Rejected drug may protect against toxic substance common to Alzheimer's and Parkinson's diseases

August 13 2012

The second of two studies on latrepirdine, recently published in Molecular Psychiatry, demonstrates new potential for the compound in the treatment of Alzheimer's disease, Parkinson's disease, sleep disorders, and other neurodegenerative conditions. An international team led by Mount Sinai School of Medicine scientists found that latrepiridine, known commercially as Dimebon, reduced the level of at least two neurodegeneration-related proteins in mice.

Latrepirdine was initially sold as an antihistamine in Russia, following its approval for use there in 1983. In the 1990s, the compound appeared effective in treating some of the earliest animal models of Alzheimer's disease. In a high profile Phase II clinical trial in Russia, overseen by a panel of top U.S. clinical trial experts, including Mount Sinai's Mary Sano, PhD, Professor of Psychiatry and Director of the Mount Sinai Alzheimer's Disease Research Center, latrepirdine showed significant and sustained improvement in cognitive behavior in Alzheimer's patients with minimal side effects. However, when the drug was tested in the U.S. in a Phase III trial, it did not demonstrate any improvement in people with the disease, causing the sponsors to halt further clinical study of the drug in Alzheimer's disease.

Before the failed trials however, Mount Sinai researchers led by Sam Gandy, MD, PhD, Professor of Neurology, and Psychiatry, and Director of the Mount Sinai Center for Cognitive Health, began studying how

latrepirdine worked.

"Despite the failure to replicate the positive Russian trial results in U.S. patients, we found unexpected evidence that latrepirdine had potential as a treatment for a number of neurodegenerative disorders," said Dr. Gandy. "Our study shows that the compound prevents neurodegeneration in multiple ways and should remain a contender for battling these devastating diseases. The anti-amyloid approach – most recently exemplified by reports that a second bapineuzumab trial has failed – might only help patients if begun before the brain pathology begins to build up."

In the new study, the researchers administered the drug to three different systems: yeast, mice and mammal cells all showing build-up of alpha-synuclein, a protein known to cause neurodegeneration. In all three systems, they determined that latrepiridine activated autophagy, the so-called "self-eating" process of cells that protects the brain from neurodegeneration, which targeted synuclein and protected against its toxicity. In mice, the drug reduced the amount of synuclein accumulated in the brain through autophagy.

John Steele, PhD, a Mount Sinai neuroscience graduate student, devoted his PhD thesis to these studies. Lenard Lachenmayer, MD, a postdoctoral fellow working under the supervision of Zhenyu Yue, PhD, Associate Professor of Neurology at Mount Sinai, shares first authorship of the new paper with Steele and with Shulin Ju, PhD, a postdoctoral fellow at Brandeis University working under the direction of Greg Petsko, PhD, and Dagmar Ringe, PhD, both professors of biochemistry, chemistry and neuroscience at Brandeis.

This study is the second of two published by Dr. Gandy's team in Molecular Psychiatry. The first, published July 31, 2012, determined that latrepiridine stopped the toxicity of amyloid-beta protein

accumulation in mice present with Alzheimer's disease by inducing autophagy. In that study, they randomly administered either latrepirdine or placebo to mice engineered to have the early stages of Alzheimer's disease and found that, through autophagy, the drug improved memory.

Dr. Petsko, an expert in protein structure who is now Professor of Neurology and Neuroscience at Weill Cornell Medical College, noted that, surprisingly, latrepirdine protects yeast cells from the toxicity of alpha-synuclein while leaving the cells vulnerable to killing by either the Huntington's disease protein or by either of the two key proteins responsible for ALS-FTD, a spectrum of diseases that includes both Lou Gehrig's disease and frontotemporal dementia.

"The specificity of latrepirdine protection of yeast cells from alpha-synuclein poisoning was unexpected but highly specific and, we believe, occurs at doses of drug potentially relevant to the clinic," Dr. Petsko said.

"We believe that the U.S. latrepirdine trial failed because of a lack of understanding of how latrepirdine works," said Dr. Sano of the Mount Sinai Alzheimer's Disease Research Center. "Many of the patients in the Russian trial may have had a subtype of Alzheimer's disease that includes excess buildup of alpha-synuclein, making them more responsive to latrepirdine. We know that this occurs by chance in about one-third of Alzheimer's patients. The data indicating that latrepirdine both stimulates alpha-synuclein breakdown and protects cells from alpha-synuclein poisoning are highly intriguing."

Drs. Gandy and Yue are testing whether latrepirdine might be beneficial in treating or preventing disorders associated with high levels of alpha-synuclein such as Parkinson's disease, Lewy body dementia, and REM sleep disorder.

Provided by The Mount Sinai Hospital