Some neural tube defects in mice linked to enzyme deficiency

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Women of childbearing age can reduce the risk of having a child born with a neural tube defect such as spina bifida by eating enough folate or folic acid. However, folate prevents only about 70 percent of these defects.

New research using mice at Washington University School of Medicine in St. Louis confirms the importance of another nutrient, inositol, to protect against the development of neural tube defects.

A research team led by Monita Wilson, Ph.D., found neural tube defects in some mouse embryos from female mice genetically modified to have low levels of ITPK1, an enzyme involved in the metabolism of inositol, a compound important for neural development and function. The finding suggests that inositol depletion is linked to these birth defects.

The research is published May 25 in the *Proceedings of the National Academy of Sciences* Early Edition.

In humans, neural tube defects usually occur during the first three to four weeks of pregnancy, before most women know they are pregnant. Certain cells in an embryo form the neural tube, which becomes the foundation of the brain, spinal cord and the bone and tissue surrounding it. A defect forms if the tube does not close properly.

The two most common neural tube defects are spina bifida and anencephaly. Spina bifida affects 1,500 to 2,000 babies born in the United States annually, causing paralysis, spine abnormalities, incontinence and other problems. Anencephaly occurs when the head end of the neural tube fails to close, resulting in the absence of a major portion of the brain, skull and scalp. That condition is fatal.

Wilson, research assistant professor of medicine, and her collaborators created genetically modified mice to have low levels of one of the inositol kinases, then took a close look at their embryos during each day of the 21-day gestation period.

"Because of the short gestation period, a mouse embryo looks very, very different from day to day," Wilson says. "When we looked at the mutant embryos, between the ninth and 12th days of gestation, we noticed that about 12 percent to 15 percent had spina bifida and exencephaly, similar to anencephaly in humans."

Some of the mutant mouse embryos had kyphoscoliosis or other skeletal deformities.

That led the team to consider that there are birth defects that don't respond to folic acid but may respond to inositol treatment, says Wilson, whose research is being funded by the National Institutes of Health and the Children's Discovery Institute at Washington University and St. Louis Children's Hospital.

"Previous animal studies suggest that administration of inositol can further reduce the incidence of neural tube defects, but the mechanism for the protective effect of inositol remains an enigma," says David B. Wilson, M.D., Ph.D., an associate professor of pediatrics and of developmental biology at Washington University and senior author of the study. "By studying these mice we hope to gain insight into the role of inositol in normal and abnormal embryonic development and on gene-nutrient interactions that underlie neural tube defects in humans."

A few studies of human mothers with low inositol levels have shown an increased risk of having children with spina bifida. A clinical trial is under way in the United Kingdom in which women who have a history of one or more pregnancies with neural tube defects and wish to become pregnant again are given folic acid plus inositol or folic acid and a placebo.

Next, Wilson and her colleagues plan to give the genetically modified mice increased doses of inositol to determine if that can prevent these neural tube defects.

More information: Wilson M, Hugge C, Bielinski M, Nicholas P, Majerus P, Wilson D. Neural Tube Defects in Mice with Reduced Levels of Inositol 1,3,4-triphosphate 5/6 kinase. Proceedings of the National Academy of Sciences *Early Edition*, 05/25/2009.

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