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Gene therapy for Parkinson's disease

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Gene therapy using the gene encoding aromatic L-amino acid decarboxylase (AADC) has been shown to produce significant recovery from Parkinson's disease (PD). These results were announced by Krys Bankiewicz (University of California, San Francisco, CA, USA) at the recent *Society for Neuroscience 31st Annual Meeting* (10–13 November 2001, San Diego, CA, USA) [1].

L-Dopa (L-3,4-hydroxy phenylalanineone), one of the main drugs used to treat PD, requires AADC to convert it to dopamine; as the disease progresses, the cells that store AADC are lost causing patients to become resistant to L-dopa treatment. Using a primate model, Bankiewicz and colleagues have shown that transfer of the *AADC* gene into the striatum of the brain restores the conversion of L-dopa to dopamine to normal levels (Fig. 1) [1,2] and they are now developing the therapy for clinical trials.

PD affects 1–2 per 1000 of the population worldwide. However the incidence rises with age and increases to one person in 100 over the age of 65 and one in 50 over the age of 80. The disease occurs after degeneration of neurons in the midbrain that normally synthesize the neurotransmitter dopamine. Dopamine deficiency causes the main symptoms of the disease: slowing of emotional and voluntary movement, muscular rigidity, postural abnormality and tremor.

L-Dopa, the precursor of dopamine, can be given orally as therapy and was originally shown to alleviate disease symptoms in the 1960s [3]. L-Dopa therapy is initially successful in many patients, but the response declines as the disease progresses and is complicated by adverse side effects. Other drugs are also used; for example, anticholinergics (effective for tremor in some patients), catechol-*O*-methyltransferase (COMT) inhibitors (which slow down the breakdown of L-dopa), and selegiline (a selective inhibitor of monoamine oxidase type B, which metabolizes dopamine). However, all are associated with numerous side effects.

The gene therapy approach

'Gene transfer technology offers the possibility of achieving prolonged delivery of proteins into specific areas of the CNS, although at the moment, gene transfer does require brain surgery', says Bankiewicz. Several enzymes are involved in the synthesis of dopamine and a successful gene therapy strategy to restore endogenous dopamine production would involve the transduction of several genes. Bankiewicz's approach is to transfer only the gene for AADC – the enzyme that completes the last step in the pathway that converts L-dopa to dopamine. 'With disease progression, there is a severe loss of dopamine terminals in the striatum; the enzyme AADC is concentrated in these terminals and is, therefore, also reduced,' says Bankiewicz.

After successful *AADC* gene transfer, subsequent administration of exogenous L-dopa should then be converted to the functional neurotransmitter and could improve symptoms. 'Furthermore, since the cells that express the *AADC* gene following gene transfer are unaffected by the PD, levels of AADC should not be affected by the ongoing disease process,' he adds.

Effects of transgene expression

The preclinical studies have also examined the effects of *AADC* transfer in the unilateral 6-hydroxydopamine (6-OHDA) rat model of PD. In this model the dopamine pathway on one side of the brain is destroyed (in this study, a left nigrostriatal lesion). This causes the rats to turn away from the side of the lesion (from left to right) when injected with a dopamine-releasing drug. 'The 35 rats studied showed a good rotational response to apomorphine, but no response to L-dopa. After transduction with the *AADC* gene, animals showed a contralateral turning response to L-dopa that was significantly higher than that in control animals,' explains Bankiewicz. The improved response to L-dopa was observed 10–14 days after *AADC* transduction and persisted for at least eight weeks [4].

'This study demonstrates that AADC activity in the striatum was correlated with increased contralateral rotation, indicating that striatal neurons express the *AADC* transgene and are able to decarboxylate exogenous L-dopa to form dopamine,' says William Langston of The Parkinson's Institute (Sunnyvale, CA, USA).

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'The fact that the expression of this transgene can be evaluated *in vivo* through a simple behavioural test is important; it will enable testing of different vectors and promoters and will allow us to study how the function of the transgene is regulated and controlled *in vivo*,' he adds.

Therapeutic implications

The decrease in the efficiency of neurons to decarboxylate L-dopa has long been suspected as a contributing factor to the reduced effects of the drug over time. 'Treatment with COMT inhibitors, which prolong dopamine half-life, initially causes an increase in dyskinesias. We hypothesize that a similar effect might occur with AADC gene therapy,' cautions Bankiewicz. 'However, reducing the L-dopa dose in patients receiving COMT therapy has controlled this side-effect, and the response to L-dopa has been improved.' He also stresses that further studies will be required to investigate the effect of gene transduction with *AADC* on dopamine receptors and on the changes in the striatum that underlie many of the late complications of long-term L-dopa therapy.

In late October 2001, Avigen (San Francisco, CA, USA) announced that it is adding the AADC gene transfer approach to PD therapy to its patent portfolio and will collaborate with Bankiewicz to develop the treatment. 'The collaboration is working well and we look forward to making progress in the coming months; carrying this approach forward to human trials could happen in the next two years,' predicts Bankiewicz.

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