Duke team finds compounds that prevent nerve damage

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Duke University Medical Center scientists have made a significant finding that could lead to better drugs for several degenerative diseases including Huntington's disease and Alzheimer's disease. Compounds that block the activity of a specific enzyme prevented brain injury and greatly improved survival in fruit flies that had the same disease process found in Huntington's disease.

"We were able to prevent Huntington's disease-like illness in mutant fruit flies by giving them orally active transglutaminase inhibitors," said Charles S. Greenberg, M.D., a Professor of Medicine and Pathology at Duke University Medical Center and senior author of the paper. The drug blocks the action of an enzyme called tissue transglutaminase (TGM2). TGM2 may damage cells by forming strong bonds between proteins. Such bonding is beneficial for blood clotting which happens outside of cells, but if this type of bonding occurs inside cells, it can be harmful, Greenberg said.

The study appears in the current issue of *Chemistry and Biology*.

Huntington's disease causes uncontrolled movement and mental deterioration that develops later in life, and though there is no cure, people can get tested to learn whether they have the gene that causes the devastating illness, Greenberg said.

Alzheimer's disease, Parkinson's disease and polyglutamine diseases including Huntington's disease may possibly be improved with the same

compounds, said Thung S. Lai, Ph.D., lead author and a Duke Associate Professor of Medicine. "Our findings may also help to develop drugs that block the pathology related to transglutaminase's action. That action has been linked to the development of tissue fibrosis, organ failure and aging."

While these compounds were promising in the animal system, they are several years away from entering any human trials, Greenberg said. "We will be studying these compounds in diseases in which TGM2 produces tissue injury."

For the study, Lai painstakingly screened 2,000 compounds. Only two groups of drugs were found to be effective TGM2 inhibitors. Some of the most potent TGM2 inhibitors were given to the fruit flies along with their food.

The most effective compound was a kinase inhibitor, a drug that had been developed several years ago for another purpose. The other beneficial compounds fell into a category of drugs that attack a sulfhydryl group in a protein.

The next step is to use the effective compounds as the backbone for developing even more effective drugs, Lai said. The scientists plan to test whether the TGM2 inhibitors they identified would prevent the fibrous tissue process that causes chronic renal, vascular and lung disease.

Source: Duke University Medical Center