Scientists Find Key to Copper Absorption, Essential to Life

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Humans, animals and plants require copper to live, and scientists have now discovered how cells absorb this mineral that fuels the brain, heart and other vital organs.

Knowing how copper enters cells could prove essential to treating copper deficiencies in humans, said the scientists from Duke University Medical Center who made the discovery. People derive copper exclusively from their diet. The mineral is found abundantly in shellfish, legumes, red wine, nuts, seeds and chocolate, among other sources.

Although too much copper is toxic, copper deficiencies in adults can trigger brain deficits, heart enlargement, visual impairment, anemia (low iron), skin and hair breakdown and other organ damage.

Babies born without the ability to absorb and transport copper -- a disorder called Menkes disease -- die in childhood. But injecting the mineral into children with Menkes has not proven beneficial, because cells may lack the ability to utilize it properly, according to the Duke researchers.

Giving copper supplements to adults has proven more effective in alleviating their symptoms, but scientists have been unclear as to what controls copper absorption in the first place.

The Duke team studied copper absorption in mice and identified, for the first time, the cellular gateway through which copper passes. An

identical gateway is present in humans, as well as in other animals and plants, the researchers said. The gateway is a copper "transporter," a specific pore on the surface of intestinal cells that funnels copper inside the intestinal walls. From there, copper is absorbed by the bloodstream and distributed throughout the body to serve as an engine to jump-start the activity of dozens of proteins that carry out essential functions.

The researchers published their findings in the Sept., 2006 issue of the journal *Cell Metabolism*, now available on line. The study was funded by the National Institutes of Health and the International Copper Association, Ltd.

"Identifying this transporter could enable the medical community to develop more effective ways of delivering copper to deficient children and adults, said study leader Dennis J. Thiele, Ph.D., professor of pharmacology and cancer biology. "Without copper, many biochemical processes either do not happen or happen at a reduced level, which results in a wide range of health impairments."

Among its roles, Thiele said, cells use copper to help destroy molecules called free radicals that contribute to aging and cancer; blood requires copper to clot properly; skin requires copper to form collagen and melanin; cells cannot absorb iron without copper; and embryos cannot grow and develop without copper. Copper imbalances have even been implicated in Alzheimer's disease, although the evidence is preliminary, according to Thiele.

In searching for the mechanism for copper absorption in cells, the researchers focused on a protein called Ctr1, a binding site or "receptor" that sits on the surface of cells in the intestine. Thiele's group, which is also affiliated with the Sarah W. Stedman Nutrition and Metabolism Center at Duke, had previously implicated Ctr1 as important in copper metabolism.

To further investigate its role, the researchers genetically manipulated pregnant mice so their developing fetuses lacked the gene that controls production of Ctr1 in the intestines. When the offspring were born, they could not absorb copper and dispatch it via the bloodstream throughout the body, the scientists found.

As a result, the pups weighed half the size of their normal counterparts, had striking defects in the enzymes that generate energy, had pale skin color, and deformed whiskers that were kinky and brittle. Within three weeks the pups had died, said Thiele.

The researchers took a second set of copper-deficient offspring and injected them with copper, within five days of birth, to determine if copper could rescue them from death. The mice are still alive after seven months -- normal mice live for two years -- and they are displaying fewer health problems associated with copper deficiency.

The researchers speculate that delivering copper shortly after birth, during critical windows of development, could stave off potential health problems due to copper deficiency. The infusion of copper would enable essential biochemical reactions to occur as organ systems are developing and forming. Once organ systems are fully developed, they are less susceptible to low levels of copper, the researchers speculate.

"Before birth and the weeks and months thereafter are crucial times when the body requires copper to build muscles, organs, brain connections and many other physiologic functions," Thiele said.

While rare in children, copper deficiencies are likely to be more common among adults than generally realized, Thiele said. People in the general population may have variations of the gene for Ctr1, called polymorphisms, which can reduce their ability to absorb and use copper without blocking it completely.

The current study will serve as a model for understanding what causes genetic errors in copper absorption and metabolism, Thiele said. His team will continue to study how the Ctr1 transporter functions and what errors in gene coding might contribute to health problems such as abnormal heart and brain function.

Thiele said that studying Ctr1 will help clarify how this copper transporter evolved in living organisms. Ctr1 has been preserved in its structure and function throughout all organisms, from yeast cells to human cells. This means the transporter evolved very early on, before organisms began to diverge in their genetic diversity, emphasizing the importance of this copper delivery mechanism.

Other researchers who participated in the study were Yasuhiro Nose and Byung-Eun Kim.

Source: Duke University Medical Center