Mouse experiments show fickle functions for folic acid

October 6 2011

(Medical Xpress) -- Dietary folic acid helps prevent a subset of neurological birth defects in humans -- although the precise mechanism by which it prevents them is unclear. Now, researchers have found that certain genetic mutations in mice that mimic these birth defects do not respond to a diet enriched with folic acid. Even more surprising, some of these mouse mutants actually have an increased incidence of the birth defect related to spina bifida when fed a diet high in folic acid.

The authors say that while folic acid supplementation is important to reduce the overall incidence of neural tube defects, the new findings could lead to ways to prevent the subset of those defects that are resistant to folic acid.

The research, by scientists at the Howard Hughes Medical Institute (HHMI) and the University of Colorado School of Medicine, appears in the September, 2011, issue of Human Molecular Genetics.

Since 1998, flour enriched in folic acid has been used in the United States food supply to help prevent some neurological birth defects, such as spina bifida. These birth defects occur when an embryonic structure called the neural tube, which will become the brain and spinal cord, does not close up properly. During the third or fourth week after conception the tissue that will become the nervous system rolls up into a tube and then 'zippers' closed. If an opening remains in the portion that will become the spinal cord, it leads to spina bifida, a severe birth defect that can result in paralysis and cognitive, urological, gastrointestinal

problems. If the opening occurs in the portion destined to become the brain, the embryo rarely survives.

Studies of women who gave birth to a child with a neural tube defect (NTD) found that folic acid significantly reduced the likelihood of NTDs in a later pregnancy. Because NTDs occur early in development, often before a woman knows she is pregnant, and because up to half of all pregnancies in the US are unplanned, flour was fortified with folic acid to increase intake of the vitamin in the overall population. At the same time, doctors began recommending that women trying to become pregnant take a prenatal vitamin containing 400 micrograms of folic acid to prevent NTDs. These steps have helped reduce the incidence of NTDs by 30 to 40 percent, but they still remain a common birth defect, affecting about 1,500 babies each year according to the March of Dimes.

“It is still pretty much a mystery what folic acid does to help the neural tube to close. That’s really where we started our studies,” says Lee A. Niswander, an HHMI investigator at University of Colorado School of Medicine.

Folic acid helps generate the building blocks for both RNA and DNA, so it is critical to processes such as cell proliferation, gene transcription, and genomic stability. Folic acid also allows S-adenosyl-methionine to transfer methyl groups onto DNA as well as other proteins, a key process in controlling gene activity. All of these things, Niswander says, could be playing a part in neural tube closure.

Niswander’s group wanted to identify the genetic and environmental influences that control neural tube closure. In humans, Niswander says, there are probably 800-1000 genes involved in proper neural tube closure. They began their studies with five genes known to be required for the developmental process. Mice with mutations in these genes are predisposed to have offspring with a NTD.

“We chose genes that represent a broad overview of the different steps of neural tube closure. It’s complex: The embryo has to roll the neural cells together and zip them up. And those neural cells are also communicating with cells in what will become the skin and muscle layers,” explains Niswander.

For instance, one mutation is in a gene called Grhl2, which is expressed in pre-skin cells and is required for the zippering process. Another mutation affects Shroom3, a gene that normally gives neural cells the right shape so they can bend and roll up.

Niswander and her colleagues fed several generations of the mice with the NTD-causing mutations either a control diet or a diet high in folic acid. The diets were designed to reflect folic acid doses similar to humans eating a fortified diet and a fortified diet plus vitamin supplementation. Then they bred the mice and scored their incidence of NTDs.

Because these mouse strains are genetically preprogrammed to have NTDs, Niswander says she was not surprised to find that many of them did not respond to the high folic acid diet in a beneficial manner. However, in two of the strains, those with mutations in L3P and Grhl2, she was surprised to find that the high folic acid diet had a detrimental effect, increasing the incidence of NTDs.

Even more surprising, two mutants, L3P and Shroom3, had increased embryo losses on the high folic acid diet--meaning the embryos died and were resorbed even before the neural tube is formed.

“Something else is going on there and that’s a mystery,” says Niswander. “By giving folic acid to women, we see a decreased incidence of NTDs in the population. That could be because the neural tube is closing, but it could also reflect that maybe some embryos with a genetic defect aren’t

even making it, they don't survive to the stage of neural tube closure."

Make no mistake, though, Niswander says, taking folic acid to prevent NTDs is a good thing. "If you are contemplating pregnancy, take the recommended dose of folic acid prior to and during pregnancy because it is really clear that that has made a significant difference in preventing NTDs," she says.

Just like some of Niswander's mouse mutants, there will be embryos that have a genetic predisposition to a NTD that cannot be prevented, even if the mother takes her prenatal folic acid as directed, she says. These cases might benefit from further research to find out why they are resistant to folic acid.

"There's no question in humans that folic acid in a variety of intake levels prevents NTDs, but it prevents only about two-thirds of these at best," says Dr. Richard B. Johnston, Jr., a pediatrician and associate dean for research development at University of Colorado School of Medicine who was not associated with the study. "What's most exciting to me about Dr. Niswander's research is the possibility that it could lead us to understand, and eventually prevent that other third--still a huge number of terrible birth outcomes across the world."

Niswander notes that some groups, including the Centers for Disease Control and Prevention, have considered increasing the recommended dose of folic acid to try to prevent more NTDs, but she thinks her results provide a reason for careful consideration before changing the recommendation.

"I think we need to be cautious, because our mouse studies indicate that at least some genetic mutations can respond detrimentally to more folic acid. There may be a balance that needs to be struck [to accommodate all of our] different genetic make-ups."

Johnston adds: “Mice are not humans, and there’s not a hint of evidence that folic acid promotes human neural tube defects. But because the U.S. and many other countries have mandated that folic acid be added to the food supply, we need to continue to be sure that it is [at safe levels] and thoughtful research like~Dr.~Niswander's~is needed.”

Provided by Howard Hughes Medical Institute