Precision Gene Therapy Reverses Parkinson's Symptoms in Monkeys

By YAN Fusheng

Can a single shot of gene therapy safely reverse Parkinson's disease? New study published in *Cell* shows that it could be feasible in monkeys, providing fresh hope for better treatment options.

Scientists developed a novel gene therapy strategy for selectively reactivating the affected neural circuits in patients suffering from Parkinson's disease. (Image by SIAT)

As reported in *Cell* on November 2, a new gene therapy approach that precisely targets and reactivates malfunctioning brain circuits shows remarkable potential for treating Parkinson's disease (PD). A single dose of the treatment quickly improved movement and motor skills in PD monkeys, with benefits lasting for over eight months.

Parkinson's disease stems from the loss of neurons that produce dopamine, an important chemical messenger in the brain.

Current Parkinson's medications aim to boost dopamine levels. For example, Levodopa (L-Dopa), one of the main medications used to treat Parkinson's disease, is a chemical precursor of dopamine that can cross the blood-brain barrier and be converted to dopamine in the brain. This helps replace the dopamine that is lost due to the death of dopamine-producing neurons in Parkinson's. But these drugs spread everywhere and can cause side effects – almost all patients given long-term L-Dopa treatment suffer from motor complications (*e.g.*, motor fluctuations and dyskinesia). Thus, precise, efficient, and stable treatments are greatly needed.

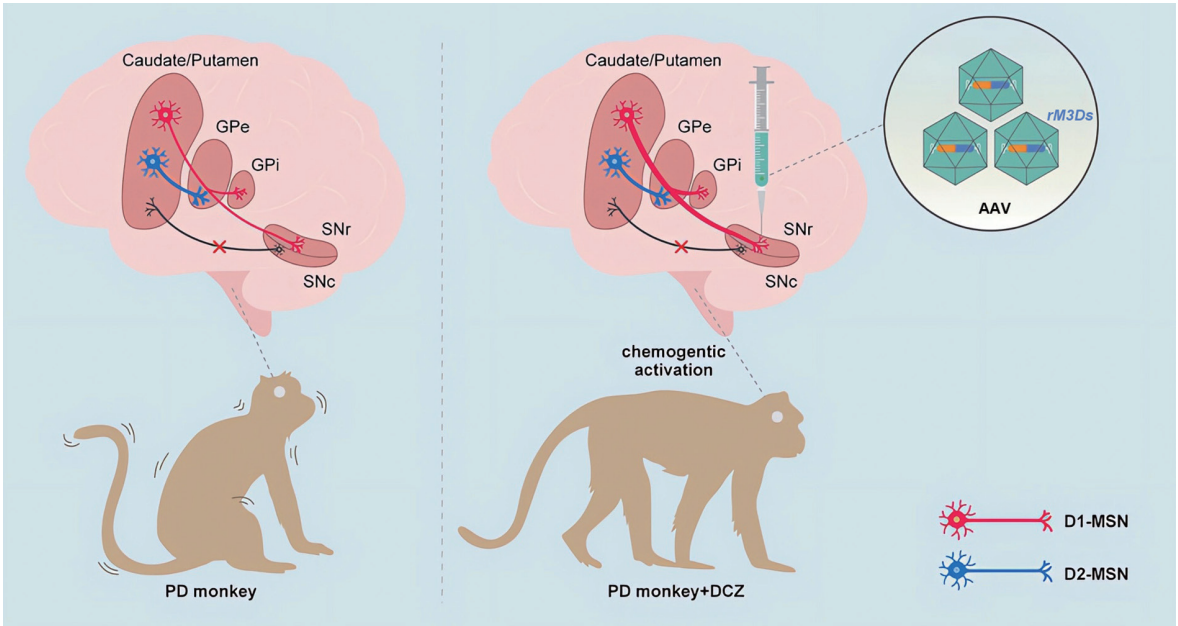
To overcome the complications of dopamine replacement, researchers from the Shenzhen Institute of Advanced Technology (SIAT) of the Chinese Academy of Sciences developed a specially engineered virus to precisely deliver genetic instructions directly into dopamine-receptor containing neurons, reactivating these malfunctioning cells.

There are two types of dopamine-receptor containing neurons in the striatum that express dopamine receptors D1 and D2 (*i.e.*, D1-MSN and D2-MSN, respectively). They both receive dopamine input from the substantia nigra pars compacta (SNc), yet play opposing roles in movement control, as illustrated in the figure.

D1-MSNs that project to the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr) constitute the direct pathway and promote movement. In contrast, D2-MSNs that project to the globus pallidus external segment (GPe) form the indirect pathway and mediate movement inhibition.

In Parkinson's disease, dopamine depletion causes underactivity of D1 direct pathway neurons and overactivity of D2 indirect pathway neurons, disrupting the balance and coordination of the pathways resulting in various motor symptoms.

To restore the balance, they leveraged recent advances in neural tracing techniques and chemogenetics – using genetic "switches" to remotely control cells. The researchers packaged a sensor protein, namely rM3Ds, within a modified virus. This virus strain was further engineered to travel backwards from the substantia



Targeting D1-type medium spiny neurons (D1-MSN) in the striatum using an efficient retrograde adeno-associated virus (AAV) and chemogentic activation that can precisely activate D1-MSN after systemic administration, the new therapy rescues core motor symptoms in Parkinson's disease (PD) monkeys. (Image by SIAT)

nigra region into the striatum area of the basal ganglia to exclusively infect D1-MSN, the set of medium spiny neurons that become underactive in Parkinson's. The infected neurons will manufacture the designer sensor protein rM3Ds at their cell surface. Subsequently, an injected chemical drug, named DCZ, binds and activates the sensor protein, re-stimulating these neurons and downstream circuits to restore normal movement control.

Tests in both normal and Parkinson's model monkeys showed that systemic drug treatment reliably improved mobility and motor skills for extended periods without side effects frequently caused by current dopamine therapies. Analyses found no signs of toxicity or treatment resistance over eight months.

While further evaluation is still needed, scientists suggest the precision, durability, and lack of complications seen in the study make this new strategy a highly promising avenue to pursue for Parkinson's treatments in humans. It impressively demonstrates that targeted circuit manipulation, rather than widespread chemical stimulation, may open new therapeutic doors for this and other neurological disorders.

Reference

Chen, Y., Hong, Z., Wang, J., Liu, K., Liu, J., Lin, J., . . . Lu, Z. (2023). Circuit-specific gene therapy reverses core symptoms in a primate Parkinson's disease model. *Cell, 186*(24), 5394-5410.e5318. doi:10.1016/j.cell.2023.10.004