Scientists show copper facilitates prion disease

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(Medical Xpress) -- Many of us are familiar with prion disease from its most startling and unusual incarnations—the outbreaks of “mad cow” disease (bovine spongiform encephalopathy) that created a crisis in the global beef industry. Or the strange story of Kuru, a fatal illness affecting a tribe in Papua New Guinea known for its cannibalism. Both are forms of prion disease, caused by the abnormal folding of a protein and resulting in progressive neurodegeneration and death.

While exactly how the protein malfunctions has been shrouded in mystery, scientists at The Scripps Research Institute now report in the journal *Proceedings of the National Academy of Sciences* (*PNAS*) that reducing copper in the body delays the onset of disease. Mice lacking a copper-transport gene lived significantly longer when infected with a prion disease than did normal mice.

“This conclusively shows that copper plays a role in the misfolding of the protein, but is not essential to that misfolding,” said Scripps Research Professor Michael Oldstone, who led the new study.

“We've known for many years that prion proteins bind copper,” said Scripps Research graduate student Owen Siggs, first author of the paper with former Oldstone lab member Justin Cruite. “But what scientists couldn’t agree on was whether this was a good thing or a bad thing during prion disease. By creating a mutation in mice that lowers the amount of circulating copper by 60 percent, we've shown that reducing copper can delay the onset of prion disease.”

Zombie Proteins

Unlike most infections, which are caused by bacteria, viruses, or parasites, prion disease stems from the dysfunction of a naturally occurring protein.

“We all contain a normal prion protein, and when that's converted to an abnormal prion protein, you get a chronic nervous system disease,” said Oldstone. “That occurs genetically (spontaneously in some people) or is acquired by passage of infectious prions. Passage can occur by eating infected meat; in the past, by cannibalism in the Fore population in New Guinea through the ingestion or smearing of infectious brains; or by introduction of infectious prions on surgical instruments or with medical products made from infected individuals.”

When introduced into the body, the abnormal prion protein causes the misfolding of other, normal prion proteins, which then aggregate into plaques in the brain and nervous system, causing tremors, agitation, and failure of motor function, and leads invariably to death.

A Delicate Balance

The role of copper in prion disease had previously been studied using chelating drugs, which strip the metals from the body—an imprecise technique. The new study, however, turned to animal models engineered in the lab of Nobel laureate Bruce Beutler while at The Scripps Research Institute. (Beutler is currently director of the Center for the Genetics of Host Defense at UT Southwestern.)

The Beutler lab had found mice with mutations disrupting copper-transporting enzyme ATP7A. The most copper-deficient mice died in utero or soon after birth, but those with milder deficiency were able to

live normally.

“Copper is something we can't live without,” said Siggs. “Like iron, zinc, and other metals, our bodies can't produce copper, so we absorb small amounts of it from our diet. Too little copper prevents these enzymes from working, but too much copper can also be toxic, so our body needs to maintain a fine balance. Genetic mutations like the one we describe here can disrupt this balance.”

Death Delayed

In the new study, both mutant and normal mice were infected with Rocky Mountain Laboratory mouse scrapie, which causes a spongiform encephalopathy similar to mad cow disease. The control mice developed illness in about 160 days, while the mutant mice, lacking the copper-carrying gene, developed the disease later at 180 days.

Researchers also found less abnormal prion protein in the brains of mutant mice than in control mice, indicating that copper contributed to the conversion of the normal prion protein to the abnormal disease form. However, all the mice eventually died from disease.

Oldstone and Siggs note the study does not advocate for copper depletion as a therapy, at least not on its own. However, the work does pave the way for learning more about copper function in the body and the biochemical workings of prion disease.

More information: “Disruption of copper homeostasis due to a mutation of Atp7a delays the onset of prion disease,” Published online before print August 6, 2012, doi: 10.1073/pnas.1211499109

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