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Copper Circuits Help Brain Function; Could Tweaking the Circuits Make Us Smarter?

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The flow of copper in the brain has a previously unrecognized role in cell death, learning and memory, according to research at Washington University School of Medicine in St. Louis. The researchers' findings suggest that copper and its transporter, a protein called Atp7a, are vital to human thinking. They speculate that variations in the genes coding for Atp7a, as well as other proteins of copper homeostasis, could partially account for differences in thinking among individuals.

Using rat and mouse nerve cells to study the role of copper in the brain, the researchers found that the Atp7a protein shuttles copper to neural synapses, the junctions that allow nerves to talk to one another.

At synapses, the metal ions affect important components responsible for making neural connections stronger or weaker. The changing strength of neural connections — called synaptic plasticity — accounts for, among other things, our ability to remember and learn.

"Why don't we think a hundred times better than we do?" asks senior author Jonathan Gitlin, M.D., the Helene B. Roberson Professor of Pediatrics at Washington University School of Medicine. "One answer to that question is, perhaps we could — if the brain could make the right connections. We've found that copper modulates very critical events within the central nervous system that influence how well we think."

The research was led by neuroscience graduate students Michelle Schlief, Ph.D., and Tim West, Ph.D., in collaboration with Anne Marie

Craig, Ph.D., and David M. Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology, and appears online this week in the *Proceedings of the National Academy of Sciences*.

The researchers found that when a chemical signal, or neurotransmitter, hits one of the microscopic antennas present at nerve synapses, Atp7a reacts and quickly brings copper ions from their storage areas within nerve cells to the cell surface.

When released into neural synapses, the copper damps down the activity of these antennas, called NMDA receptors. The activity of NMDA receptors determines how strong the connections between nerves cells are and changes in the receptors' activity are critical to cell survival, learning and memory.

"In the brain, some neurons have strong connections, and some have weak connections, but this is changing all the time," says Gitlin, who is also director of genetics and genomic medicine at St. Louis Children's Hospital and scientific director of the Children's Discovery Institute. "The plasticity of the connections between neurons is important for nerve cell survival and for our ability to think the way we do. The NMDA receptors are a large component of this process, and we've found that Atp7a and copper are key factors controlling them."

Since the Atp7a protein is responsible for moving copper in nerves, variations in the gene for Atp7a could influence copper flow in the nervous system and the function of NMDA receptors.

The researchers' findings stem from earlier research on the rare neurodegenerative disorder Menkes disease, which results from an abnormal Atp7a gene. The loss of properly functioning Atp7a protein in Menkes patients leads to impairment of copper distribution in the body.

Children born with the disease have intractable seizures and mental retardation and seldom live beyond the age of ten.

The current research showed that in mouse nerve cells that lacked Atp7a and so were not able to bring copper to synapses, the resulting high activity of NMDA receptors caused excitotoxic cell death, a process that kills nerve cells that have been overstimulated. This suggests that in the brains of people with Menkes, NMDA receptors, no longer appropriately modulated by copper, may kill important neurons and cause neuronal degeneration.

Pharmaceutical companies are working on drugs that inhibit excitotoxic nerve cell death, and Gitlin thinks, in light of these new findings, such compounds may someday lead to an effective treatment for Menkes disease.

To find out more about how copper and Atp7a influence thinking, the researchers next plan to breed laboratory mice in which they can selectively knock out Atp7a in the hippocampus, an area of the brain essential to memory. Then they can investigate whether these mice have problems performing tasks they had once learned.

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