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Gene Therapy Reduced L-Dopa–Induced Dyskinesia

Parkinson's disease patients who develop dyskinesia induced by long-term use of L-dopa might one day benefit from treatments that dampen the sensitivity of dopamine receptors to the drug, the results of a recent study of rodent and primate models of the disease suggest.

BY IRENE LITVAN, M.D.

Overexpression of a particular signaling molecule in the striatum of rats and macaques desensitized dopamine receptors in this brain region to chronic L-dopa administration and thereby improved L-dopa–induced dyskinesia (LID) while preserving or even enhancing the antiparkinsonian effects of L-dopa, reported Mohamed R. Ahmed of Vanderbilt University, Nashville, Tenn., and his associates (Sci. Transl. Med. 2010 Apr. 21 [doi:10.1126/scitranslmed.3000664]).

"This amelioration of LID is combined with a longer duration of the antiparkinsonian benefits of L-dopa, offering the hope of achieving the elusive goal of controlling both LID and motor fluctuations," the investigators wrote.

Chronic L-dopa treatment is known to sensitize the activation of dopamine receptors by suppressing the expression of G protein–coupled receptor kinases, which normally serve as the first rate-limiting step in the termination of the signaling cascade that activates dopamine receptors. Previous research suggested to Mr. Ahmed and his colleagues that G protein–coupled receptor kinase 6 (GRK6) may serve this role in the striatum.

The investigators found that lentiviral-delivered overexpression of GRK6 in the striatum of 6-hydroxydopamine–hemilesioned rats could prevent contralateral rotations in response to dopamine agonists if GRK6 was overexpressed prior to receipt of apomorphine or stop them if given after 5 days of L-dopa treatment. GRK6 overexpression alleviated abnormal involuntary movements (AIMs)—the rodent analog of dyskinesia—in rats that received repeated administration of L-dopa. The researchers were able to produce the opposite effect and worsen the sensitized rotation response to L-dopa and AIMs in the hemilesioned rats by silencing the expression of GRK6, showing that "decreased availability of GRK6 exacerbates dyskinesia."

GRK6 appeared to exert its desensitizing effect on dopamine agonists in the rats by increasing the number of D1 dopamine receptors that were internalized by neurons in the striatum and by suppressing the increase in dopamine receptor levels that is normally observed with chronic L-dopa treatment.

In experiments with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaques, the accepted standard model of Parkinson's disease, those that received GRK6 benefited longer from L-dopa than did controls. These monkeys also had significantly less intense LID and locomotor activity during the "on" state, which suggested that GRK6 expression had "diminished LID intensity without interfering with the antiparkinsonian action of L-dopa."

Further testing showed that half the optimal dose of L-dopa in the macaques with GRK6 overexpression still provided nearly the same duration of antiparkinsonian effect as that of the 100% dose. GRK6 overexpression also reduced the severity of LID in macaques that received either a D1 or D2 dopamine receptor agonist instead of L-dopa, which is a D1 or D2 indirect agonist. This indicated that the "anti-LID effect of GRK6 is mediated by reduced supersensitivity of both D1 and D2 receptors."

The experiments were funded by the Agence Nationale de al Recherche (France), the Biothèque Primat–Centre National de la Recherche Scientifique, the National Institutes of Health, and the Michael J. Fox Foundation for Parkinson Research. The researchers declared no competing interests.

***Dr. Litvan's comment*:** LID is a common complication of dopaminergic therapy for Parkinson's disease. Patients with Parkinson's disease who take high dosages of levodopa, are younger at disease onset, and have increased disease severity have an increased risk for developing LID.

Once established, LIDs are difficult to treat and adversely affect both the quality of life of our patients and health care costs. Current therapeutic strategies for LID include the use of a lower dosage of levodopa, dopamine agonists or rasagiline as initial Parkinson's disease therapy, amantadine, and deep brain stimulation.

