

New drug could treat Alzheimer's, multiple sclerosis and brain injury

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A new class of drug developed at Northwestern University Feinberg School of Medicine shows early promise of being a one-size-fits-all therapy for Alzheimer's disease, Parkinson's disease, multiple sclerosis and traumatic brain injury by reducing inflammation in the brain.

Northwestern has recently been issued patents to cover this new drug class and has licensed the commercial development to a [biotech company](#) that has recently completed the first human Phase 1 clinical trial for the drug.

The drugs in this class target a particular type of [brain inflammation](#), which is a common denominator in these neurological diseases and in [traumatic brain injury](#) and stroke. This [brain](#) inflammation, also called neuroinflammation, is increasingly believed to play a major role in the progressive damage characteristic of these [chronic diseases](#) and brain injuries.

By addressing brain inflammation, the new class of drugs -- represented by MW151 and MW189 -- offers an entirely different [therapeutic approach](#) to Alzheimer's than current ones being tested to prevent the development of beta [amyloid plaques](#) in the brain. The plaques are an indicator of the disease but not a proven cause.

A new preclinical study published today in the *Journal of Neuroscience*, reports that when one of the new Northwestern drugs is given to a mouse genetically engineered to develop Alzheimer's, it prevents the

development of the full-blown disease. The study, from Northwestern's Feinberg School and the University of Kentucky, identifies the optimal therapeutic time window for administering the drug, which is taken orally and easily crosses the blood-brain barrier.

"This could become part of a collection of drugs you could use to prevent the development of Alzheimer's," said D. Martin Watterson, a professor of [molecular pharmacology](#) and [biological chemistry](#) at the Feinberg School, whose lab developed the drug. He is a coauthor of the study.

In previous animal studies, the same drug reduced the neurological damage caused by closed-head traumatic [brain injury](#) and inhibited the development of a multiple sclerosis-like disease. In these diseases as well as in Alzheimer's, the studies show the therapy [time window](#) is critical.

MW151 and MW189 work by preventing the damaging overproduction of brain proteins called proinflammatory cytokines. Scientists now believe overproduction of these proteins contributes to the development of many degenerative [neurological diseases](#) as well as to the [neurological damage](#) caused by traumatic brain injury and stroke.

When too many of the cytokines are produced, the synapses of the brain begin to misfire. Eventually the entire organization of the brain falls into disarray, like a computer failing. The neurons lose their connections with each other and can eventually die. The resulting damage in the cortex and hippocampus can compromise memory and decision-making.

"In Alzheimer's disease, many people now view the progression from mild cognitive impairment to full-blown Alzheimer's as an indication of malfunctioning synapses, the pathways that allow neurons to talk to each other," said Watterson, the John G. Searle Professor of Molecular Biology and Biochemistry. "And high levels of proinflammatory

cytokines can contribute to synaptic malfunction."

Because this harmful inflammatory mechanism also appears to be a major player in other neurodegenerative disorders in addition to Alzheimer's, the class of drugs represented by MW151 might hold bright potential as co-therapies for Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis, M.S. and the longer term complications of brain injury, Watterson said.

"We need more studies of therapeutic time windows in models of these other diseases so we can better plan future clinical trials," Watterson noted.

In the new study by Northwestern's Watterson and Linda Van Eldik, director of the University of Kentucky Sanders-Brown Center on Aging, a mouse model of Alzheimer's received MW151 three times a week starting at six months of age, right at the time the proinflammatory cytokines began to rise. This would be the comparable stage when a human patient would begin to experience mild cognitive impairment.

When the mice brains were later evaluated at 11 months (at a time when disease pathology is usually present), cytokine levels in the mice receiving the drug were restored to normal levels and their synapses were functioning normally. The inflammatory cytokine levels of the mice not receiving the drug, however, were still at abnormally high levels, and the mice had misfiring synapses.

"The drug protected against the damage associated with learning and memory impairment," Van Eldik noted. "Giving this drug before Alzheimer's memory changes are at a late stage may be a promising future approach to therapy."

DRUG INHIBITS MULTIPLE SCLEROSIS

DEVELOPMENT

In M.S., overproduction of the proinflammatory cytokines damage the central nervous system and the brain. The proteins directly or indirectly destroy the insulation or coverings of the nerve cells that transmit signals down the spinal cord. When the insulation is stripped, messages aren't properly conducted down the spinal cord.

When mice that were induced to develop an M.S.-like disease received MW151 orally, they did not develop disease as severe.

"We inhibited the development of the disease," said William Karpus, the Marie A. Fleming Research Professor of Pathology at the Feinberg School. "Now we need to learn if the drug can prevent relapses of M.S." That study is ongoing in mice and the results will determine whether a patient trial will be planned.

The only current oral drug treatment for M.S. acts at the level of the lymph nodes, Karpus said. Because the brain is the site of the inflammation and damage, a drug that works in the brain is an ideal therapy.

DRUG PROTECTS BRAIN AFTER TRAUMATIC BRAIN INJURY

After a traumatic brain injury, the glia cells in the brain become hyperactive and release a continuous cascade of proinflammatory cytokines that -- in the long term -- can result in cognitive impairment and epilepsy. As a result of this hyperactivity, researchers believe the brain is more susceptible to serious damage following a second neurological injury.

In a study with mice, Mark Wainwright, M.D., professor of pediatric neurology at Northwestern's Feinberg School and a physician at the Ann & Robert H. Lurie Children's Hospital of Chicago, showed that when MW151 is given during an early therapeutic window three to six hours after the injury, it blocks glial activation and prevents the flood of proinflammatory cytokines after a traumatic brain injury.

"If you took a drug like this early on after traumatic brain injury or even a stroke, you could possibly prevent the long-term complications of that injury including the risk of seizures, cognitive impairment and, perhaps, mental health issues," Wainwright said.

Stroke also causes inflammation in the brain that may also be linked to long-term complications including epilepsy and cognitive deficits. As in traumatic brain injury, this inflammatory response is part of the recovery mechanisms used by the brain, so the use of brief and focused treatments like MW151 could prevent the harmful effects of inflammation while allowing the protective effects to occur unimpeded.

In another study, Wainwright showed MW151, when given after a traumatic brain injury, prevented the increased risk of epileptic seizures.

Provided by Northwestern University

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