NEUROLOGICAL DISORDERS

New neurons repair Parkinson's brain

The idea that endogenous progenitor cells might be harnessed to replace neurons lost in neurodegenerative diseases is popular, but requires the development of methods to stimulate their proliferation and differentiation. Hopes for this approach have now received a boost from a study by Van Kampen and Eckman, showing that activation of a particular dopamine receptor subtype stimulates neurogenesis and functional repair in a Parkinson's disease model.

Parkinson's disease involves the degeneration of dopaminergic neurons in the nigrostriatal tract, which projects from the substantia nigra pars compacta (SNc) in the midbrain to the striatum and is essential for the control of movement. Current treatments that boost striatal dopamine levels have adverse side effects, lose efficacy over time and do not alter the underlying pathology, making cell-replacement strategies desirable. Utilizing endogenous progenitor cells for this purpose could have advantages over invasive transplantation strategies. Encouragingly, such progenitors have been identified in the SNc, and previous work has demonstrated that activation of D_3 dopamine receptors stimulates neurogenesis in this region in healthy adult rats.

The new study demonstrates the effects of a preferential D_3 agonist, 7-OH-DPAT, in a common rat model of Parkinson's disease, the 6-hydroxydopamine model. By labelling cells undergoing DNA synthesis, the researchers showed that chronic drug treatment increased proliferation in the SNc. Many newborn cells subsequently expressed proteins typically found in mature dopaminergic neurons. To achieve functional recovery and repair of the nigrostriatal tract, these newly generated neurons must generate new projections to the striatum. This was assessed by injecting a fluorescent tracer into the striatum. After retrograde transport of the tracer to the SNc, increased numbers of neurons with axons projecting along this tract were revealed. Finally, two different behavioural tests were used to demonstrate recovery of motor function in the treated animals. These effects lasted several months after treatment ended, providing further evidence of changes in the underlying neuronal pathways.

These findings show that endogenous progenitor cells can be stimulated to contribute to the functional repair of damaged neuronal tracts, providing hope for neurodegenerative disease therapy and giving further support for targeting the D_3 receptor as a therapeutic strategy for Parkinson's disease. Several D_3 receptor agonists are already in use for Parkinson's disease, which could encourage the development of similar therapeutics and lead to a better understanding of the underlying molecular pathways, revealing further therapeutic targets.

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ORIGINAL RESEARCH PAPER Van Kampen, J. M. & Eckman, C. B. Dopamine D_3 receptor agonist delivery to a model of Parkinson's disease restores the nigrostriatal pathway and improves locomotor behaviour. *J. Neurosci.* **26**, 7272–7280 (2006)