Newsfronts

Stem Cell Therapy Grows on Parkinson's-Afflicted Monkeys

A new primate study offers tantalizing evidence of the potential for embryonic stem (ES) cells to combat the symptoms of a devastating neurological disease.

Parkinson's disease (PD) patients undergo loss of dopaminergic (DA) neurons within the substantia nigra, a brain region that regulates motor function. This neuronal death and drop in dopamine levels lead to disease progression, with patients finding body movements ever harder to control as neurodegeneration proceeds. Pharmacological treatments offer some relief but are of limited efficacy for long-term therapy.

Fetal brain tissue transplants have shown some therapeutic promise, but the extent of recovery seen with this treatment is limited, and the legal and ethical issues associated with such approaches have discouraged further investigation. Studies in mice have suggested that by stimulating the differentiation of ES cells into neurons, a suitable transplant substrate can be produced. Now, a group of Japanese investigators takes this new strategy a step further, presenting an ES cell–based treatment that seems to relieve PD symptoms in cynomolgus monkeys (*J. Clin. Invest.*, January).

ES cells cultured atop a layer of stromal cells tend to differentiate along a neuronal pathway; Kyoto University investigator Yasushi Takagi and his colleagues took this system a step further and found that by detaching their cells from this feeder layer and culturing them in the presence of specific growth factors, they could produce floating 'neurospheres' consisting of incompletely differentiated neural progenitor cells. Takagi's group was able to refine their culture technique further, so that roughly 20% of these cells became DA neurons.

Monkeys treated with a neurotoxin called MPTP develop symptoms closely resembling those observed in PD. The researchers grafted cells from their neurospheres into the brains of symptomatic MPTP-treated monkeys and found significant improvements in their posture and movement relative to sham-operated control animals, improvements that were still apparent up to 10 weeks following transplant. In addition, the animals showed no signs of dyskinesia, a movement disorder that is a common side effect of pharmacological treatment. Histological examination demonstrated that ES-derived cells had repopulated the graft site, resulting in considerably more DA neurons than were detectable in controls.

In an accompanying commentary for the article, Parkinson's Institute (Sunnyvale, CA) researcher J. William Langston describes this work as an important 'milestone': "These investigators have prepared what appear to be authentic DA neurons and used those to reverse parkinsonism in a primate model ... [that] has been proven highly predictive of new symptomatic approaches in the treatment of Parkinson's disease." He and the authors caution that much work remains; the long-term impact of this treatment, including risk of tumor formation, has not been assessed, and the extent of DA neuron repopulation may not be sufficient to fully retard the progression of PD. Nonetheless, Langston concludes that this work "will advance research aimed at validating the use of stem cells to treat neurodegenerative disease."

—Michael Eisenstein

New Career Possibilities for Certain Antibiotics?

Amid concerns about excessive prescription and resistance, antibiotics might be able finally to look forward to some good press again, because a new study in *Nature* (6 January) suggests that certain of these compounds may confer protection against a variety of neurological disorders.

Excessive levels of the neurotransmitter glutamate, typically resulting from defects in transport, have been linked to such neurological disorders as epilepsy and amyotrophic lateral sclerosis (ALS). However, even though the pathology of glutamate transporter dysfunction is relatively well understood, an effective therapeutic strategy has yet to emerge. "Glutamate excess is well known to cause injury," explains Jeffrey Rothstein, a researcher at Johns Hopkins Medical Institute (Baltimore, MD). "But offsetting that by increasing transporters is a theoretical approach, not necessarily a proven approach. [Transgenic studies suggest that] it has potential, but ... we knew that if we were going to hope to use this as a neuroprotective approach, we had to have drugs that could do this."

Thus, Rothstein and his colleagues set out to identify new neuroprotective agents. Starting with an NIH-generated library of 1,040 FDA-approved pharmaceutical and nutritional compounds, they treated sections of rat spinal cord and attempted to identify treatments that led to increased expression of the glutamate transporter gene, *GLT1*. Much to his group's surprise, among the top compounds found to increase *GLT1* expression were 15 members of a family of widely used antibiotics, the β-lactams, which include such compounds as penicillin and amoxicillin.

This observation represents the first association of these compounds with neuroprotective properties, and Rothstein admits that, initially, "we all thought this was some error!" But repeated studies confirmed that the β-lactam antibiotics were triggering a significant increase in *GLT1* transcription, with an attendant increase in actual glutamate uptake for treated spinal cord sections. To test these compounds *in vivo*, Rothstein and his colleagues worked with a transgenic mouse model for ALS. They treated the mice with ceftriaxone at the onset of disease symptoms and observed a marked delay in the loss of muscle strength and body weight relative to untreated controls. Drug treatment also extended the life span of the mice and reduced the extent of motor neuron loss.

Encouraged by these findings, investigators in the Rothstein lab are now trying to determine the direct targets of β-lactam action. At the same time, he adds, "if this class of drugs working on glutamate transporters is a valid therapeutic [approach], then you really don't want to be using antibiotics," and his team is currently looking for nonantibiotic β-lactam compounds with similar neuroprotective properties.

—M.E.