UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers identify compound that frees trapped cholesterol

DALLAS – Jan. 26, 2009 – Researchers at UT Southwestern Medical Center have identified in mice a compound that liberates cholesterol that has inappropriately accumulated to excessive levels inside cells.

The findings shed light on how cholesterol is transported through the cells of the body and suggest a possible therapeutic target for Niemann-Pick type C disease (NP-C), an inherited neurodegenerative disorder characterized by abnormally high cholesterol levels in every organ.

"What we've shown is that very quickly after administration of this compound, the huge pool of cholesterol that has just been accumulating in the cells is suddenly released and metabolized normally," said Dr. John Dietschy, professor of internal medicine at UT Southwestern and senior author of the study appearing online this week and in an upcoming issue of the *Proceedings of the National Academy of Sciences*. "With just one dose, you excrete a large portion of this pool of cholesterol."

Cholesterol in the body comes from dietary sources and is also made by the body itself. It is essential for many biological processes, including the construction and maintenance of cell membranes. Cholesterol normally is transported through cells and is excreted by the body.

People with Niemann-Pick type C have a genetic mutation that causes excessive amounts of cholesterol to accumulate in compartments within cells called lysosomes. This cholesterol accumulation leads to liver disease, neurodegeneration and dementia. There is no specific level at which cholesterol levels become abnormal, but the vast majority of children diagnosed with NP-C die before they are 20 years old and many before age 10. Late onset of neurological symptoms such as clumsiness, mild retardation and delayed development of fine motor skills can lead to longer life spans, but few people diagnosed with NP-C reach age 40.

In the current research, researchers injected a single dose of a cholesterol-binding agent known as CYCLO into 7-day-old mice with the Niemann-Pick mutation. Shortly after administration, the mice that received CYCLO began to process cholesterol just as their healthy counterparts did. After 49 days, the mice treated with a single injection continued to show substantially lower tissue cholesterol levels than the untreated mice, as well as improved liver function and decreased neurodegeneration.

Dr. Dietschy, who has been studying cholesterol metabolism for nearly 50 years, cautioned that

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the findings in no way represent a Niemann-Pick disease cure.

"The key idea is that we appear to have overcome the transport defect in the lysosome that is brought about by the genetic defect or mutation," Dr. Dietschy said. "We do not yet understand what is happening at the molecular level, but it is clear that this compound somehow overcomes the genetic defect that causes individuals to accumulate cholesterol."

The next step in Dr. Dietschy's investigation is to determine the concentration of CYCLO needed to trigger the cholesterol's release. Researchers also hope to determine in animals the additional lifespan CYCLO administration provides, as well as how long the drug's affects lasts.

"By treating at seven days, we eliminated approximately one-third of the accumulated cholesterol almost immediately," Dr. Dietschy said. "Now we want to see what happens if we give it every week. Can we maintain low cholesterol levels? That's what we're looking at now."

Other UT Southwestern researchers involved in the research were Dr. Benny Liu, lead author of the study and postdoctoral researcher in internal medicine; Dr. Stephen Turley, professor of internal medicine; Dr. Dennis Burns, professor of pathology; Anna Miller, student research assistant; and Dr. Joyce Repa, assistant professor of physiology.

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