High folic acid intake in aged mice causes a lowered immune response

January 11 2016

Credit: martha sexton/public domain

Previous studies have shown an association between high folic acid intake and a reduction in the immune system defenses needed to fight

viral infections and cancer. In a new study in mice published in the *Journal of Nutritional Biochemistry*, scientists at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University (HNRCA) set out to determine if excess folic acid intake caused adverse changes in the immune system.

Their study in aged mice indicates that high folic acid intake causes lowered immune function because natural killer (NK) cells, a particular type of immune cell, are less effective. NK cells are important for defense against viral infections and cancer because they identify and attack infected cells. Impairment in their function may lead to increased susceptibility to certain diseases such as viral infections and cancer. They are particularly important in the elderly because immune system function diminishes with age, making the elderly more susceptible to infections and cancer.

The researchers used an aged mouse model to confirm that the associations previously observed in women over 60 years of age did not occur by chance. They used NK cell cytotoxicity, the ability of NK cells to destroy other cells, as an index of immune function in aged mice and focused on the implications of these findings on the health of an aging population.

Key findings:

- The study established a causal relationship between excess folic acid intake and lowered NK cell activity in an aged mouse model.
- Mice fed excess folic acid had a high proportion of naive and less effective NK cells compared to mature, active NK cells, suggesting that their development process had been impaired.

In this study, researchers gave a control group of mice a level of folic

acid equivalent to the Recommended Daily Allowance (RDA) for humans. A treatment group of mice were given an intake of folic acid 20 times greater than the RDA for humans: while the folic acid dosage consumed by most adults is lower and taken over a longer period of time, a higher dose was used in this study to account for the fact that mice are more efficient in metabolizing folic acid than humans.

Mice fed high folic acid in the treatment group had higher concentrations of unmetabolized folic acid in blood plasma and higher folate concentrations in the spleen when compared to mice in the control group. Importantly, mice in the treatment group were observed to have lowered NK cell activity.

"If we want to optimize the efforts of NK cells to increase resistance to infections, the use of folic acid in some contexts may need to be reassessed. Among older adults, additional research might show that it is important to take supplements only if one has been documented to be folate-deficient," said last author Ligi Paul, Ph.D., nutrition scientist in the Vitamin Metabolism Laboratory at the HNRCA.

The lead author, Hathairat Sawaengsri, M.S., a doctoral student in the biochemical and molecular nutrition program at the Friedman School of Nutrition Science and Policy at Tufts University and a member of the HNRCA Vitamin Metabolism Lab, explained, "Our aim was to look at excess folic acid and its impact on immune function. Taking what we have found in this study, the next step is to determine if excess folic acid actually increases our susceptibility to infections."

These results build upon the findings of a previous study in 2005 by the same lab that found that 78 percent of healthy postmenopausal women had unmetabolized folic acid in their blood plasma, which is indicative of excess folic acid intake. These women had significantly lower NK cell activity. Ligi continued, "The potential role of excess folic acid intake in

increasing susceptibility to disease must also be taken into consideration."

According to the National Institute of Health's Office of Dietary Supplements, approximately 35 percent of people in the U.S. consume folic acid in dietary supplements. Some population groups, according to the NIH, are at risk of obtaining excess folate. People aged 50 years and older have the highest total folate intakes; about 5 percent have intakes exceeding the established tolerable upper intake level of 1,000 micrograms per day.

In an effort to reduce the number of babies born with neural tube defects in the U.S., folic acid supplements have been recommended to pregnant women for more than 20 years. These recommendations, along with fortification, have reduced the rate of neural tube defects by as much as 35 percent. The findings of the current study offer a building block in increasing understanding of how folic acid in the diet is metabolized and potential adverse health impacts of excess folic acid in the body over the long-term.

Folate is found in a variety of natural food sources including green and leafy vegetables, beans, eggs, grains and fish. Folic acid is the synthetic form of folate used in vitamin supplements and fortified cereal products. The federal government's 2010 Dietary Guidelines for Americans advises that nutrients are best obtained from foods rather than supplements. The Recommended Daily Allowance is 400 micrograms of dietary folate equivalents, and 600 micrograms for women who are pregnant.

More information: Hathairat Sawaengsri et al. High folic acid intake reduces natural killer cell cytotoxicity in aged mice, *The Journal of Nutritional Biochemistry* (2016). DOI: 10.1016/j.jnutbio.2015.12.006

Provided by Tufts University