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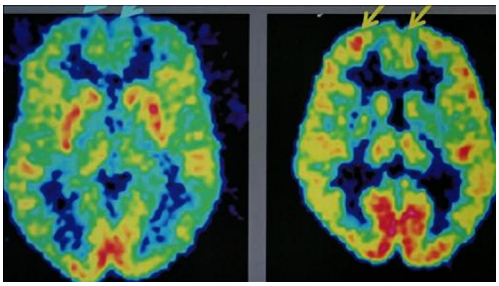
A New Target in Fighting Brain Disease: Metals

By SHIRLEY S. WANG

Research into how iron, copper, zinc and other metals work in the brain may help unlock some of the secrets of degenerative diseases like Alzheimer's and Parkinson's.



One of the many theories explaining Alzheimer's disease is that some of the harm is caused by toxic metals accumulating in brain. Now a new study lends more credibility to the toxic metal theory. Shirley Wang has details on Lunch Break.

Iron and copper appear to accumulate beyond normal levels in the brains of people with these diseases, and a new, Australian study published Sunday shows reducing excess iron in the brain can alleviate Alzheimer's-like symptoms—at least in mice.

A genetic mutation related to regulating iron is linked to ALS, or Lou Gehrig's disease. Zinc, on the other hand, appears to impair memory if its levels get too low or if it gets into a brain region where it doesn't belong, as it can with traumatic brain injury.

Research into the complicated, invisible roles these metals play in brain diseases has lagged behind study of the more-visible proteins that are damaged or clump together in the brains of Alzheimer's and Parkinson's sufferers. But better understanding metals' role in the brain could help shed light on a range of medical conditions and might offer a new route for developing treatments, scientists say.

"The field is coming around to the idea of the cause of Alzheimer's being multifactorial," and disturbed metal regulation could be one of those factors, says Ralph Nixon, chairman of the Alzheimer Association's medical and scientific advisory council and director of the Silberstein Alzheimer's Institute at New York University.

Tiny metal ions—charged particles of the elements—serve several essential functions in the body, including facilitating chemical reactions to generate energy and preserving the structure of proteins. Strict checks and balances in a healthy body keep metal levels within a tight range.

But the biological changes that come with disease and aging—as opposed to poisoning from outside sources like food, supplements or metal pans—can knock levels of these metals out of whack in the brain.

Iron, for instance, is a "double-edged sword" because it interacts with oxygen to help the body generate energy, but also can produce free radicals, highly reactive molecules that can cause cell damage, says James Connor, professor and vice chairman of neurosurgery at Penn State University in Hershey.

If the body has too little iron, such as with anemia, the body doesn't generate enough energy to sustain important functions. But an overabundance of iron accumulated in the brain is toxic. Significantly higher accumulations of metal have been observed in the brains of people with Parkinson's and Alzheimer's disease than in healthy people of the same age, says Ashley Bush, a professor of pathology at the University of Melbourne.

The new study, conducted by Dr. Bush and colleagues and published in the journal Nature Medicine, examined the amount of iron in the brains of mice that were bred unable to produce the tau protein, which helps stabilize the structure of neurons. Tau damage is associated with Alzheimer's and Parkinson's.

As the mice aged, they suffered symptoms similar to people with both diseases, including impaired short-term memory, and also exhibited an accumulation of iron in their brains. When the researchers gave them a drug removing excess iron, the symptoms reversed. This means normally functioning tau is necessary for removing iron in the brain, Dr. Bush says. The finding bolsters previous research showing that bringing down iron may be a path to new treatments.

"An accumulation of iron in neurons seems to be a final end-stage event in neurodegeneration, whether it be Alzheimer's or Parkinson's, [or] any [condition] related to tau abnormalities," says Dr. Bush, who is also a fellow at the university's Mental Health Research Institute.

Other proteins affected in Alzheimer's also play a role in metal regulation. The amyloid precursor protein is important in helping export iron from the brain, according to work published in the journal Cell in 2010. Presenilin, another protein that aids in metal uptake, is also disturbed in diseased brains, according to a study published in Journal of Biological Chemistry last year.

Similar findings link copper accumulation and brain disease, though not as much research has been conducted as with iron, scientists say.

In addition to iron accrual, lower-than-normal levels of zinc have been found in patients with Alzheimer's and Parkinson's disease, according to work by George Brewer, an emeritus professor at the University of Michigan, and Edward Fitzgerald at the University at Albany-SUNY, published last year in the American Journal of Alzheimer's Disease and Other Dementias. Dr. Brewer now is a consultant to Adeona Pharmaceuticals Inc., based in Ann Arbor, Mich., which is developing a zinc-based treatment for Alzheimer's, he says.

Besides Adeona, a handful of other biotechnology companies have also been testing experimental metal-lowering drugs for treatment of Alzheimer's or Parkinson's. But developing such drugs is tricky because it is hard to target metals in specific parts of the brain. Simply lowering or increasing the amount overall in the body may not be beneficial, researchers say.

Metals may play a vital role in other brain conditions.

Stephen Lippard, a chemistry professor at the Massachusetts Institute of Technology, and colleagues from Duke University and the University of Toronto, found zinc helps neurons communicate in the hippocampus, a brain region involved in learning and memory. Disturbing this interaction, or ushering zinc into a brain region where it doesn't belong, could affect memory formation and the occurrence of epileptic seizures, says Dr. Lippard, who studies the role of metal ions in biology, neuroscience, and medicine. Their work was published in September in Neuron.

"It's important that the medical community continue to be alerted to the connection between metal ions and neurological disease," says Dr. Lippard.

Dr. Connor and his Penn State team have shown that patients with ALS have a higher rate of mutation in a gene, HFE, that regulates iron absorption. Carriers of the mutation have higher levels of iron in the brain and a fourfold increase in risk of ALS, according to a 2004 study published in the Journal of Neurological Sciences.

They have also been trying to figure out why the patients with multiple sclerosis lose the protective coating, called myelin, surrounding their axons, the part of the nerve cell that conducts electrical impulses. The cells responsible for making the myelin have elevated iron, making them more vulnerable to damage and death, says Dr. Connor.

Metals, Positive and Negative

Several metals play vital roles in the human body, but diseases can disturb their balance, causing harm.

Iron

Normal function: Involved in oxygen transport; needed to make energy for cells.

In the brain: Excess levels of iron are linked to Alzheimer's and Parkinson's diseases. Proteins and mutations related to iron delivery or absorption appear to be connected to Lou Gehrig's disease and multiple sclerosis.

Copper

Normal function: Helps transport oxygen, often works in tandem with iron.

In the brain: Wilson disease stops the body from getting rid of copper, which can cause speech problems, tremors and muscle stiffness. Disruption in copper regulation causes Menkes disease, which leads to abnormally low copper levels.

Zinc

Normal function: Helps make DNA and RNA, regulates cell death, and plays a role in short-term memory and learning.

In the brain: Low levels or the presence of the metal in areas of the brain where it isn't normally found are thought to impair memory.

ð Source: WSJ reporting

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