in a cohort of 37 patients it has been reported to be safe and well tolerated.²⁸ Trials are ongoing.

Chondroitinase. The enzyme chondroitinase cleaves chondroitin sulphate proteoglycans and reduces the growth-inhibiting properties of glial scar-derived astrocyte cultures *in vitro*.²⁹ In

rats, locally administered chondroitinase has been shown to improve locomotor and sensory recovery after cervical cord injury,³⁰ to improve locomotion and bladder function after thoracic cord contusion,³¹ and to facilitate regeneration of axons in the brain after nigrostriatal tractotomy.³² Human trials are anticipated.

Olfactory ensheathing cells. The active element of the olfactory epithelium in the upper nasal cavity is the olfactory receptor neuron, whose apical surface carries receptors for specific airborne molecules. Axons from these cells are grouped into bundles that pass superiorly through perforations in the cribriform plate of the ethmoid bone to reach the anterior cranial fossa, where they enter the olfactory bulbs lying on the inferior surface of the frontal lobes. There they synapse with second-order neurons whose axons pass posteriorly in the olfactory tracts to enter the brain. Olfactory ensheathing cells are glial cells that have features of both astrocytes and peripheral Schwann cells. They wrap (but do not myelinate) the olfactory receptor cell axons all the way up and into the olfactory bulb.³³ Uniquely among CNS glia, however, the olfactory ensheathing cells are conducive to axon growth in adulthood. Olfactory receptor neurons, like other epithelial cells, are continuously turned over, being replenished several times each year from a basal pool of olfactory stem cells.³⁴ Olfactory ensheathing cells conduct the axons of new olfactory receptor cells towards and into the olfactory bulb to re-establish contact with the second-order neurons.³⁵ Strikingly, if the olfactory bulbs are removed the olfactory ensheathing cells are capable of conveying the axons into the frontal lobe instead,³⁶ although it

should be noted that this was observed in the neonatal mouse, where myelin is both less abundant and immature.

Might, then, transplants of such cells be capable of conducting regenerating spinal axons through the milieu of the lesion site itself and onward into more normal CNS tissue? In rat models of spinal cord injury, transplanted olfactory ensheathing cells encourage axonal growth,^{37,38} and this appears to translate into functional improvements in locomotion and climbing,³⁹ although other authors have disputed their growth-promoting effects.⁴⁰ Early human studies in spinal cord injury have involved the implantation of various forms of graft,⁴¹⁻⁴³ including suspensions of cultured autologous olfactory ensheathing cells. Unfortunately, most of these studies have been without control groups or follow-up data, and have therefore given little convincing indication of the safety or efficacy of the treatment. There has been one small safety trial with a control group in Australia,⁴⁴ which demonstrated no adverse effects in three patients with the American Spinal Injury Association (ASIA) grade A (complete) thoracic cord injury after follow-up of one-year post grafting.⁴⁵

Echoing their normal function of guiding olfactory axons from the periphery into the CNS, there is also experimental evidence that olfactory ensheathing cells can conduct the regrowing proximal axons of dorsal root ganglion cells back into the spinal cord after dorsal root transection and reimplantation.⁴⁶ This has obvious potential for the treatment of brachial plexus root avulsion, and trials of olfactory ensheathing cells in this setting are expected to begin soon.

Other experimental treatments

Prevention of glial scar formation. The cytotoxic drug cytosine arabinoside has been used to eliminate proliferating cells after a lesion of the nigrostriatal tract.³ This removes oligodendrocyte precursor cells from the lesion site and has a short-lived effect on the astrocytic response, but unfortunately produces only a transient increase in axonal regeneration, with the axons subsequently retracting. Ethidium bromide ablates all glial cells, and when administered in a similar model produces a more robust increase in numbers of regrowing axons.⁴⁷

Administration of growth factors. Neurotrophin-3 (NT3) has been shown to promote the regeneration of ascending and descending fibres after spinal cord injury in the rat.⁴⁸ The most successful strategy has been to graft an island of fibroblasts or bone marrow cells derived from the same animal and engineered to secrete NT3 into the spinal cord below a lesion. This attracts axons, including those from the corticospinal tract, and partly restores function.^{49,50} Grafts of bone marrow cells⁵¹ or fibroblasts⁵² modified to secrete brain-derived neurotrophic factor have also been shown to stimulate axonal growth in the dorsal columns and rubrospinal tract,^{51,52} respectively, in the rat, accompanied in the latter case by significant functional recovery.

