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Muscle protein that makes vertebrates more fit linked to limited lifespan

Why 'Antioxidants' Don't Stop Aging Process

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Source: Johns Hopkins Medicine

Summary: Researchers say they have added to evidence that a protein called CaMKII improves strength, endurance, muscle health and fitness in young animals. Their experiments working with mice and fruit flies, however, found that the gene for CaMKII also contributes to an evolutionary tradeoff: increased susceptibility to age-associated diseases, frailty and mortality.

FULL STORY

Researchers from Johns Hopkins Medicine say they have added to evidence that a protein called CaMKII improves strength, endurance, muscle health and fitness in young animals. Their experiments working with mice and fruit flies, however, found that the gene for CaMKII also contributes to an evolutionary tradeoff: increased susceptibility to age-associated diseases, frailty and mortality.

The research, published May 26 in *Nature Communications,* indicates that future therapies targeting CaMKII could stave off diseases of old age, the investigators say.

According to the study leaders, the evolutionary conservation of genes that enable the young to run faster and respond robustly to "fight or flight" responses makes sense: It helps them to catch prey or evade predators, thereby ensuring their reproductive success. However, some of these genes carry a steep price that animals need to pay when they grow older. The new research shows that turning on CaMKII through a chemical reaction caused by adding oxygen, known as oxidation, strengthens these survival responses for young animals. However, oxidative stress increases with aging, which leads to excessive activation of CaMKII. Elevated CaMKII activity has long been linked to tissue damage seen in heart failure, atrial fibrillation, cancer, lung and neurodegenerative diseases, says study co-lead Mark Anderson M.D., Ph.D., professor of medicine and director of the department of medicine at the Johns Hopkins University School of Medicine.

In a bid to further explore oxidative stress and its links to aging and fitness, Anderson and his research team genetically engineered mice so their CaMKII is resistant to oxidation. They then used mouse-sized treadmills to compare the athletic performance of mice with and without CaMKII oxidation.

They found that mice with oxidized CaMKII were able to run, on average, about 150 meters further and about 5 meters per minute faster than the mice with oxidation-resistant CaMKII.

When the researchers biopsied muscle tissue from the mice and searched for other genes previously linked to muscle growth, recovery from exercise, improved blood flow and immune cell activation -- factors that increase physical endurance -- they found them activated only in mice with oxidizable CaMKII.

Further experiments showed that CaMKII activity in the mouse muscle tissue increased the expression of cellular pathways related to inflammation, diabetes, enlarged heart, seizures and obesity.

These experiments are further evidence that diseases of aging are natural tradeoffs built into our genetic makeup, says Qinchuan Wang, Ph.D., co-lead and assistant professor of medicine at the Johns Hopkins University School of Medicine. "But they give us some hope that it may be possible to target this genetic architecture to combat age-related illnesses."

The Johns Hopkins Medicine team also performed experiments in genetically modified fruit flies to see whether an oxidizable CaMKII produced similar performance and health effects in invertebrates, which do not naturally have an oxidation-sensitive CaMKII protein.

The researchers used a gene-cutting and insertion tool called CRISPR to add the oxidation site to the CaMKII gene in fruit fly DNA.

In one experiment, the flies were placed into glass tubes and allowed to climb to the top of the tube. The researchers found that flies genetically modified to have the oxidizable CaMKII climbed higher and 5mm per second faster than flies with the oxidation-resistant CaMKII. The result suggested that a physiological level of oxidative stress can enhance physical performance by oxidizing and activating CaMKII.

When the researchers fed the flies an antioxidant diet to cancel out the oxidative stress effects on the modified CaMKII, flies with and without the genetic modification performed similarly in the climbing test.

In another experiment, the researchers fed the flies a diet containing the herbicide paraquat, which overloads the flies with an excess of oxidants that activate CaMKII only in the genetically modified, but not the unmodified, flies. They found that the climbing performance of flies with the oxidant-resistant CaMKII gene was not affected by the paraquat diet, which was expected since there is no protein to activate.

In contrast, under such an oxidative stress, the genetically modified flies with the oxidizable CaMKII suffered a significant reduction in climbing performance: They climbed almost 10mm per second slower than their counterparts fed normal diets, suggesting that excessive oxidative stress leads to physical decline through oxidizing and activating CaMKII.

The researchers made similar observations in the fly hearts. They found that the hearts of flies with the oxidizable CaMKII contracted more forcefully and relaxed more quickly than flies with oxidation-resistant CaMKII. However, the performance advantage of the hearts in the genetically modified flies was reversed when the researchers neutralized the oxidants with an antioxidant. The researchers also found that the hearts of the genetically modified flies are more vulnerable to damaging effects of excessive oxidant, as they became dysfunctional or stopped beating altogether when treated by paraquat, the oxidant-generating chemical.

The most striking finding, says Wang, was that despite having better physical performance and cardiac function, the genetically modified flies experienced a more rapid age-related decline and they died at a younger age.

"A main role of evolution is to improve the ability to carry on the species, including producing more offspring and being adept at finding food. Our findings affirm that improvements in the longevity or lifespan of a species is not always necessary for this to happen," explains Gabriel Bever, Ph.D., associate professor of Functional Anatomy and Evolution at the Johns Hopkins University School of Medicine and a collaborator on the study. "In fact, some of the very adaptations that make a species successful also contribute to aging and age-associated diseases."

Overall, the researchers say these findings may provide new targets to address diseases related to an abundance of oxidative damage and may also provide an explanation for why studies of broad spectrum antioxidants, such as Vitamins C and E, have yielded mixed results in the treatment of heart diseases, Parkinson's disease and Huntington's disease.

The scientists say that designing treatments to specifically target gene regulators such as CaMKII may work better.

"For hundreds of millions of years, these diseases have been programmed into animal genomes to plague us at the end of our lives," says Bever. "It's evident we need a more complete understanding of their evolutionary roots if we ever hope to find cures."

The researchers found additional evidence that CaMKII activates genes associated with early immune responses, an adaptation of early vertebrates that confers fitness by helping to ward off infectious diseases. Scientists have found that when people get older, abnormal activation of the immune system contributes to systemic and chronic inflammation and increases the risk for all major age-related diseases. "CaMKII's ability to activate immune response in the face of oxidative stress may hold the clue for its involvement in aging and disease," says Wang.

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