Prenatal intervention reduces learning deficit in mice

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Mice with a condition that serves as a laboratory model for Down syndrome perform better on memory and learning tasks as adults if they were treated before birth with neuroprotective peptides, according to researchers at the National Institutes of Health.

Down syndrome results when an individual receives an extra copy of chromosome 21. According to the Centers for Disease Control and Prevention, Down syndrome occurs in 1 of every 691 births. Features of Down syndrome include delays in mental and physical development and poor muscle tone. These features may vary greatly, ranging from mild to severe.

The researchers studied growth factors that are important at certain key stages of brain development in the womb. Named for the first three amino acids making up their chemical sequence, NAP and SAL, are small peptides (small protein sub units) of two proteins. These two proteins enhance the ability of brain cells to receive and transmit signals, and enable them to survive. (NAP is an abbreviation for NAPVSIPQ and SALfor SALLRSIPA.)

The mice in the study had an extra copy of mouse chromosome 16, which has mouse counterparts to 55 percent of the genes on human chromosome 21.The researchers treated pregnant mice with NAP and SAL for five days, then tested the mouse offspring at 8 to 12 months of age, comparing them to mice treated with a saline solution (placebo). Mice with the extra chromosomal material that were treated with NAP

and SAL in the womb learned as well as mice that did not have the extra chromosome, and significantly faster than mice with the extra chromosome that were treated with saline solution.

"Our study has provided important information that may help in the understanding of Down syndrome," said senior author Catherine Y. Spong, M.D., chief of the unit on perinatal and developmental neurobiology at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the NIH institute where the research was conducted.

Dr. Spong collaborated with first author Maddalena Incerti, M.D., Kari Horowitz MD, Robin Roberson, Daniel Abebe, Laura Toso, M.D., and Madeline Caballero, all of the NICHD Unit on Perinatal and Developmental Neurobiology. Dr. Incerti also is affiliated with the University of Milano-Bicocca, Italy, and Dr. Horowitz now is affiliated with the University of Connecticut, Farmington.

Their findings appear online in *PLOS ONE.*

In an earlier study, Dr. Spong and her colleagues found that, if treated with NAP and SAL in the womb, mice with the extra copy of chromosome 16, achieved developmental milestones earlier than did mice with an extra copy of chromosome 16 that had not been treated. In that study, the researchers examined developmental milestones for sensory, motor skill, and muscle tone development in the first three weeks of life.

"In our earlier work, we showed that treating the mice during pregnancy could prevent developmental delay as assessed with milestones," Dr. Spong said. "In this study, we showed that treatment with NAP and SAL not only puts the animals on a typical developmental trajectory, it also improves their ability to learn.

For the current study, pregnant mice received injections of the two protein fragments starting eight days after conception. This is equivalent to the end of the first trimester in a human pregnancy.

The researchers tested the learning skills of the mice when the animals reached adulthood. The mice were placed in a tank of water on a clear platform. The tank had symbols on each wall that the mice could use to orient themselves. Researchers then placed the mice directly in the water and timed how long it took them to locate the platform. With repeated trials, the mice become more adept at the task and take less time to reach the platform.

Over five days of testing, the researchers found that the time spent searching for the platform decreased substantially for all groups except the mice with the extra copy of chromosome 16 that were not treated with NAP and SAL in the womb.

The research of Dr. Spong's team is part of an NIH-wide focus on Down syndrome outlined in a 2007 Down syndrome research plan. The plan highlights research priorities for the field, including establishing a Down syndrome patient registry, which was announced Oct. 25, 2012.

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