

Public release date: 3-Jul-2008

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Resveratrol found to improve health, but not longevity in aging mice on standard diet

Scientists have found that the compound resveratrol slows age-related deterioration and functional decline of mice on a standard diet, but does not increase longevity when started at middle age. This study, conducted and supported in part by the National Institute on Aging (NIA), part of the National Institutes of Health, is a follow-up to 2006 findings that resveratrol improves health and longevity of overweight, aged mice. The report confirms previous results suggesting the compound, found naturally in foods like grapes and nuts, may mimic, in mice, some of the effects of dietary or calorie restriction, the most effective and reproducible way found to date to alleviate age-associated disease in mammals.

The findings, published July 3, 2008, in *Cell Metabolism*, may increase interest in resveratrol as a possible intervention for age-related declines, said NIA scientists. The authors emphasized, however, that their findings are based on research in mice, not in humans, and have no immediate and direct application to people, whose health is influenced by a variety of factors beyond those which may be represented in the animal models.

The study is a collaborative effort between the laboratories of Rafael de Cabo, Ph.D., of the Laboratory of Experimental Gerontology at the NIA; David A. Sinclair, Ph.D., of the Glenn Laboratories for Molecular Biology of Aging at Harvard Medical School; and an international group of researchers. The investigators compared mice fed a standard diet, a high-calorie diet, or an every-other-day feeding regimen with or without high- or low-dose resveratrol to study the impact of resveratrol on aging and health. In previous studies, different forms of dietary restriction, including every-other-day feeding, have been shown to improve markers of health.

"Research is attempting to understand the process of aging and to determine how interventions can influence this process. Dietary restriction has well-documented health benefits in mammals, and the study of possible mimetics of it, such as resveratrol, are of great interest," said NIA Director Richard J. Hodes, M.D. "Resveratrol has produced significant effects in animal models, now including mice, where it mimics some, but not all, consequences of caloric restriction. Its effects in humans remain to be studied."

A major finding of the study reported today is that resveratrol prevented age-related and obesity-related cardiovascular functional decline in the mice as determined by several parameters. Total cholesterol was significantly reduced in 22-month-old non-obese mice after 10 months of resveratrol treatment, although triglyceride levels had only a slight, non-significant trend toward a decrease. Further, the aortas of 18-month-old obese and non-obese mice treated with resveratrol functioned significantly better than untreated mice. Resveratrol also moderated inflammation in the heart.

In addition to cardiovascular function, the scientists found resveratrol to have a variety of positive effects on other age-related problems in mice:

- Treated mice tended to have better bone health, as measured by thickness, volume, mineral content and density, and bending stiffness compared to the non-treated control group.

- At 30 months of age, resveratrol-treated mice were found to have reduced cataract formation, a condition found to increase with age in control-group mice.
- Resveratrol enhanced balance and motor coordination in aged animals. Scientists found significant improvement in performance at 21 and 24 months versus 15 months in the resveratrol-treated mice but not in the untreated mice.
- Resveratrol partially mimicked the effects of dietary restriction on the gene expression profiles of liver, skeletal muscle and adipose (fatty) tissue in mice.

Along with determining the effect of resveratrol on the health of mice, scientists also studied the effect of resveratrol on longevity.

"We found that while quality of life improved with resveratrol, the compound did not significantly affect overall survival or maximum lifespan for mice on a standard diet, compared to mice on the same diet without resveratrol," said de Cabo.

Resveratrol did not have a significant effect on lifespan in animals fed standard chow, suggesting that the intervention did not affect all aspects of the basic aging process. Mice on a high-calorie diet without resveratrol lived the shortest length of time and mice on an every-other-day regimen lived the longest, regardless of resveratrol treatment. However, for mice on a high-calorie diet, mean and maximum lifespan increased for mice on resveratrol when compared with the control mice. Researchers found that resveratrol's effects on longevity could be completely uncoupled from changes in body weight, meaning that mice on a high-calorie diet with resveratrol did not necessarily lose weight but did experience a longer (and healthier) life than mice on the same high-calorie diet not taking resveratrol. They speculate that improved cardiovascular health and reduced fatty changes in the liver may have contributed to the increased lifespan of resveratrol-treated mice.

Researchers still have much to learn before resveratrol can be recommended for human use. Basic questions of safety and biological effect in humans remain to be studied experimentally.

"We are learning a great deal about how resveratrol affects the health and survival of mammals," said Sinclair. "Continued study of calorie restriction mimetics such as resveratrol may eventually point the way to new medicines to treat diseases of aging."

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In addition to scientists from the NIA and Harvard Medical School, researchers from the following institutions collaborated in this study: New York Medical College, Valhalla, N.Y.; University of Michigan, Ann Arbor; University of Sydney in Australia; Thomas Jefferson University, Philadelphia; University of California, San Diego, La Jolla; Hospital for Special Surgery, New York, N.Y.; University of Cincinnati, Ohio; University of Texas Health Science Center at San Antonio and Audie Murphy VA Hospital, San Antonio, Texas; Universidad Pablo de Olavide, Sevilla, Spain; Pennington Biomedical Research Center, Baton Rouge, La.; University of Washington, Seattle; and Sirtris Pharmaceuticals of Cambridge, Mass., a company founded by Harvard University co-lead author Sinclair.

De Cabo is a scientist in the NIA's Intramural Research Program. In addition, the research was funded by grants from the NIA, the primary supporter of the work, as well as grants from the National Institute of General Medical Sciences; the National Heart, Lung, and Blood Institute; the National Institute of Child Health and Human Development; the National Eye Institute; and the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH. The Ellison Medical Research Foundation, the American Heart Association, the Australian and Spanish governments

and Paul F. Glenn and The Paul F. Glenn Laboratories for the Biological Mechanisms of Aging also provided support to members of the research team.

The NIA leads the federal government effort conducting and supporting research on the biomedical and social and behavioral aspects of aging and the problems of older people. For more information on healthy aging, aging-related research and the NIA, please visit the Institute's website at www.nia.nih.gov.

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