Schwann cells. The growth-promoting properties of peripheral nerve grafts are largely due to the components of the

extracellular matrix and neurotrophic factors secreted by Schwann cells.⁵³ Grafting Schwann cells into CNS injury sites has therefore been explored as a possible means of promoting regeneration. Grafts implanted into rat spinal cord contusions immediately after injury have been shown to reduce astrogliosis and cavitation.⁵⁴ Schwann cells loaded into polymeric guidance support the growth of axons from both proximal and distal stumps of the transected rat thoracic cord.⁵⁵ Unfortunately, most axons come from neurons close to the injury, with relatively few supraspinal neurons sending their axons through the grafts. There is also a problem with Schwann cell grafts, known as the 'off-ramp' problem, which means that axons will enter and grow through the grafts but cannot cross back into CNS tissue at the other end. The addition of growth factors (brain-derived neurotrophic factor and NT3) to the graft can induce regeneration of some types of supraspinal axons through it,⁵⁶ with a few being able to exit it, but probably not in clinically significant numbers.

Growth beyond the lesion site

We must first persuade axons to grow from the lesion site back into the CNS. The fact that olfactory ensheathing cells can conduct axons from the peripheral system to the CNS suggests that they might be the basis of one possible solution to this problem.³⁶ Once across this boundary, however, axons must elongate over considerable distances in the CNS tissue beyond in order to reach their target. Encouragingly, there is some evidence that the uninjured CNS may not be as inhibitory as previously thought. This is technically difficult to demonstrate because it is hard to perform experiments to test how well axons grow in the CNS without damaging it and creating a glial scar. This confounding element was removed in a rat model where suspensions of dorsal root ganglion neurons were injected into cerebral white matter in extremely small volumes so as to avoid tissue damage.⁵⁷ Neurons in those transplants that were judged atraumatic (as evidenced by low levels of reactive extracellular matrix molecules) were seen to extend axons for considerable distances along white matter tracts. It appears that the inhibitory myelin-associated molecules may only exert their influence when the myelin has been damaged.

Having deployed various treatments to make the injury site and surrounding area as permissive as possible, and possibly implanted cells or injected molecular cues a short distance away in order to entice axons through the lesion boundary into the 'normal' CNS tissue, we are now asking the axon to grow away from these attractants. During development, axon guidance cues are progressively regulated so that attractants are always expressed ahead of the growing axon and removed from behind it. Such regulation may not be possible in, for example, growth factor-secreting fibroblast transplants. It has been suggested that multiple grafts may be required at intervals along the regenerating tract as a series of 'relay islands' to provide chemoattraction from ahead.

Finally, it may not be necessary for axons to grow all the way back to their original target in order to provide useful

reinnervation. An axon that regrows a relatively modest distance may be able to establish a connection with, for example, a neuron in the premotoneuronal network of the cervical cord⁵⁸ that will relay its signals into an uninjured axon nearby. Plastic changes will allow the brain to adapt to this rerouting.

Plasticity

Regeneration of lost axons or tissue is not the sole mechanism by which recovery of function after CNS injury might be achieved. The majority of spinal cord transections are incomplete,⁵⁹ and disability could potentially be reduced by allowing those neurons with surviving axons to be 'rewired' to make best use of the residual connectivity with the distal cord. Likewise, disability due to loss of cerebral grey matter as a result of head injury or stroke might be ameliorated if surviving cortex could be persuaded to take over some of the functions previously subserved by damaged areas. Neuronal 'rewiring' is termed plasticity, and occurs through alterations in the potency of synapses between neurons and through the sprouting of side branches from axons to form entirely new synapses with other neurons.

