Movement disorder symptoms are lessened by an antibiotic

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Discovery of an antibiotic's capacity to improve cell function in laboratory tests is providing movement disorder researchers with leads to more desirable molecules with potentially similar traits, according to University of Alabama scientists co-authoring a paper publishing March 10 in the journal *Disease Models & Mechanisms*.

"It's our hope that this discovery serves as the impetus for a proper clinical trial to evaluate the potential of drugs like ampicillin for early-onset torsion dystonia," said Dr. Guy Caldwell, associate professor of biological sciences at The University of Alabama.

Dystonia is, like Parkinson's disease, a movement disorder. Combined, this class of diseases affects millions worldwide. People with early-onset dystonia have one good copy of the gene DYT1, and one problematic copy, in their DNA. These genes contain the information to make a protein called torsinA.

"When proteins go bad, they often cause disease, but they always have a normal function in our cells," Guy Caldwell said. "We looked to find molecules - not necessarily that reversed the mutated form of the protein - but instead enhanced the normal activity of the protein, thereby overcoming the deficiency caused by the mutant."

The UA researchers discovered that ampicillin, a common antibiotic of the penicillin group, serves to activate torsinA, which, in its normal form, appears to protect cells from stresses, such as protein misfolding -

a problem known to impact various movement disorders.

Using a nematode animal model designed to evaluate torsinA activity, the UA lab rapidly screened through hundreds of compounds to identify those that were most effective at enhancing torsinA's normally protective function.

"From there, we collaborated with researchers at Harvard and UAB to validate our findings in human patient cells and mice," said Dr. Kim Caldwell, associate professor of biological sciences at UA.

"In human dystonia patient cells, ampicillin was efficacious and restored the patient cells back to the normal function," Kim Caldwell said. "And, the drug restored normal movement to mice that were genetic mimics of dystonia."

Collaborators in the UA-led study were Drs. Xandra O. Breakefield and her colleagues at Harvard and Yuqing Li and his colleagues at The University of Alabama at Birmingham, known as UAB. Dr. Songsong Cao, a former doctoral student in the Caldwell Lab, is the study's lead author; two UA doctoral students, Alexander J. Burdette and Pan Chen; and one former UA student, Amber Clark Buckley, are among the co-authors.

Furthermore, the research shows ampicillin enhances the capacity of torsinA to protect, within animal models, the neurons which produce dopamine from dying. The death of these neurons in human brains leads to the hallmark symptoms of Parkinson's disease.

In a statement accompanying the paper, the researchers caution against the long-term use of an antibiotic in disease treatment.

"We have taken ampicillin and used that as a base structure to find

things that work like ampicillin but which aren't ampicillin," Guy Caldwell said. "Finding molecules that are not antibiotic and still have the capacity to activate torsinA has been an ongoing effort of our lab, and we have some exciting leads in that direction."

UA filed patents covering the use of antibiotics and other novel chemicals as activators of torsinA for treatment of dystonia and other diseases, including Parkinson's disease. The University has also entered into a collaborative research and licensing agreement with QRxPharma, a clinical stage pharmaceutical company, to identify, develop and commercially exploit new torsinA activator drugs.

The UA/QRxPharma research program is directed at re-engineering existing drug therapies for new clinical applications and identifying new drug candidates for uses including the treatment of dystonia, Parkinson's disease and other neurological disorders.

The project exemplifies, the researchers said, how disease model systems can be used to accelerate the development of gene and drug discovery and bring pharmaceuticals more quickly to the clinical trial stage.

Bringing a drug that does not already have FDA approval from the research and development stage to a patient takes an estimated 12 years and $800 million dollars, said Kim Caldwell. By evaluating the potential of molecules already pre-screened for toxicity and that have FDA approval provides a potentially quicker route to clinical trials.

"What we were hoping to do was circumvent a lot of the cost in bringing pharmaceutical help to dystonia patients," Kim Caldwell said.

More information: This work is published in Issue 3/4 of Volume 3 in the medical research journal Disease Models and Mechanisms (DMM)