Compound improves health, increases lifespan of obese mice

22 August 2011

(Medical Xpress) -- Researchers have reported that obese male mice treated with a synthetic compound called SRT1720 were healthier and lived longer compared to non-treated obese mice. The experimental compound was found to improve the function of the liver, pancreas and heart in mice.

The National Institute on Aging (NIA) supported the study, in collaboration with Sirtris, a GlaxoSmithKline company. The study was primarily conducted by the NIA, part of the National Institutes of Health, and is published online in the Thursday, August 18, 2011, issue of *Scientific Reports.*

"This study has interesting implications for research on the biology of aging. It demonstrates that years of healthy life can be extended in an animal model of diet-induced obesity by a synthetic compound that modulates a gene pathway associated with aging," said NIA Director Richard J. Hodes, M.D. More research is needed to assess the relevance of these findings in people, Hodes and the researchers noted.

SRT1720, a patented molecule, has been shown to activate the SIRT1enzyme, part of a class of enzymes called sirtuins. Sirtuins have been previously implicated in aging processes and are thought to contribute to the positive effects of dietary restriction (also known as calorie restriction) in higher organisms, including nonhuman primates.

In this study, scientists compared the health of 1-year-old, or middle-aged, male mice fed a high-fat diet with a high dose of SRT1720, a low dose of SRT1720 or no SRT1720. Additionally, these mice were compared to a control group of 1-year-old male mice fed a standard diet.

"As we hypothesized, SRT1720 mimics dietary restriction, moderating many of the harmful effects of the high-fat diet and obesity. Furthermore, we found that the higher dose of the compound had a stronger effect and there were no signs of toxicity from SRT1720 even after 80 weeks of treatment," said study leader and senior author Rafael de Cabo, Ph.D., of the Laboratory of Experimental Gerontology at the NIA.

Scientists reported changes caused by SRT1720 in following areas:

• Lifespan. While all mice on the high-fat diet gained weight, mice treated with SRT1720 had an increased average and maximum lifespan compared to mice on the high-fat diet without SRT1720. From birth, the mice on the higher dose lived an average of 18 percent longer, and the mice on the lower dose lived an average of 4 percent longer than the mice on the high-fat diet without SRT1720. From 56 weeks of age, mean lifespan in low-dose mice increased by 11 percent and in high-dose mice by 44 percent.

• Liver. Mice treated with SRT1720 had less fat accumulation on their livers compared to non-treated, high-fat-diet mice. Scientists also tested liver function using two measurements. In both tests, mice treated with SRT1720 demonstrated better liver function than non-treated mice on a high-fat diet, but only one test showed the liver of treated mice to have equal function as mice on standard diet. Livers of treated mice were smaller than those from untreated mice on a high-fat diet, although they were still larger than livers of mice on a standard diet. In addition, SRT1720 suppressed liver inflammation and protected mice against cell death in the liver.

• Pancreas. SRT1720 protected high-fat-diet mice from resistance to insulin, which is often associated with obesity and can precede diabetes. Glucose (blood sugar) measurements were approximately equal for all groups of mice, including mice on a standard diet. Insulin levels were approximately

double in mice on the high-fat diet without SRT1720 aging."

compared to mice on the standard diet and on a high-fat diet with SRT1720.

• Heart. High-density lipoprotein (HDL), associated with good cardiovascular health, was highest in mice on a high-fat diet with a high dose of SRT1720, even compared to mice on a standard diet. SRT1720 protected mice against cell death in the heart and suppressed inflammation. All groups of mice on a high-fat diet experienced the same increase in cholesterol, compared to mice on a standard diet.

• Exercise and oxygen metabolism. Mice on a high-fat diet had higher levels of oxygen consumption during periods typically characterized by less activity. SRT1720 reversed this trend; treated mice had lower resting levels of oxygen. High-fat-diet mice with no or a low dose of SRT1720 were less active than mice on a high dose of SRT1720 or on a standard diet.

• Genes. SRT1720 suppresses genes typically expressed in mice on a high-fat diet. For example, SRT1720 suppressed genes that are associated with aging in the liver and previously identified as associated with aging in the kidney and brain.

To verify that the positive health effects caused by SRT1720 were, at least in part, dependent on the Sirt1 pathway, scientists conducted a series of experiments using cell cultures. The researchers also assessed changes to mitochondrial respiration in adult Sirt1-specific knockout mice. The tests showed that SRT1720 did not have an effect in mice or cultures lacking the Sirt1 gene although it did have an effect in mice and cultures with Sirt1.

While the findings are promising, scientists emphasize the limitations of their research.

"In mice, SRT1720 reversed many of the health problems associated with a high-fat diet and did not have toxic side effects, but it is too early to know whether these findings could be replicated in other animal models, much less humans," said de Cabo. "The bottom line is that we need much more research before considering SRT1720 or related compounds as a possible treatment for diseases of

The study is a collaborative effort between the laboratories of de Cabo; James L. Ellis of Sirtris, and David A. Sinclair, Ph.D., co-director of the Glenn Laboratories for Molecular Biology of Aging at Harvard Medical School, Boston and consultant to Sirtris. Researchers from the following institutions also collaborated in the study: University of Pennsylvania School of Medicine, Philadelphia; University of Oklahoma Health Sciences Center, Oklahoma City; Ècole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; University of Michigan, Ann Arbor; and University of Kentucky, Lexington.

This research was performed under a Cooperative Research and Development Agreement between the NIA and Sirtris, a GSK company.

Provided by National Institutes of Health