

Potential new class of drugs protects nerve cells in models of Parkinson's disease, amyotrophic lateral sclerosis

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Researchers at the University of Iowa and the University of Texas Southwestern Medical Center in Dallas, have identified a new class of small molecules that block nerve cell death in animal models of Parkinson's disease and amyotrophic lateral sclerosis. These small molecules could be a starting point for developing drugs that might help treat patients with these diseases.

Diseases that progressively destroy nerve cells in the brain or spinal cord, such as [Parkinson's disease](#) (PD) and [amyotrophic lateral sclerosis](#) (ALS), are devastating conditions with no cures.

Now, a team that includes a University of Iowa researcher has identified a new class of small molecules, called the P7C3 series, which block cell death in animal models of these forms of neurodegenerative disease. The P7C3 series could be a starting point for developing drugs that might help treat patients with these diseases. These findings are reported in two new studies published the week of Oct. 1 in *PNAS Early Edition*.

"We believe that our strategy for identifying and testing these molecules in animal models of disease gives us a rational way to develop a new class of neuroprotective drugs, for which there is a great, unmet need," says Andrew Pieper, M.D., Ph.D., associate professor of psychiatry at the UI Carver College of Medicine, and senior author of the two studies.

About six years ago, Pieper, then at the University of Texas Southwestern Medical Center, and his colleagues screened thousands of compounds in living mice in search of small, drug-like molecules that could boost production of [neurons](#) in a region of the brain called the hippocampus. They found one compound that appeared to be particularly successful and called it P7C3.

"We were interested in the hippocampus because new neurons are born there every day. But, this [neurogenesis](#) is dampened by certain diseases and also by normal aging," Pieper explains. "We were looking for small drug-like molecules that might enhance production of new neurons and help maintain proper functioning in the [hippocampus](#)."

However, when the researchers looked more closely at P7C3, they found that it worked by protecting the newborn neurons from cell death. That finding prompted them to ask whether P7C3 might also protect existing, mature neurons in other regions of the nervous system from dying as well, as occurs in neurodegenerative disease.

Using mouse and worm models of PD and a mouse model of ALS, the research team has now shown that P7C3 and a related, more active compound, P7C3A20, do in fact potently protect the neurons that normally are destroyed by these diseases. Their studies also showed that protection of the neurons correlates with improvement of some disease symptoms, including maintaining normal movement in PD worms, and coordination and strength in ALS mice.

Of mice and worms

In the ALS mouse model, a highly active variant of the original P7C3 molecule, known as P7C3A20, which the investigators synthesized, largely prevented death of the [nerve cells](#) within the spinal cord that are normally destroyed by this disease. The P7C3 molecule also worked, but

was not as effective at protecting neurons in this model.

As cell survival increased in the ALS model, coordination and strength of the mice improved as well. Mice that were given P7C3A20 were able to stay on a rotating rod much longer than untreated animals or animals that received the less active compounds. Animals receiving P7C3A20 also performed better in analysis of their walking gait, which typically worsens in these animals as the disease progresses.

In PD, dopamine-producing neurons necessary for normal movement are gradually destroyed. In patients, loss of these brain cells leads to tremors, stiffness, and difficulty walking. The study again showed that P7C3 protects these neurons from cell death and the more active analogue, P7C3A20, provided even greater protection.

The two compounds also potently blocked cell death of dopaminergic neurons in a *C. elegans* worm model of PD. Moreover, reduced [cell death](#) in this model was associated with improved movement in the worms.

Healthy *C. elegans* worms have a very characteristic swimming motion. This movement is disrupted in the PD worm. Hector De Jesus-Cortes, a graduate student of neuroscience at UT Southwestern Medical Center and lead author of the Parkinson's study, videotaped and analyzed the PD worms' mobility with and without treatment. Normal swimming was almost completely preserved with P7C3A20, and was also fairly well preserved with P7C3.

Tweaking the molecule

The research team compared the activity of several new P7C3-related compounds that they synthesized, in both the hippocampal neurogenesis screen and the mouse model of PD.

"Every variation of our P7C3 molecule that works in the neurogenesis assay also works in the PD model," Pieper says. "As we continue to refine the molecule, our hope is that the results from the neurogenesis assay will accurately predict the neuroprotective potency of the compound, and thus aid in more rapidly optimizing a new neuroprotective agent."

The team plans to continue tweaking the structure of the P7C3 molecule to improve its neuroprotective ability while eliminating potential side effects.

"Our hope is that this work will form the basis for designing a neuroprotective drug that could eventually help patients," Pieper says.

Provided by University of Iowa

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