Medical Xpress

# Researchers find potential 'dark side' to diets high in beta-carotene

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New research suggests that there could be health hazards associated with consuming excessive amounts of beta-carotene.

This antioxidant is a naturally occurring pigment that gives color to foods such as carrots, sweet potatoes and certain greens. It also converts to vitamin A, and foods and supplements are the only sources for this essential nutrient.

But scientists at Ohio State University have found that certain molecules that derive from beta-carotene have an opposite effect in the body: They actually block some actions of vitamin A, which is critical to human vision, bone and skin health, metabolism and immune function.

Because these molecules derive from beta-carotene, researchers predict that a large amount of this antioxidant is accompanied by a larger amount of these anti-vitamin-A molecules, as well.

Vitamin A provides its health benefits by activating hundreds of genes. This means that if compounds contained in a typical source of the vitamin are actually lowering its activity instead of promoting its benefits, too much beta-carotene could paradoxically result in too little vitamin A.

The findings also might explain why, in a decades-old clinical trial, more people who were heavily supplemented with beta-carotene ended up with lung cancer than did research participants who took no beta-carotene at all. The trial was ended early because of that unexpected outcome.

The scientists aren't recommending against eating foods high in beta-carotene, and they are continuing their studies to determine what environmental and biological conditions are most likely to lead to these molecules' production.

"We determined that these compounds are in foods, they're present under normal circumstances, and they're pretty routinely found in blood in humans, and therefore they may represent a dark side of beta-carotene," said Earl Harrison, Dean's Distinguished Professor of Human Nutrition at Ohio State and lead author of the study. "These materials definitely have anti-vitamin-A properties, and they could basically disrupt or at least affect the whole body metabolism and action of vitamin A. But we have to study them further to know for sure."

The study is scheduled for publication in the May 4, 2012, issue of the *Journal of Biological Chemistry*.

Previous research has already established that when beta-carotene is metabolized, it is broken in half by an enzyme, which produces two vitamin A molecules.

In this new study, the Ohio State researchers showed that some of these molecules are produced when beta-carotene is broken in a different place by processes that are not yet fully understood and act to antagonize vitamin A.

Harrison is an expert in the study of antioxidants called carotenoids, which give certain fruits and vegetables their distinctive colors. Carotenoids' antioxidant properties are associated with protecting cells and regulating cell growth and death, all of which play a role in multiple disease processes.

For this work, he joined forces with co-authors Robert Curley, professor of medicinal chemistry and pharmacognosy, and Steven Schwartz, professor of food science and technology, both at Ohio State. Curley specializes in producing synthetic molecules in the pursuit of drug development, and Schwartz is an expert at carotenoid analysis.

Curley manufactured a series of beta-carotene-derived molecules in the lab that match those that exist in nature. The researchers then exposed these molecules to conditions mimicking their metabolism and action in the body.

Of the 11 synthetic molecules produced, five appeared to function as inhibitors of vitamin A action based on how they interacted with receptors that would normally launch the function of vitamin A molecules.

"The original idea was that maybe these compounds work the way vitamin A works, by activating what are called retinoic acid receptors. What we found was they don't activate those receptors. Instead, they inhibit activation of the receptor by retinoic acid," Curley said. "From a drug point of view, vitamin A would be called an agonist that activates a particular pathway, and these are antagonists. They compete for the site where the agonist binds, but they don't activate the site. They inhibit the activation that would normally be expected to occur."

Once that role was defined, the researchers sought to determine how prevalent these molecular components might be in the human body. Analyzing blood samples obtained from six healthy human volunteers, the scientists in the Schwartz lab found that some of these anti-vitamin-A molecules were present in every sample studied, suggesting that they are a common product of beta-carotene metabolism.

The compounds also have been found previously in cantaloupe and other orange-fleshed melons, suggesting humans might even absorb these molecules directly from their diet.

Harrison noted that the findings might explain the outcome of a well-known clinical trial that has left scientists puzzled for years. In that trial, people at high risk for lung cancer - smokers and asbestos workers - were given massive doses of beta-carotene over a long period of time in an attempt to lower that risk. The trial ended early because more supplemented participants developed cancer than did those who received no beta-carotene. This outcome was reinforced by results of a follow-up animal study.

"Those trials are still sending shockwaves 20 years later to the scientific community," said Harrison, also an investigator in Ohio State's Comprehensive Cancer Center. "What we found provides a plausible explanation of why larger amounts of beta-carotene might have led to unexpected effects in these trials."

The research also has implications for efforts to bio-engineer staple crops in developing countries so they contain excess beta-carotene, which is considered a sustainable way to provide these populations with pro-vitamin A. Existing projects include production of golden rice in Asia, golden maize in South America and cassava in Africa.

"A concern is that if you engineer these crops to have unusually high levels of beta-carotene, they might also have high levels of these compounds," Harrison said.

The researchers are continuing to study these compounds, including whether food processing or specific biological processes affect their prevalence. Previous studies have suggested that oxidative stress, which can result from smoking and air pollution exposure, can lead to higher production of these anti-vitamin-A molecules, Harrison noted.

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