UT SOUTHWESTERN MEDICAL CENTER NEWS

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Reducing Alzheimer's-related protein in young brains improves learning in Down syndrome animal model, UT Southwestern researchers find

DALLAS – June 3, 2010 – Reducing a protein called beta-amyloid in young mice with a condition resembling Down syndrome improves their ability to learn, researchers at UT Southwestern Medical Center have found.

"This preliminary study in the animal model raises the intriguing possibility that drugs that lower beta-amyloid levels might offer some benefit to children with Down syndrome," said Dr. Craig Powell, assistant professor of neurology at UT Southwestern and co-lead author of the study, which is available in *PLoS One*, the *Public Library of Science's* online journal.

Down syndrome, a genetic disease that causes learning disabilities and physical problems, is caused by an extra copy of chromosome 21. This chromosome includes the genes for proteins that produce beta-amyloid, a protein that accumulates in the brains of people with Alzheimer's disease and is believed to contribute to cognitive decline.

Children with Down syndrome have increased normal levels of beta-amyloid in their brains, but it is unknown whether the increased levels affect intellectual abilities, Dr. Powell said. By age 40, nearly all adults with Down syndrome develop signs of Alzheimer's, with dementia developing in their 50s and 60s.

For the study, the researchers used mice with a genetic anomaly that closely mimics human Down syndrome. This type of mice have three copies of a stretch of genes, including those related to beta-amyloid production, and also display learning disabilities, including difficulties learning a standard water maze.

The scientists treated four-month-old genetically altered mice with DAPT, an experimental drug that blocks gamma-secretase, an enzyme essential for beta-amyloid production. A four-day treatment lowered beta-amyloid levels by 40 percent and significantly improved the rodents' performance to the point that they learned the maze as quickly as normal mice.

Dr. Powell, however, cautioned that the blocked enzyme is involved in many brain functions besides creating beta-amyloid.

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"Current gamma-secretase inhibitors may have untoward side effects," he said. "The goal now is to identify drugs that block the ability of gamma-secretase to create amyloid without blocking its ability to perform its other tasks."

Dr. Jacqueline Blundell, former postdoctoral fellow at UT Southwestern, also participated in the study, as did researchers from The Rockefeller University and Columbia University Medical Center.

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