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In research on middle-aged mice, scientists find a metabolite that leads to a longer, healthier life

By Pratibha Gopalakrishna

September 1, 2020

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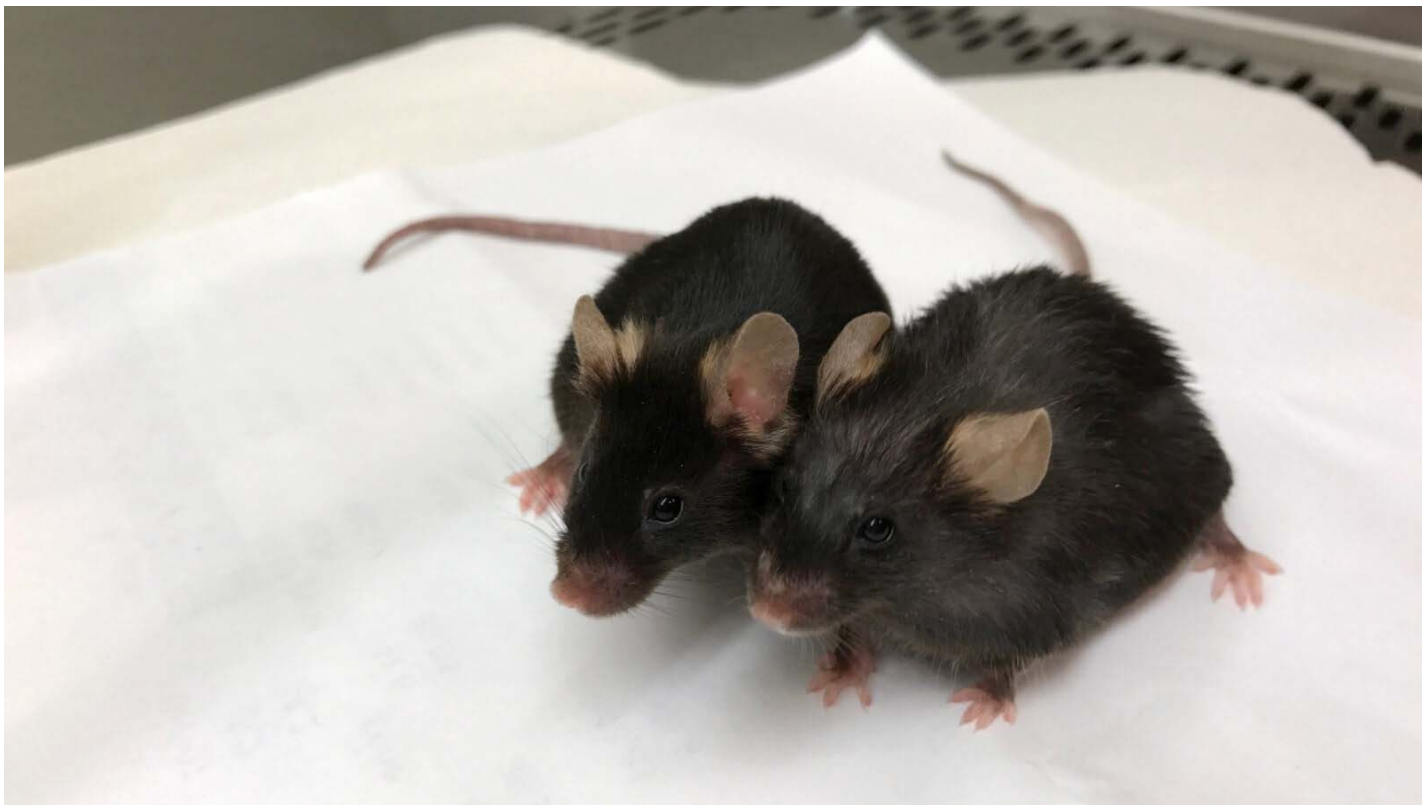

A mouse given AKG — a naturally occurring metabolite shown to increase lifespan in roundworms — is shown on the left. A mouse from the control group, which didn't receive AKG, is shown on the right. *Buck Institute*

The field of aging research is increasingly asking not just how people can live longer, but also how they can age healthier.

The latest example, a new study on middle-aged mice, found that mice given a metabolite naturally found in the body were not only healthier as they grew older, but also were sick for a far shorter time before they died than mice in a control group. The research, led by scientists at the Buck Institute for Research on Aging,

was published Tuesday in Cell Metabolism.

The study centered around a metabolite called alpha-ketoglutarate, or AKG, which is produced by the body and is involved in a number of biological processes, including metabolism, protein synthesis, and stem cell growth. Previous research has shown that AKG levels decline dramatically in humans between ages 40 and 80. But studies have also shown that giving roundworms a dose of AKG can extend their lifespan.

The researchers wanted to test AKG's effects on 18-month-old mice, the equivalent of age 55 to 60 in human years. They fed the mice AKG in the form of a calcium salt, which is also part of the mice's diets. Then, they tracked the mice's health until their death using what's known as a frailty index, which captures more than a dozen characteristics such as tail flexibility, coat color, weight, and physical activity. The mice fed with AKG walked better, had better posture, and maintained a healthier coat than the control group.

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"One of the impressive features of the paper is that they studied health instead of just longevity," said Douglas Seals, a professor and aging researcher at the University of Colorado, Boulder. Seals was not involved in the research.

The researchers also found early evidence to suggest that AKG might reduce inflammation, which occurs as the body fights infection and is thought to play a key role in aging. They measured levels of inflammatory cytokines — small proteins released by cells in response to infection — in the mice's blood serum. They found decreased levels, though only in the female mice. That finding falls in line with previous research in pig intestines after AKG supplementation.

"It makes sense that if some kind of treatment is going to improve our health with aging, that might act through reducing inflammation," said Seals.

The researchers also saw other sex-specific differences, including that the change

in coat color was far more pronounced in the female mice.

“Even a kid can make out the difference,” said Azar Shahmirzadi, a co-author of the paper and an aging researcher at the Buck Institute.

Notably, the mice who received AKG didn’t show any improvement in cardiac function compared to the mice who didn’t get it. The study also found that AKG doesn’t have an effect on an outcome called exercise tolerance, which is a measure of how well the body — and specifically, the heart — can stand up to the strain of exercise.

“Exercise tolerance is a major risk factor for all-cause mortality in humans, so evidence that AKG enhances exercise tolerance would be an important addition,” said Seals.

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There are still a number of unanswered questions about how AKG might affect longevity and why some aging-related outcomes seem to vary by sex. The study also has several limitations, including that it was conducted only in mice. Still, the authors said they are hopeful the research will pave the way for future studies on treatments that might help improve quality of life in elderly people.

“We hope that more people [conduct] research on understanding the mechanisms of AKG and other metabolites,” said Gordon Lithgow, a co-author of the new study and a professor at the Buck Institute.

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