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Researchers make new discoveries in key pathway for neurological diseases

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A new intermediate step and unexpected enzymatic activity in a metabolic pathway in the body, which could lead to new drug design for psychiatric and neurodegenerative diseases, has been discovered by researchers at Georgia State University.

Their findings are published in the journal *Nature Communications* this week.

The research team has been studying a metabolic pathway called the tryptophan kynurenine pathway, which is linked to psychiatric and neurodegenerative disorders, including depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's disease, AIDS dementia complex, asphyxia in newborns and epilepsy. The medical potential of this pathway warrants detailed study to provide information about the pathway's enzymes and their regulation.

This pathway produces several neurotransmitter regulators and is responsible for metabolizing nearly 99 percent of the tryptophan in the body. Tryptophan is a precursor of serotonin, the neurotransmitter responsible for mood.

The researchers determined the structure and mechanism of an enzyme in the kynurenine pathway, AMSDH.

To better understand the rapid chemical reaction catalyzed by this enzyme, Dr. Aimin Liu, professor in the Department of Chemistry and

core member of the Center for Diagnostics and Therapeutics at Georgia State, organized a research team, including graduate students Lu Huo, Ian Davis, Fange Liu and Shingo Esaki, and researchers at Brookhaven National Laboratory and Kansai University in Osaka, Japan. They used new scientific techniques, including time-lapse crystallography and single-crystal spectroscopy, to slow down the reaction rate by nearly 10,000 times. This allowed them to observe a new intermediate step, the thiohemiacetal intermediate, and discover an unexpected isomerase activity in AMSDH.

"By doing this, we find new chemistry, and we also open up avenues for others to design specific drugs to target this pathway," Liu said. "This pathway is highly associated with neurodegenerative diseases and depression."

The researchers took a high concentration of the purified protein, grew single crystals, mixed them with their substrate and froze them at different time points in liquid nitrogen at 77 Kelvin to stop all molecular activity. They sent the crystals to Argonne National Laboratory for remote data collection. The X-ray diffraction patterns collected there were used to create an electron density map, a 3-D, atomic-level resolution of the molecule's shape. The researchers used time-lapse crystallography and single-crystal spectroscopy to observe intermediate steps of the reaction.

"This is the first absorbance spectrum of this intermediate," Davis said. "When we look for this in solution assays, we don't see this absorbance band because this intermediate is very short-lived in solution. But by doing it in crystal and freezing it down, you can actually see it in the crystalline state.

"Enzymes work by stabilizing reactive intermediates. Through this isomerization mechanism, we found a new reactive intermediate

stabilized by this enzyme. So if you want to design a drug, your best bet is to try and make something that looks very similar to this so that it will bind to the enzyme. That's a general strategy for drug design. You want to try and make drugs that look very similar to transition states. Basically, we found a new transition state in this work."

Information from the study has been deposited in the protein database, which can be accessed by other scientists.

In the next phase of this project, the researchers will determine how the enzymes in this pathway affect one another. They will partner with Dr. Andy Miller, director of psychiatry at Emory University, to determine the physiological application of this pathway in humans.

More information: *Nature Communications*, dx.doi.org/10.1038/ncomms6935

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