Can Copper Status Affect Aging?

Could a marginal intake of the essential element copper contribute to the aging process? ARS physiologist Jack T. Saari thinks that's a strong possibility—based on rat studies, along with a good bit of indirect evidence.

Saari and a colleague, chemist Gwen Dahlen, at the Grand Forks Human Nutrition Research Center in North Dakota wanted to see if copper deficiency spurs sugar molecules to attach to proteins. The process—nonenzymatic glycosylation, or protein glycation for short—is a spontaneous binding of sugar to protein without the aid of enzymes. It is thought to cause much of the tissue damage in people with diabetes. And it increases in all of us as we age, Saari says.

Tiny sugar molecules attached to a huge protein molecule may be likened to fleas on a dog. But the attached sugars can be more than annoying; they can be deadly to the protein. That's because their free ends tend to hook up to other proteins or other sites on the same protein, forming cross-links. These cross-links bend the protein out of shape so that it no longer functions properly. The useless protein soon gets degraded and hauled off for recycling or disposal.

In the early 1980s, Saari's colleague, Leslie M. Klevay, M.D., reported that copper-deficient rats had glycated hemoglobin—the oxygen-carrying molecule in red blood cells. Klevay heads the Mineral Nutrient Requirements Unit at Grand Forks.

Saari says this and more recent indirect evidence led him to look for a connection between copper deficiency and protein glycation.

Two pieces of indirect evidence come from studies at ARS' Beltsville (Maryland) Human Nutrition Research Center, as well as Saari's laboratory. Rats fed copper-deficient diets have high blood sugar, says Saari. This raises the odds for glycation.

"Their condition is like type-II diabetes," says Meira Fields, who conducted the Beltsville studies. Unlike Saari, Fields finds that the copper-deficient rats exhibit high blood sugar only when their diets are high in sugar—either fructose or sucrose. This sugar-laden diet also causes the rats to secrete less insulin, she says, which is needed to move sugar out of the blood and into the cells to serve as fuel.

What's more, Fields' studies have repeatedly shown that rats suffer the most tissue damage from this diet when the sugar is fructose. Saari notes that in the test tube, fructose is a better glycator than glucose.

RUSS HANSON (K8524-10)

Searching for possible functional consequences of glycation—the attaching of sugar molecules to protein—physiologist Jack Saari measures heart performance and blood pressure in a copper-deficient laboratory rat.

Two more pieces of indirect evidence come from Saari's own studies. He reduced the symptoms of copper deficiency—such as an enlarged heart—by two different treatments. First, he fed the rats only a portion of the food they would normally eat. This kept blood glucose levels low, he says, reducing the chance of glycation. Second, he treated the rats with a chemical—aminoguanidine—known to block advanced glycation or cross-linking of sugars. And it worked.

Fractured Proteins

Armed with this evidence, Saari and Dahlen designed a study to look directly for increases in protein glycation. The results bore out their suspicions. Both the early and advanced stages of protein glycation increased significantly in the rats fed a copper-deficient diet.

One sensitive indicator of advanced glycation is a measure of the proteins that it has rendered ineffective. This indicator was at least six times higher in the copper-deficient rats. It was nearly undetectable in the control rats, he says, noting that Dahlen made this very delicate analysis possible by refining an existing analytical method. They published their findings in the April 1999 issue of the *Journal of Nutritional Biochemistry*.

Treating the rats with aminoguanidine did not reduce cross-linking in this study as it did in the earlier one, says Saari, probably because the dosage was too low. So he and Dahlen did a follow-up study using a higher dosage. The earliest results available at this writing are showing a reduction in glycation caused by copper deficiency.

Copper Intake Lags

Humans consume more copper than rats do. But the average copper content of diets in the United States, Canada, Great Britain, and Belgium still falls below the U.S.-suggested intake range of 1.5 to 3 milligrams per day.

Klevay, a physician, pulled together data from the chemical analyses of 849 diets in the four countries. He says they show that 61 percent contained less than 1.5 mg of copper daily, and nearly a third of the diets provided less than 1 mg.

"That's in the range that has proved insufficient for both men and women in controlled dietary experiments," he says.

Vegetarian diets had more copper than nonvegetarian diets. That's because nuts, seeds, mushrooms, whole grains, and legumes—such as soybeans, peas, chickpeas, lentils, and peanuts—are good sources of the mineral. The richest sources of copper are animal—oysters, crabs, and liver—which are not common in the daily diet.

Estimated copper intake in the United States, based on USDA's latest nationwide food consumption survey, averages 1.2 mg/day for all individuals—below the 1.5 mg suggested minimum. The estimates show men averaging just the minimum 1.5 mg/day, while women average only 1 mg/day.

