Parkinson's disease stopped in animal model

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(Medical Xpress) -- Millions of people suffer from Parkinson's disease, a disorder of the nervous system that affects movement and worsens over time. As the world's population ages, it's estimated that the number of people with the disease will rise sharply. Yet despite several effective therapies that treat Parkinson's symptoms, nothing slows its progression.

While it's not known what exactly causes the disease, evidence points to one particular culprit: a protein called α-synuclein. The protein, which has been found to be common to all patients with Parkinson's, is thought to be a pathway to the disease when it binds together in "clumps," or aggregates, and becomes toxic, killing the brain's neurons.

Now, scientists at UCLA have found a way to prevent these clumps from forming, prevent their toxicity and even break up existing aggregates.

UCLA professor of neurology Jeff Bronstein and UCLA associate professor of neurology Gal Bitan, along with their colleagues, report the development of a novel compound known as a "molecular tweezer," which in a living animal model blocked α-synuclein aggregates from forming, stopped the aggregates' toxicity and, further, reversed aggregates in the brain that had already formed. And the tweezers accomplished this without interfering with normal brain function.

The research appears in the current online edition of the journal *Neurotherapeutics*.

There are currently more than 30 diseases with no cure that are caused

by protein aggregation and the resulting toxicity to the brain or other organs, including Parkinson's, Alzheimer's and Type 2 diabetes. It is therefore critical, Bronstein said, to find a way to stop this aggregation process. Over the last two decades, researchers and pharmaceutical companies have attempted to develop drugs that would prevent abnormal protein aggregation, but so far, they have had little or no success.

While these aggregates are a natural target for a drug, finding a therapy that targets only the aggregates is a complicated process, Bronstein said. In Parkinson's, for example, the protein implicated in the disorder, α-synuclein, is naturally ubiquitous throughout the brain.

"Its normal function is not well understood, but it may play a role in aiding communication between neurons," Bronstein said. "The trick, then, is to prevent the α-synuclein protein aggregates and their toxicity without destroying α-synuclein's normal function, along with, of course, other healthy areas of the brain.

Molecular tweezer

Bronstein collaborated with Bitan, who had been working with a particular molecular tweezer he had developed called CLR01. Molecular tweezers are complex molecular compounds that are capable of binding to other proteins. Shaped like the letter "C," these compounds wrap around chains of lysine, a basic amino acid that is a constituent of most proteins.

Working first in cell cultures, the researchers found that CLR01 was able to prevent α-synuclein from forming aggregates, prevent toxicity and even break up existing aggregates.

"The most surprising aspect of the work," Bronstein said, "is that despite the ability of the compound to bind to many proteins, it did not show

toxicity or side effects to normal, functioning brain cells."

"We call this unique mechanism 'process-specific,' rather than the common protein-specific inhibition," Bitan added, meaning the compound only attacked the targeted aggregates and nothing else.

The researchers next tried their tweezers in a living animal, the zebrafish, a tropical freshwater fish commonly found in aquariums. The zebrafish is a popular animal for research because it is easily manipulated genetically, develops rapidly and is transparent, making the measurement of biological processes easier.

Using a transgenic zebrafish model for Parkinson's disease, the researchers added CLR01 and used fluorescent proteins to track the tweezer's effect on the aggregations. They found that, just as in cell cultures, CLR01 prevented α-synuclein aggregation and neuronal death, thus stopping the progression of the disorder in the living animal model.

Being able to prevent α-synuclein from aggregating, prevent toxicity and break up existing aggregates is a very encouraging result, but still, at the end of the day, "we've only stopped Parkinson's in zebrafish," Bronstein said.

"Nonetheless," he said, "all of these benefits of CLR01 were found without any evidence of toxicity. And taken together, CLR01 holds great promise as a new drug that can slow or stop the progression of Parkinson's and related disorders. This takes us one step closer to a cure."

The researchers are already studying CLR01 in a mouse model of Parkinson's and say they hope this will lead to human clinical trials.

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