Rat studies point to a novel treatment strategy for ALS

Researchers have found a way to protect dying motor neurons in a rat model of familial amyotrophic lateral sclerosis (ALS) by transplanting human neural stem cells producing glial-cell-line-derived neurotrophic factor (GDNF) into the rodent's spinal cord.

ALS is a progressive neurodegenerative disease that leads to the death of motor neurons in the spinal cord and brainstem. GDNF has been shown to protect motor neurons from degeneration *in vitro*, but delivery of the protein *in vivo* has proved difficult.

Suzuki and colleagues genetically modified human neural progenitor cells to release GDNF, and transplanted these cells into the spinal cord of the rat model of familial ALS to act as long-term 'mini pumps'.

The researchers were able to show that the transplanted cells were migrating to the regions of motor neuron degeneration and that GDNF was being successfully delivered to these regions. At early stages of ALS, GDNF preserved nearly 100% of the motor neurons, and it preserved over 30% at end stages of the disease. Muscle innervation was not maintained, however, and there were no changes in ipsilateral limb function. Human neural progenitor cells that were not secreting GDNF had no effect on the survival of degenerating motor neurons.

The authors conclude that their findings point towards the possibility of new stem-cell treatment strategies for ALS, although further studies are needed to investigate loss of muscle innervation in this setting.

Original article Suzuki M *et al.* (2007) GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS. *PLoS ONE* **2:** e689

Study raises questions about use of sodium-channel blockers in neuroinflammatory disorders

Several studies examining the use of sodium-channel blockers in patients with multiple sclerosis are currently underway. Questions about the long-term effects of these agents in neuroinflammatory disorders have, however, recently been raised by the demonstration of acute worsening of symptoms caused by withdrawal of these agents in a murine model of experimental autoimmune encephalomyelitis (EAE).

In this study, EAE mice were given feed supplemented with phenytoin from day 10 after disease induction. On day 28, a proportion of the population was switched to normal feed, while the remainder continued to receive phenytoin-supplemented feed. A separate control population of EAE mice received normal feed throughout the 40-day experiment. Consistent with earlier results, mice treated with phenytoin had markedly lower clinical EAE scores than did untreated mice. The withdrawal of phenytoin from EAE mice, however, resulted in a striking increase in clinical dysfunction within 1–2 days. The dramatic worsening of EAE symptoms following phenytoin withdrawal was accompanied by substantially increased inflammatory infiltrate and the death of 59.1% of the population between day 28 and day 40; none of the untreated mice or those that continued to receive phenytoin died during this period. Similar experiments were conducted with carbamazepine to determine whether the clinical worsening observed after phenytoin withdrawal is a general effect of sodium-channel blocker withdrawal. Following carbamazepine withdrawal, acute worsening of EAE symptoms, increased inflammatory infiltrate and the death of 7.7% of the carbamazepine-withdrawal population were observed. The authors highlight the need for the careful planning of clinical studies examining sodium-channel blockers in neuroinflammatory disorders.

Original article Black JA *et al.* (2007) Exacerbation of experimental autoimmune encephalomyelitis after withdrawal of phenytoin and carbamazepine. *Ann Neurol* **62:** 21–33

Deep brain stimulation promotes late functional recovery after traumatic brain injury

Severe traumatic brain injury often leads to widespread loss of cerebral connectivity and the consequent failure of brain mechanisms that support communication and goal-directed behavior. Patients in a minimally conscious state (MCS) can, however, show unexpected preservation of large-scale cerebral networks. Schiff *et al.* have reported the use of bilateral deep brain stimulation (DBS) of the central thalamus in a patient in a chronic MCS. The subject was a 38-year-old man who had sustained a closed head injury 6 years before enrollment.