Researchers find new path to promising Parkinson's treatment

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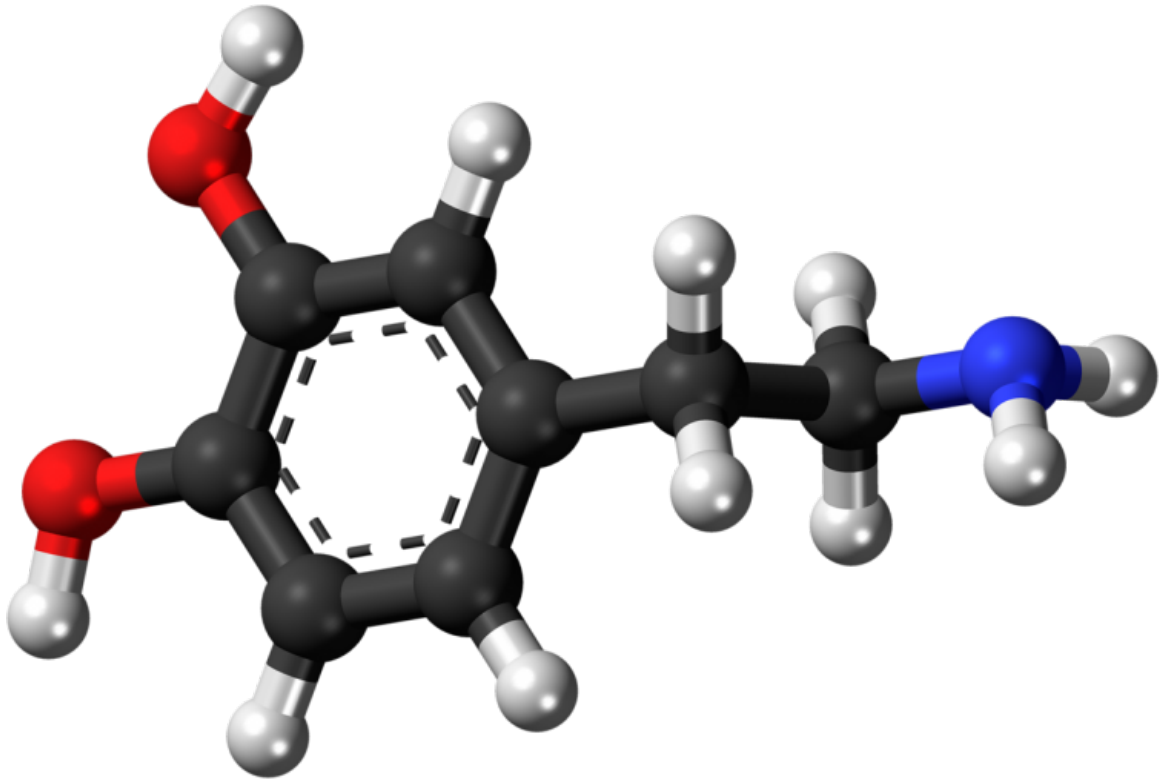

Ball-and-stick model of the dopamine molecule, a neurotransmitter that affects the brain's reward and pleasure centers. Credit: Jynto/Wikipedia

Three researchers at The University of Alabama are part of work that is leading to a new direction for drug discovery in the quest to treat

Parkinson's disease.

Findings from the study are published today in the journal *Nature Neuroscience*, with the UA researchers among the co-authors.

"This provides real evidence for a long-sought mechanism, and, simultaneously, it provides a good rationale for a different path for drug discovery," said Dr. Guy Caldwell, University Distinguished Research Professor in biological sciences. "This path and these ideas have been out there. This paper really brings it together and supports the evidence for those ideas."

Guy Caldwell is a co-author on the paper that includes Dr. Kim Caldwell, professor of biological sciences at UA, and Hanna Kim, a doctoral student in the Caldwell lab who is the primary UA contributor.

Parkinson's disease, a neurodegenerative disorder, is estimated to afflict between seven and 10 million people worldwide with approximately 60,000 Americans diagnosed each year. Current therapies include treating the symptoms of the disease such as tremor and involuntary shakes, but there is no cure or treatment to halt the disease's progression.

Hallmarks of Parkinson's disease are the loss of cells, or neurons, that send information to other parts of the brain, specifically neurons that produce a type of information-carrying chemical known as dopamine, along with the accumulation, or clumping, of proteins in the neurons.

To work, proteins must fold properly within cells. When extra copies or mutations of the protein alpha-synuclein are present in dopamine-producing neurons, a series of misfoldings can occur, leading to aggregation of proteins. Such protein aggregation within the brain's dopamine-producing neurons can lead to their malfunction or cell death, triggering the symptoms of Parkinson's.

When a Parkinson's patient is exhibiting symptoms of the disease, they have likely lost up to 80 percent of the dopamine neurons in their bodies, Guy Caldwell said.

The mystery in Parkinson's research is why dopamine neurons are vulnerable to alpha-synuclein clumping, he said. The answer, according to the latest findings, is dopamine. Dopamine has the ability to bind alpha-synuclein, making it more toxic, according to the study.

"This seems to be possibly a real root mechanism of pathogenesis that is a direct interaction between dopamine and the pathogenic protein alpha-synuclein," he said. "If we can find a way to block the interaction of dopamine and alpha-synuclein directly, then that would be therapeutic."

The idea that dopamine causes the clumping has been shown in test tubes using chemicals, but the latest work proved its consequences in animal models.

At UA, researchers in the Caldwell lab work with tiny roundworms known as C. elegans, which shares roughly half its genes with humans. Its basic features allow inexpensive and rapid testing for a range or neurological diseases, and UA researchers can induce Parkinson's-like effects in the worm for testing.

Hanna Kim was able to demonstrate dopamine's effects on alpha-synuclein within the worm, and researchers at the University of Pennsylvania, the lead institution on the study, also showed the mechanism in mice. An impetus for this work came from previously published UA-based research from the Caldwell lab that showed excess dopamine production was toxic in the worm model.

The group has already moved onto the next step of finding ways to block the process, and Kim has shown that removing spots of interaction, or

sequences of amino acids in a protein, between dopamine and alpha-synuclein enhances the survival of neurons, halting the progression of the disease state.

"It was a nice confirmation that in a living animal model system, preventing the interaction between dopamine and alpha-synuclein could alleviate the neurotoxicity that occurred," Guy Caldwell said.

The paper "Dopamine induces soluble α-synuclein oligomers and nigrostriatal degeneration" is published online today and will appear in an upcoming issue of Nature Neuroscience. The work was supported by the National Institutes of Health.

More information: Danielle E Mor et al. Dopamine induces soluble α-synuclein oligomers and nigrostriatal degeneration, *Nature Neuroscience* (2017). DOI: 10.1038/nn.4641

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