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# Prospective Alzheimer's drug builds new brain cell connections

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Washington State University researchers have developed a new drug candidate that dramatically improves the cognitive function of rats with Alzheimer's-like mental impairment.

Their compound, which is intended to repair brain damage that has already occurred, is a significant departure from current Alzheimer's treatments, which either slow the process of cell death or inhibit cholinesterase, an enzyme believed to break down a key neurotransmitter involved in learning and memory development. Such drugs, says Joe Harding, a professor in WSU's College of Veterinary Medicine, are not designed to restore lost brain function, which can be done by rebuilding connections between nerve cells.

"This is about recovering function," he says. "That's what makes these things totally unique. They're not designed necessarily to stop anything. They're designed to fix what's broken. As far as we can see, they work."

Harding, College of Arts and Sciences Professor Jay Wright and other WSU colleagues report their findings in the online "Fast Forward" section of the *Journal of Pharmacology and Experimental Therapeutics*.

Their drug comes as the pharmacological industry is struggling to find an effective Alzheimer's treatment. Last month, the Pharmaceutical Research and Manufacturers of America, or PhRMA, reported that only three of 104 possible treatments have been approved in the past 13 years.

"This 34 to one ratio of setbacks to successes underlines the difficulty of developing new medicines for Alzheimer's," the trade group said in a news release. Development of the WSU drug is only starting. Harding and Wright must first satisfy the Food and Drug Administration that it is safe. Only then would clinical trials begin to see if a drug that works in a rat will work in a human.

Safety testing alone could cost more than $1 million, says Harding, who is looking to fund the drug's development through his and Wright's company, M3 Biotechnology Inc., the WSU Research Foundation, and ultimately large pharmaceutical company partners.

Harding, a medicinal chemist, and Wright, a neuroscientist, have been working on their compound since 1992, when they started looking at the impact of the peptide angiotensin IV on the hippocampus, a brain region involved in spatial learning and short-term memory. Typically, angiotensins have been linked to blood pressure regulation, but Harding and Wright noticed that angiotensin IV, or early drug candidates based on it, were capable of reversing learning deficits seen in many models of dementia.

The practical utility of these early drug candidates, however, was severely limited because they were very quickly broken down by the body and couldn't get across the blood-brain barrier, a cellular barrier that prevents drugs and other molecules from entering the brain. The only way the drug could be delivered was by direct brain application.

Says Harding: "We said, 'That's useless. I mean, who wants to drill holes in people's heads? It's not going to work. It's certainly not going to work for the big population.'"

Five years ago, Harding designed a smaller version of the molecule that he and Wright called Dihexa. Not only is it stable but it can cross the

blood-brain barrier. An added bonus is it can move from the gut into the blood, so it can be taken in pill form.

The researchers tested the drug on several dozen rats treated with scopolamine, a chemical that interferes with a neurotransmitter critical to learning and memory. Typically, a rat treated with scopolamine will never learn the location of a submerged platform in a water tank, orienting with cues outside the tank. After receiving the WSU drug, however, all of the rats did, whether they received the drug directly in the brain, orally, or through an injection.

"Same result, every time," says Harding.

Harding and Wright also reported similar but less dramatic results in a smaller group of old rats. In this study the old rats, which often have difficulty with the task, performed like young rats. While the results were statistically valid, additional studies with larger test groups will be necessary to fully confirm the finding. Currently, the "gold standard" compound for creating neuronal connections is brain-derived neurotrophic factor, or BDNF, a growth-promoting protein associated with normal brain development and learning. Autopsies of Alzheimer's patients have found lower levels of BDNF in the brain.

In bench assays using living nerve cells to monitor new neuronal connections, Harding, Wright, and their colleagues found Dihexa to be seven orders of magnitude more powerful than BDNF, which has yet to be effectively developed for therapeutic use. In other words, it would take 10 million times as much BDNF to get as much new synapse formation as Dihexa.

"We quickly found out that this molecule was absolutely, insanely active," says Harding. These results further suggest that Dihexa or molecules like it may have applications in other neurodegenerative

disease or brain traumas where neuronal connections are lost.

Provided by Washington State University