Copper Identified as Culprit in Alzheimer's Disease

University of Rochester Medical Center

Copper appears to be one of the main environmental factors that trigger the onset and enhance the progression of Alzheimer's disease by preventing the clearance and accelerating the accumulation of toxic proteins in the brain. That is the conclusion of a study appearing today in the journal Proceedings of the National Academy of Sciences.

"It is clear that, over time, copper's cumulative effect is to impair the systems by which amyloid beta is removed from the brain," said Rashid Deane, Ph.D., a research professor in the University of Rochester Medical Center (URMC) Department of Neurosurgery, member of the Center for Translational Neuromedicine, and lead author of the study. "This impairment is one of the key factors that cause the protein to accumulate in the brain and form the plaques that are the hallmark of Alzheimer's disease."

Copper's presence in the food supply is ubiquitous. It is found in drinking water carried by copper pipes, nutritional supplements, and in certain foods such as red meats, shellfish, nuts, and many fruits and vegetables. The mineral plays an important and beneficial role in nerve conduction, bone growth, the formation of connective tissue, and hormone secretion.

However, the new study shows that copper can also accumulate in the brain and cause the blood brain barrier – the system that controls what enters and exits the brain – to break down, resulting in the toxic accumulation of the protein amyloid beta, a by-product of cellular activity. Using both mice and human brain cells Deane and his colleagues conducted a series of experiments that have pinpointed the molecular mechanisms by which copper accelerates the pathology of Alzheimer's disease.

Under normal circumstances, amyloid beta is removed from the brain by a protein called lipoprotein receptor-related protein 1 (LRP1). These proteins – which line the capillaries that supply the brain with blood – bind with the amyloid beta found in the brain tissue and escort them into the blood vessels where they are removed from the brain.

The research team – "dosed" normal mice with copper over a three month period. The exposure consisted of trace amounts of the metal in drinking water and was one-tenth of the water quality standards for copper established by the Environmental Protection Agency.

"These are very low levels of copper, equivalent to what people would consume in a normal diet." said Deane.

The researchers found that the copper made its way into the blood system and accumulated in the vessels that feed blood to the brain, specifically in the cellular "walls" of the capillaries. These cells are a critical part of the brain's defense system and help regulate the passage of molecules to and from brain tissue. In this instance, the capillary cells prevent the copper from entering the brain. However, over time the metal can accumulate in these cells with toxic effect.

The researchers observed that the copper disrupted the function of LRP1 through a process called oxidation which, in turn, inhibited the removal of amyloid beta from the brain. They observed this phenomenon in both mouse and human brain cells.

The researchers then looked at the impact of copper exposure on mouse models of Alzheimer's disease. In these mice, the cells that form the blood brain barrier have broken down and become "leaky" – a likely combination of aging and the cumulative effect of toxic assaults – allowing elements such as copper to pass unimpeded into the brain tissue. They observed that the copper stimulated activity in neurons that increased the production of amyloid beta. The copper also interacted with amyloid beta in a manner that caused the proteins to bind together in larger complexes creating logjams of the protein that the brain's waste disposal system cannot clear.

This one-two punch, inhibiting the clearance and stimulating the production of amyloid beta, provides strong evidence that copper is a key player in Alzheimer's disease. In addition, the researchers observed that copper provoked inflammation of brain tissue which may further promote the breakdown of the blood brain barrier and the accumulation of Alzheimer's-related toxins.

However, because metal is essential to so many other functions in the body, the researchers say that these results must be interpreted with caution.

"Copper is an essential metal and it is clear that these effects are due to exposure over a long period of time," said Deane. "The key will be striking the right balance between too little and too much copper consumption. Right now we cannot say what the right level will be, but diet may ultimately play an important role in regulating this process."

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