The experiments of Mr. Ahmed and his coauthors show that lentiviral overexpression of GRK6 in rats and primates has a great potential in the treatment of LID by normalizing oversensitized D1 and D2 receptor signaling pathways caused by chronic levodopa usage. In addition to showing that overexpression of GRK6 improves LID, parkinsonian symptoms, and levodopa therapeutic duration, this study confirms that the development of LID not only involves D1 but also D2 receptor sensitivity.

It is expected that this novel therapeutic approach will be soon translated into human clinical trials. Lentiviral overexpression of GRK6 is an extremely promising therapeutic paradigm shift.■

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Research report by Jeff Evans, Managing Editor

REM Sleep Behavior Disorder May Portend Impairments

BY AMY ROTHMAN SCHONFELD

TORONTO — People who act out their dreams as a result of having REM Sleep Behavior Disorder have an increased risk of developing mild cognitive impairment or parkinsonism within 3 years of follow-up, according to researchers affiliated with the Mayo Clinic Study of Aging.

Evidence also suggests that knowledge of a REM sleep behavior disorder (RBD) diagnosis might enhance the accuracy of diagnosing associated dementia, in addition to predicting future cognitive or motor impairment.

Knowledge of a diagnosis of REM sleep behavior disorder might enhance the accuracy of predicting cognitive or motor impairment or diagnosing associated dementia.

"We already knew from studies of clinic-based samples that between 45% and 85% of patients with RBD develop one of the synucleinopathies [Parkinson's disease, Parkinson's disease with dementia, dementia with Lewy bodies (DLB), or multiple system atrophy]," said Dr. Brendon P. Boot, a fellow at the Mayo Clinic in Rochester, Minn. "We were interested to know what the risk is for the elderly living in the community."

The synucleinopathies are a group of neurodegenerative disorders characterized by aggregation of alpha-synuclein, a protein normally found in neuronal synapses.

Diagnosing RBD requires polysomnographic testing. However, the researchers used the Mayo Sleep Questionnaire (MSQ) to screen for RBD by asking the subject's bed partner: Has your spouse ever "acted out his or her dreams" while sleeping? This includes punching or flailing arms in the air or shouting or screaming.

In one of the Mayo Clinic studies presented at the annual meeting of the American Academy of Neurology, Dr. Boot reported that the MSQ has a sensitivity of 100% and a specificity of 95% for the diagnosis of RBD, based on testing of 96 cognitively normal, 29 mildly cognitively impaired, and 3 mildly demented community-dwelling elderly individuals from Olmsted County, Minn.

Dr. Boot and his colleagues then administered the MSQ in another study of 543 cognitively normal individuals between 70 and 89 years old and found that 44 had probable RBD. After a median follow-up of 33 months, 1 of these 44 patients developed Parkinson's disease and 13 developed mild cognitive impairment (MCI).

Those with MCI are at increased risk of developing dementia, and so RBD plus MCI may represent an early sign of a synucleinopathy. After adjustment for age, sex, education, and medical comorbidity, patients with probable RBD had 2.5 times greater risk of developing MCI or a synucleinopathy than did those without RBD.

In a related study, these investigators found that older, cognitively normal people with probable RBD had significantly worse olfaction than those without probable RBD, using the University of Pennsylvania Brief Smell Identification Test.

Hyposmia frequently precedes other symptoms of the synucleinopathies, Dr. Boot said.

In another study, Tanis J. Ferman, Ph.D., from the Mayo Clinic in Jacksonville, Fla., explored the diagnostic value of RBD in 82 patients with DLB and 64 patients with Alzheimer's disease.

According to the 2005 Consensus Criteria, diagnosis of DLB requires dementia plus one or more core clinical features fluctuating alertness and cognition, visual hallucinations, and parkinsonism. The criteria were modified in 2005 to include RBD as a suggestive feature, where the presence of RBD plus one core feature yields a diagnosis of probable DLB (Neurology 2005;65:1863-72).

In autopsy examinations of patients with dementia, the presence of RBD was associated with nearly sixfold higher odds of having DLB rather than Alzheimer's disease.

RBD appears to be a useful early clinical indicator of DLB, Dr. Ferman said.

Dr. Boot and Dr. Ferman said they had no relevant disclosures. ■