Vitamin A Detectives Probe Puzzling Nutrient

Vitamin A helps your body's immune system fight off many infections and inflammations. These include measles and some foodborne infections. But in the case of some other familiar ailments, including asthma, common colds, or pneumonia, this essential nutrient may not be quite as helpful.

Charles B. Stephensen, an ARS physiologist, is interested in solving the mystery of why this vitamin interacts in these differing ways with our immune system. He explains, "We want to take full advantage of vitamin A's ability to boost our immune system. But to do that, we have to know precisely how vitamin A will act when the immune system of an otherwise healthy person is challenged by a particular disease organism. Right now, our knowledge is still quite limited."

Earlier work by Stephensen and others in the 1990s suggested that, although vitamin A enhanced kids' recovery from measles and other infections, it did not help, or perhaps even slowed, their recovery from bacterial pneumonia.

Now, new studies with immune system cells removed from laboratory mice may help explain why. Stephensen is doing the work at the ARS Western Human Nutrition Research Center, Davis, California, in collaboration with scientists from the University of California, Davis; University of Alabama, Birmingham; and Allergan, Inc., Irvine, California.

Immune System Scrutinized

"Our team has shown that vitamin A influences the types and amounts of immune cells—such as T-helper cells—and immune system molecules, called interferons and interleukins, that your body produces in response to infection," Stephensen says. "These cells and molecules have specialized jobs. That means the types and amounts of each that your body mobilizes can strongly affect how slowly or quickly you overcome a particular infection or inflammation."

For the research, Stephensen exposed mouse immune-system cells, in petri dishes, to a form of vitamin A known as retinoic acid, along with a protein that mimics an infectious microbe. This procedure simulates the immune system response of a mouse that has sufficient vitamin A. In principle, the cells in the petri dishes respond as if they were still in the mouse's body.

Stephensen's team then determined the kinds and relative amounts of several key immune cells and molecules that the mouse cells produced. Of particular interest: the amounts of two kinds of T-helper (Th) cells. "Your body produces these white cells as part of your immune defense," Stephensen explains. "Because the cells originate without specialized abilities to fight specific diseases, they are known as T-zero helper cells, or Th0 for short. Later, in response to invasion by specific diseases, they become either Th1 or Th2 cells, but we don't know all the details about that specialization. In general, Th1 cells seem to be of most use in fighting viral infections, such as HIV. Th2 cells apparently have the lead role in defending against certain bacteria or intestinal parasites, like roundworms."

Stephensen's group demonstrated—for the first time—that retinoic acid promotes development of Th0 cells into Th2 cells rather than Th1 cells. Stephensen and colleagues plan to repeat the experiment in laboratory mice—not just in samples of their cells. Depending on those findings, the scientists will follow up with studies of human volunteers.

Loophole in Vitamin A Test

But the work with humans requires a rapid, accurate, and precise procedure for determining vitamin A levels at any given time—a sort of biological snapshot. The most widely used assay for estimating vitamin A reserves in the liver—the body's main storage organ for this nutrient—is a serum retinol test. Retinol is a form of vitamin A similar to the retinoic acid measured in the mouse-cell tests. The serum retinol assay is less invasive and less expensive than a liver biopsy, in which a very long needle is used to extract a small piece of liver for analysis.

But Stephensen and others are concerned about a flaw in the serum retinol test and are working to resolve it. "The problem stems from vitamin A's interaction with the immune system," he says. "If you are ill with a fever or an inflammation, your serum retinol level may decrease. That means a serum retinol test would no longer reflect the correct amount of vitamin A stored in your liver."

There are probably several reasons for this decline in serum retinol. First, more vitamin A may be used by the immune system during an infection. Second, when we are sick, some vitamin A is lost from serum into urine. This doesn't happen when we are healthy. Third, more vitamin A appears to remain in the liver during an infection, rather than being transported to other parts of the body through the bloodstream.

According to Stephensen, this glitch in the serum retinol test has been well documented in studies of children with infectious diseases serious enough to bring them to a doctor for treatment. More recently, Stephensen and coinvestigators found the same underlying problem when analyzing data from relatively healthy adults who were participants in NHANES III, the third National Health and Nutrition Examination Survey. Stephensen's team observed that a recent bout with a cold,

the flu, arthritis, or even the gum disease gingivitis may skew serum-retinol test results. Stephensen and co-workers also showed that NHANES III participants who tested high in another assay—serum C-reactive protein—had lower-than-normal serum retinol levels.

Retesting Recommended

Notes Stephensen, "Levels of serum C-reactive protein go up when you have an inflammation or infection. That same inflammation or infection can disrupt your body's normal use and transport of vitamin A."

Kids and adults, whether visiting a doctor or participating in a broad survey such as NHANES "should probably be retested for serum retinol when their serum C-reactive protein levels aren't elevated by illness," he recommends. Specifically, levels should be less than 10 milligrams per liter.

Among other applications, the findings about these assays should be useful in improving the interpretation of data from NHANES or other surveys. Government and university researchers use NHANES data to evaluate the health of Americans and to learn more about what we eat.

The scientists have published their findings in the *American Journal of Clinical Nutrition* and the *Journal of Immunology*.

Good sources of vitamin A include pumpkin; sweetpotatoes; carrots; spinach; turnip, dandelion, collard, and beet greens; kale; mangoes; tomato products; beef; chicken; and turkey.—By **Marcia Wood,** ARS.

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PEGGY GREB (K10329-1)

In an ongoing study, physiologist Charles Stephensen uses a neutralizing antibody test to measure immune response in individuals receiving vitamin A supplements.