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Drug holds promise to halt debilitating condition of diabetes

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A drug developed at the University of Kansas has the potential to stop a debilitating condition of diabetes that often leads to pain in the extremities and even amputations, KU researchers have found.

The researchers recently published an article showing that KU-32 can stop and even reverse diabetic peripheral neuropathy, or DPN, in mice. The condition leads to death of nerves in the extremities of individuals with diabetes.

"People with DPN can be very sensitive to light touch, which can cause significant pain," said Rick Dobrowsky, professor of pharmacology and toxicology and one of the paper's authors. "The other side is eventually diabetes causes death of the nerves. DPN often leads to loss of feeling in the hands and feet, which can make diabetics susceptible to wounds and infections and often leads to amputations of toes and feet."

DPN is the second leading cause of amputations, after injuries.

Dobrowsky co-authored the paper with Brian Blagg, professor of medicinal chemistry; Roger Rajewski, professor of pharmaceutical chemistry; Joanna Krise and Michelle McIntosh, research associates with the Biotechnology Innovation and Optimization Center; Cuijuan Yu, research associate with the Higuchi Biosciences Center; postdoctoral researcher Yuanming Lu; and graduate students Michael Urban and Cuijuan Yu. It was published in the American Society of Neurochemistry's journal, *ASN Neuro*.

The researchers administered KU-32 to diabetic mice. The compound stopped DPN and showed it could restore sensory neuron function to damaged nerve tissue. KU-32 inhibits a specific member of a family of proteins called molecular chaperones.

"These studies provide the first evidence that targeting molecular chaperones reverses the sensory hypoalgesia associated with DPN," the authors wrote.

There are approximately 24 million diabetics in the United States. Dobrowsky said nearly 60 percent of them suffer from DPN at some point. The researchers hope that eventually the drug could be used to help to treat the condition in humans. Their research shows KU-32 can be administered orally as infrequently as once a week and still be effective. It has been shown to have long-term efficacy, meaning it could be administered in small doses, potentially reducing severity of side effects.

"Our tests so far indicate that KU-32 is completely nontoxic and is absorbed in the blood stream very well," said Blagg. "It has long-term efficacy. It is a promising treatment."

There are only two FDA-approved drugs used for treatment of DPN, Blagg said. However, one is an anticonvulsant and the other is an antidepressant, and neither has the potential to reverse nerve degeneration.

The research, funded by grants from the Juvenile Diabetes Research Foundation and the National Institutes of Health, is ongoing. The team is hoping to discover how long the drug can be effective in combating DPN. People often find out they have diabetes when they are suffering from the nerve-degenerating condition.

"The idea is to try to determine at what point in nerve degeneration will be most effective and at what point the drug will not be efficacious," Dobrowsky said. "We'd like to know at what stage in the progression of DPN a window of opportunity exists for the beneficial use of KU-32."

The researchers also hope to determine exactly how the drug stopped and reversed DPN in mice. It's not immediately evident if it improved existing nerve fibers or generated new ones.

The drug is still in pre-clinical development. It will likely need another year or two of study, then the researchers hope it could be advanced to clinical trials in humans.

Dobrowsky said the collaboration of researchers with different areas of expertise was key to the study.

"This is an excellent example of how collaboration allows us to achieve one of the School of Pharmacy's goals, to discover medications that enhance and extend life," he said.

More information: The article, "Inhibiting heat-shock 90 protein 90 reverses sensory hypoalgesia in diabetic mice," is available on the *ASN Neuro* site.

Provided by University of Kansas