Plasticity is a normal process in post-natal development, when sensory input is crucial in sculpting immature neuronal circuitry throughout the CNS to produce the eventual normally functioning pattern of connections seen in adulthood. A well-studied example is the visual system. An adult with the visual acuity of a newborn baby would be considered legally blind; rapid modification and refinement of retinal and cortical circuitry allows acuity to approach that of an adult after approximately six months, but the process is not complete for several years. Development is absolutely dependent on the presence of normal sensory input, and abnormal input during this period can permanently prevent the acquisition of normal vision. In the visual cortex individual neurons are grouped into small alternating zones of 'ocular dominance' that preferentially respond to input from one or other eye. Classic experiments in kittens⁶⁰ demonstrated that if sensory input is abnormal, these areas of ocular dominance fail to develop properly. Animals with one eye sutured shut after birth ('monocular deprivation') do not develop areas primarily responsive to that eye, devoting the entire cortex to the open eye. Opening the eye allows dominance areas for that eye to develop, but only when it is opened before the animal reaches a characteristic age. The time up until this age is called the critical period, because of this vulnerability of development to abnormal input. After the end of the critical period, even if the eye is opened the corresponding ocular dominance areas never develop properly and the vision in the eye is never normal. Conversely, monocular deprivation starting after the critical period has closed does not abolish the cortical representation of the deprived eye: adult cataract patients promptly recover normal vision in the eye when the lens is replaced, even if the eye has been blind for many years. This is all because the critical period is a time of great plasticity. At the closure of the critical period plasticity is dramatically reduced, cementing in place the now fully developed neural circuitry. The critical

period in humans appears to close at about the age of six years.

Some plasticity does occur physiologically in adulthood, although to a much lesser degree than during the critical period in infancy. Adult monkeys with an amputated finger initially have a corresponding 'silent' area of primary sensory cortex, but in time re-organise their cortical maps to apportion the vacated part of the sensory homunculus to adjacent digits.⁶¹ Monkeys trained in a task that involves intensive sensory input from one or two digits expand the cortical representation of the areas concerned at the expense of neighbouring regions,⁶² so as to allow a finer spatial resolution in these highly active sites. Studies on adult humans using magnetoencephalography show similar effects of training on the distribution of cortical maps; thus Braille readers have expanded cortical areas representing their reading finger,⁶³ and violinists have enlarged representations of the fingers of the left hand.⁶⁴ The adult brain, however, does not have sufficient plasticity to cope so well with significant tissue damage. The effect of stroke on the motor areas of the brain has been studied using functional MRI and positron emission tomography (PET).⁶⁵ Initially there are widespread changes in motor cortical activity, but gradually the ectopic activity becomes focused in perilesional areas as they adapt plastically to take over the function of the damaged region, and it appears that the better such localisation, the better the functional recovery. The ability of the brain to do this will depend on its age and premorbid state, and the extent of the damage.

Just as with failure of axonal regeneration, the relatively low level of adult neural plasticity is now known to be largely a result of inhibitory extracellular factors rather than an intrinsic property of CNS neurons. Closure of the critical period coincides temporally with the synthesis and deposition of extracellular matrix components,⁶⁶ including chondroitin sulphate proteoglycans that envelop neuronal cell bodies in a structure known because of its reticular microscopic appearance as the 'perineuronal net',⁶⁷ which prevents the formation of new synapses. Cleavage of the chondroitin sulphate proteoglycans with chondroitinase has been shown to reactivate ocular dominance plasticity in the adult rat visual cortex.⁶⁸ After experimental spinal cord injury in the rat, chondroitinase treatment causes extensive sprouting of axons when delivered to the brainstem⁶⁹ or spinal cord,⁷⁰ and leads to functional improvement.

Nogo-A also has a prominent role in the limitation of plasticity. Inhibition with the monoclonal antibody IN-1 in a rat model of stroke causes an increase in dendritic arborisation and spine density,⁷¹ which is associated with improved functional recovery. After a focal adult rat sensorimotor cortex lesion, IN-1 permits the reinnervation of denervated subcortical areas by axons from the intact contralateral hemisphere,⁷² which also improves functional outcome.⁷³

Inosine is a purine nucleoside which has been shown to promote axonal sprouting in adult CNS neurons by activating an intracellular signalling pathway which regulates several genes involved in axonal growth.⁷⁴ Unlike chon-

Fig. 2

Diagram showing mechanisms of treatment to promote plasticity.

droitinase, which needs to be injected at the target site, inosine is a small molecule that diffuses widely throughout the cerebrospinal fluid and into CNS tissue. When given by continuous infusion into the cerebrospinal fluid in rats it has been shown to improve outcome after experimentally-induced middle cerebral artery territory stroke.⁷⁵ Recently we have demonstrated therapeutic benefit from intraventricular infusion of inosine in a rat model of traumatic brain injury.⁷⁶ Brain-derived neurotrophic factor administered in the vicinity of the cell bodies of injured corticospinal neurons promoted axonal sprouting, and these sprouts connected with spared descending interneurons.⁷⁷ These effects were correlated with functional improvement, albeit not significantly so.

