Parkinson's breakthough could slow disease progression

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In an early-stage breakthrough, a team of Northwestern University scientists has developed a new family of compounds that could slow the progression of Parkinson's disease.

Parkinson's, the second most common neurodegenerative disease, is caused by the death of dopamine neurons, resulting in tremors, rigidity and difficulty moving. Current treatments target the symptoms but do not slow the progression of the disease.

The new compounds were developed by Richard B. Silverman, the John Evans Professor of Chemistry at the Weinberg College of Arts and Sciences and inventor of the molecule that became the well-known drug Lyrica, and D. James Surmeier, chair of physiology at Northwestern University Feinberg School of Medicine. Their research was published Oct. 23 in the journal *Nature Communications*.

The compounds work by slamming the door on an unwelcome and destructive guest—calcium. The compounds target and shut a relatively rare membrane protein that allows calcium to flood into dopamine neurons. Surmeier's previously published research showed that calcium entry through this protein stresses dopamine neurons, potentially leading to premature aging and death. He also identified the precise protein involved—the Cav1.3 channel.

"These are the first compounds to selectively target this channel," Surmeier said. "By shutting down the channel, we should be able to slow

the progression of the disease or significantly reduce the risk that anyone would get Parkinson's disease if they take this drug early enough."

"We've developed a molecule that could be an entirely new mechanism for arresting Parkinson's disease, rather than just treating the symptoms," Silverman said.

The compounds work in a similar way to the drug isradipine, for which a Phase 2 national clinical trial with Parkinson's patients –- led by Northwestern Medicine neurologist Tanya Simuni, M.D.—was recently completed. But because isradipine interacts with other channels found in the walls of blood vessels, it can't be used in a high enough concentration to be highly effective for Parkinson's disease. (Simuni is the Arthur C. Nielsen Professor of Neurology at the Feinberg School and a physician at Northwestern Memorial Hospital.)

The challenge for Silverman was to design new compounds that specifically target this rare Cav1.3 channel, not those that are abundant in blood vessels. He and colleagues first used high-throughput screening to test 60,000 existing compounds, but none did the trick.

"We didn't want to give up," Silverman said. He then tested some compounds he had developed in his lab for other neurodegenerative diseases. After Silverman identified one that had promise, Soosung Kang, a postdoctoral associate in Silverman's lab, spent nine months refining the molecules until they were effective at shutting only the Cav1.3 channel.

In Surmeier's lab, the drug developed by Silverman and Kang was tested by graduate student Gary Cooper in regions of a mouse brain that contained dopamine neurons. The drug did precisely what it was designed to do, without any obvious side effects.

"The drug relieved the stress on the cells," Surmeier said.

For the next step, the Northwestern team has to improve the pharmacology of the compounds to make them suitable for human use, test them on animals and move to a Phase 1 clinical trial.

"We have a long way to go before we are ready to give this drug, or a reasonable facsimile, to humans, but we are very encouraged," Surmeier said.

Provided by Northwestern University