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Researchers link metal ions to neurodegenerative disease

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A multi-institutional team of researchers led by Emory University has defined for the first time how metal ions bind to amyloid fibrils in the brain in a way that appears toxic to neurons. Amyloid fibrils are linked to the development of neurodegenerative diseases such as Alzheimer's, Parkinson's and Creutzfeldt-Jakob. Although metal ions, most notably copper, can bind to amyloid in several specific ways, the researchers found that only one way appears toxic.

The findings will appear in the *Proceedings of the National Academy of Sciences*, Early Edition online during the week of Aug. 6-10 and in the Aug. 14 print edition.

Copper ions, atoms that have acquired an electric charge by gaining or losing one or more electrons, are found naturally in the brain, as are other ions such as zinc and iron. Increasing evidence now links these naturally occurring ions to amyloid assembly and to Alzheimer's disease, says David Lynn, PhD, Emory professor and chair of chemistry and principal investigator of the study.

While little is known about the exact mechanisms governing the formation of amyloid fibrils, the study's results suggest that the exact way amyloid binds to copper ions affects the fibers' architecture, rate of propagation and their effect, if any, on surrounding neurons.

"Not all amyloid fibrils are toxic," says Dr. Lynn. "Amyloid is made of proteins and proteins normally fold into beautiful structures. However,

for whatever reason, some misfold and the resulting misfolded structures are also beautiful, but sticky. They stick to themselves and then propagate to form fibrils, but only some of the fibrils turn out to be toxic."

Those who suffer from Alzheimer's disease, for example, have an unusual amount of sticky amyloid fibrils in their brains. Over time, the fibrils accumulate instead of decomposing and increasingly interfere with the brain's structure and function. In contrast, normally folded proteins are cleared from the brain shortly after they are produced.

The scientists, collaborating throughout the United States and across Emory, focused on the smallest individual unit of amino acids that make up amyloid fibrils. By determining only an individual unit's physical and chemical properties when binding with metal, the researchers were able to determine the activity governing the assembly and toxicity of whole fibrils with respect to their effect on brain cells.

"We showed that the activity of this minimal unit actually replicates the activity of the whole fibril on the neuronal cell. And it does so by binding the metal in a specific way," says Dr. Lynn.

Forty years ago, scientists began exploring a possible link between overexposure to metals and Alzheimer's disease. Because some people with the disease had aluminum deposits in their brains, it was thought that there was a direct connection between aluminum exposure and Alzheimer's. However, after many years of study, no conclusive evidence links aluminum to neurodegenerative disease, which leaves researchers to focus on zinc, iron and copper.

The researchers also found that several distinct types of structures could be assembled from individual units of amino acids. "We found that we could build lots of different types of structures with an individual unit:

fettuccine-shaped structures, tubes, vesicles, and so on, not just fibers. And this is remarkable," says Dr. Lynn.

"Our findings now lead us to ask what other types of structures these individual units can make, what exactly happens when the units bind to one another, and whether these individual units are important to neurodegenerative diseases or whether the entire fibril must be involved," says Dr. Lynn.

"Like many scientific findings, we know about amyloid because of the diseases it's associated with rather than because of its benefits," says Dr. Lynn. "However, researchers are also finding situations in which amyloid is beneficial, such as in long-term memory and synapse maintenance in the marine snail."

Source: Emory University