Regenerating axons have a tendency to misroute and reinnervate the wrong target. In peripheral nerves, regenerating axons regrow down the columns of Schwann cells left behind when the axon distal to the injury degenerates⁷⁸ after losing its connection to the cell body. If the injury is a crush or stretch, so that the axons are damaged but the connective tissue structure of the nerve is preserved (axonotmesis), then these Schwann cell columns should guide each axon back to its original target. However, if the nerve is severed (neurotmesis) and has to be stitched together, it is highly unlikely that many of the Schwann cell columns in the proximal and distal stumps will be correctly paired up, so this guidance system is lost and axons frequently take the wrong path.⁷⁹ Motor axons growing to sensory targets and *vice versa* are functionally useless, and even if the fibre type is correct the regenerating axon may grow down a track leading to a completely different muscle or area of skin from the original fibre it replaces, with function-

ally poor results. This is more of a problem with proximal injuries, where fascicles contain mixed-fibre types and are highly plexiform,⁸⁰ and is one of the factors to blame for the generally poor results of proximal nerve and brachial plexus repair.⁸¹ It has recently been shown that cervical cord treatment with chondroitinase enhanced functional recovery after median and ulnar nerve repair in the adult rat.⁸² There is no obvious reason why regenerating axons in the CNS should be immune from such misrouting problems. Thus even if a majority of CNS axons can be persuaded to regenerate and establish distal connections with grey matter, these connections are likely to be at best approximately correct, and we will therefore probably need plasticity treatments as well as regenerative treatments in order to re-organise the new connections. It is fortuitous that some of the treatments that promote axon regeneration are also key players in the induction of plasticity (Fig. 2). Chondroitin sulphate proteoglycans and Nogo-A inhibit both the long-range regrowth of axons and the short-range sprouting of collaterals that underlies plasticity. Administration of chondroitinase and anti-Nogo antibodies will, in general, facilitate both processes.

How good a repair do we need?

During removal of slow-growing extramedullary spinal tumours such as meningiomas, in humans it is sometimes observed that the cord has been gradually compressed over a long period into little more than a ribbon, yet the patient has frequently only recently developed neurological symptoms. This suggests that, as with many other body systems, there is a substantial degree of functional reserve and quite large amounts of damage may be tolerated without major deficit.

The corollary is that it should be possible to produce a good functional recovery by restoring only a relatively small part of the original neuronal circuitry. Improved forepaw function following corticospinal tract division in the rat and olfactory ensheathing cells transplantation has been associated with regeneration of just 1% of corticospinal tract axons.⁸³ Plasticity may well have a role to play in optimising recovery if regeneration-promoting treatments are successful in restoring a small number of axonal connections across the divide.

The difficulties of extrapolation from rat to humans

Only about one-third of promising results from animal models successfully translate into therapeutic successes in human trials,⁸⁴ and where there is success the process takes a median of seven years. In the CNS, the most obvious difference between the rat (the most common model) and the human is in scale. The human spinal cord is ten times as long as that of the rat, yet the neurons which are expected to regenerate their axons are biologically very similar, so a much greater feat of restoration is required of the human nerve cell. Not only that, but axons regrow slowly. Regenerating peripheral axons in humans manage about a millimetre per day, and it is doubtful that central ones, even if freed from all their normal inhibitions, would move any faster, as even under favourable conditions their regenerative efforts are intrinsically less robust than those of peripheral neurons.⁸⁵ We will therefore have to wait much longer than in the animal model to judge whether our regenerative treatments have been a success. Plasticity-based treatments may be less affected by issues of physical and temporal scale, being dependent on synaptic modulation, which requires no growth, and on axonal sprouting to form new connections, which requires relatively short-range growth. Plasticity treatments have another attraction, which is that they will probably be effective for a considerable period after the damage has occurred, whereas axon regeneration treatments are mainly effective just after injury.

Conclusion

Repair of the human CNS has until recently appeared impossible, but we now have four potential treatments that are either in or approaching early clinical trials. Early trials of the Rho inhibitor cethrin are encouraging, and anti-Nogo is also in a phase I study. Trials of chondroitinase and olfactory ensheathing cells are expected in the near future. Looking to the future, the regeneration of severed axons by cellular and molecular treatments and the induction of plasticity to rewire, and thus make optimal use of, surviving and regenerated CNS tissue are goals that are looking ever more achievable.

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