Drug found to thwart mental decline, grow brain cells in rodents

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Scientists have discovered a chemical that they say restores memory-forming capacity in aging rats, likely by promoting the survival and growth of new cells in the brain's memory hub.

The research has turned up clues to a mechanism that could lead to a treatment for Alzheimer's disease, the investigators said.

The compound may work similarly to two drugs already studied as a treatment for the memory-robbing illness—one of them with disappointing recent results, they added. On the brighter side, they went on, their findings point the way to possibly much stronger drugs that work by a similar mechanism.

The compound P7C3 was found by testing more than 1000 small molecules in mice. Its chemical structure is indicated by the standardized diagram at right. (Credit: Andrew Pieper, UT Southwestern Medical Center)

"This striking demonstration… points the way to potential development of the first cures that will address the core illness process in Alzheimer's disease," said Thomas Insel, director of the U.S. National Institute of Mental Health, which partly funded the research.

The newfound substance, called P7C3, "holds special promise" because it's safely tolerated in mice, can be taken orally and enters the brain easily, said said researcher Steven McKnight, who co-led the investigation with Andrew Pieper, both of University of Texas Southwestern Medical Center. The scientists report on their findings July 9 in the research journal *Cell*.

Physical activity and enriching experiences promote the birth and maturation of new brain cells called neurons, researchers say. This takes place in the dentate gyrus, a key area of the brain's memory hub, the hippocampus. But most of these newborn neurons die during the month it takes to develop and get wired into brain circuitry. To survive, the cells must run a gauntlet of challenges. Newborn hippocampus neurons fare much worse in aging-related disorders like Alzheimer's, marked by runaway cell death.

"It takes a long time—two to four weeks—from the birth of a new neuron until it becomes functional," McKnight said. "Most of them die along the way."

In hopes of finding compounds that might protect these vulnerable cells, Pieper, McKnight and colleagues tested more than 1,000 small molecules in mice. They found that one, P7C3, corrected deficits in the brains of adult mice engineered to lack a gene needed for the newborn neurons' survival.

"We really didn't know if the screen would turn up a favorable compound," said McKnight. "It was blind luck."

Giving the chemical to the mice reduced programmed death of newborn cells, the group said, normalizing stunted growth of branch-like neuronal extensions and thickening an abnormal ly thin layer of cells by 40 percent. Among clues to the mechanism by which P7C3 works, the researchers

found that it protects the integrity of machinery for maintaining a cell's energy level.

To find out if it could also stem aging-associated neuronal death and cognitive decline, the researchers also gave the compound to aged rats. These treated rodents significantly outperformed peers on a water maze task, a standard test of hippocampus-dependent learning, the researchers said. This was traced to a threefold higher-than-normal level of newborn neurons in the dentate gyrus of the treated animals.

The researchers pinpointed a derivative of P7C3, called A20, which they said is even more protective than the parent compound. They also produced evidence suggesting that two other compounds studied as possible Alzheimer's cures may work through the same mechanism as P7C3.

These drugs, called Dimebon and Serono, bear structural similarities to P7C3 and encourage new neurons to grow, the investigators said. Dimebon came to scientists' attention based on anecdotal reports by Russian doctors that it may help attenuate age-related cognitive decline. Unfortunately, unpublished reports from a phase 3 clinical trial have since failed to show the drug's effectiveness against Alzheimer's. In light of the new findings, it may be worth another look, the scientists said.

The A20 derivative proved an estimated 300 times more potent than Dimebon, they added, suggesting even stronger brain-protective agents could potentially be discovered using similar methods. Following up on these leads, the they're now searching for which molecules in the brain are affected by P7C3, key to discovering its underlying mechanism of action.