Copper's previously unknown exit strategy

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(Medical Xpress) -- Scientists have long known that the body rids itself of excess copper and various other minerals by collecting them in the liver and excreting them through the liver's bile. However, a new study led by Johns Hopkins researchers and published June 22 in PLoS One suggests that when this route is impaired there's another exit route just for copper: A molecule sequesters only that mineral and routes it from the body through urine.

The researchers, led by Svetlana Lutsenko, Ph.D., a professor of physiology at the Johns Hopkins University School of Medicine, found this additional copper escape hatch by studying an animal model of Wilson's disease, a rare disorder most often diagnosed in children. People with this disease accumulate abnormally large amounts of copper in the liver, eventually leading to liver damage and failure.

Micronutrients such as copper, zinc and iron are indispensible for human development. Copper is required for embryonic development, respiration, and cardiovascular function, among other processes; too little copper can be fatal whereas too much can cause neurological impairment and organ failure.

One diagnostic test for Wilson's disease is to check for high amounts of copper in the urine; copper levels could be especially high in advanced stages of this disorder. For decades doctors and scientists have blamed this high urinary copper on the breakdown of cells in the liver, which purportedly dumped their contents into the bloodstream as they died. These contents were thought to be picked up by the kidneys and

eventually excreted in the urine.

However, Lutsenko says, this theory had never been tested. To verify this explanation, she and her colleagues examined mice genetically modified to have Wilson's disease. As in people, these animals' liver function gradually worsens over time due to copper accumulation. Eventually the animals' livers regenerate and liver function improves and with this the researchers expected to see less urinary copper. However, at this stage in the disease, urinary copper in the animal models continued to increase. Additionally, the researchers found no increased urine concentrations of other minerals stored in liver cells, which would be expected if these cells were releasing all their entire contents and not just copper. Together, these findings suggest that liver cell death isn't the main source of urinary copper in Wilson's disease.

Delving deeper, the researchers gave the mice radioactive copper, which they could trace as it made its way through the body. They found that when copper reached a certain threshold level in the liver, it was directed it to the kidneys instead. At the same time, they saw that levels of a protein used to transport copper to the liver decreased. Both of these observations strengthened the idea that another mechanism must exist to remove copper from the body.

To figure out what that mechanism might be, Lawrence Gray, a graduate student on Lutsenko's team searched the animals' urine to see what molecules copper might be bound to. Their pursuit turned up an unidentified molecule that they've temporarily named "small copper carrier," or SCC. Further tests showed that as liver function decreased, more SCC appeared in the animals' blood, and that SCC could compete for copper with the proteins that normally transport this mineral to the liver.

"These findings all suggest that SCC indeed represents a previously

unknown agent that the body uses to excrete excess copper," Lutsenko explains.

She and her colleagues are now trying to learn more about SCC, both to identify this molecule and to determine whether it could be a unique marker that's only present during Wilson's disease. If so, it could save pediatric patients the pain of liver biopsy, a test often used to definitively diagnose this condition. In addition, SCC may also represent a treatment for this rare disorder. If scientists could develop a way to raise SCC concentration in the blood, Lutsenko says, it could increase copper export and prevent further harm to the liver.

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