Saari speculates that years of eating a diet low in the mineral may be a factor contributing to the age-related decline in tissue function from increasing protein glycation.

"It's a low-grade phenomenon," he says. "It's not like diabetes where blood glucose stays high after an overnight fast." Instead, he says, blood glucose peaks higher than normal after a meal—increasing glycation—but it doesn't stick around. "The only way you know this increase is happening is through a glucose tolerance test or a test of glycated hemoglobin."

The early stage of glycation—when the sugar first attaches to the protein—is reversible. As blood sugar drops, the sugar can detach. Once the cross-links are formed, however, they don't come apart, Saari says. So far, he has looked only at glycation of hemoglobin and serum proteins. But it can also happen to structural proteins that form tissues.

Copper and Oxidation

The most accepted theory of aging holds that it results from cumulative damage to tissues by oxygen free radicals. These radicals are generated during normal metabolism and delivered by environmental pollution. Saari says his thesis fits hand in glove with the oxidation theory because glycation appears to increase oxidation.

According to reports in the diabetes literature, both free and attached sugar molecules can convert the benign oxygen molecule into a free radical. What's more, glycated proteins are more vulnerable to oxidation.

Copper is important to the body's defense against oxidation through a copper-containing enzyme—superoxide dismutase, or SOD. Saari notes that SOD activity reportedly decreases with aging, while oxidative damage increases.

Over the long term, a low copper intake could plausibly weaken this inherent antioxidant defense, slightly elevate blood sugar, and increase attachment of sugar to proteins—all of which tend to increase oxidative damage.—By **Judy McBride,** ARS.

This research is part of Human Nutrition Requirements, Food Composition, and Intake, an ARS National Program described at http://www.nps.ars.usda.gov/programs/appvs.htm.

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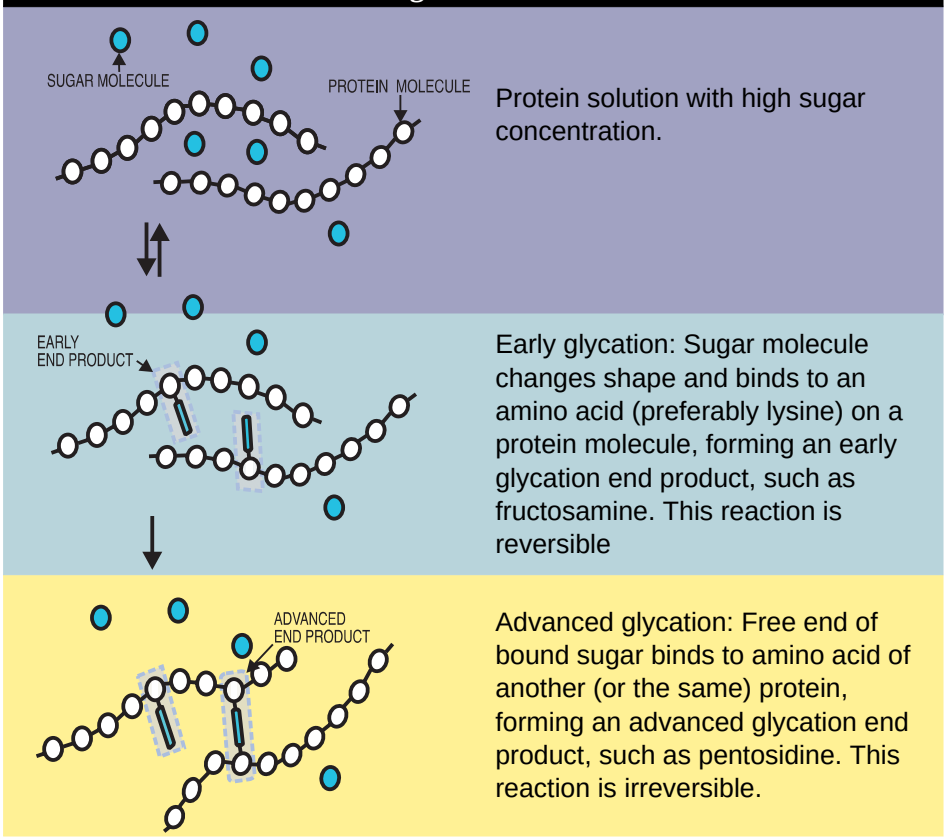
Glucose-Induced Protein Damage



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Technician Peter Leary performs a test to determine the degree of glycation of hemoglobin in blood drawn from copper-deficient rats.