PRESS RELEASE

Dietary supplements make old rats youthful, may help rejuvenate aging humans, according to UC Berkeley study

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By Robert Sanders, Media Relations

Berkeley - Two dietary supplements straight off the health food store shelf put the spark back into aging rats, and might do the same for aging baby boomers, according to a study at the University of California, Berkeley, and Children's Hospital Oakland Research Institute.

A team of researchers led by Bruce N. Ames, professor of molecular and cell biology at UC Berkeley, fed older rats two chemicals normally found in the body's cells and available as dietary supplements: acetyl-L-carnitine and an antioxidant, alpha-lipoic acid.

In three articles in the February 19 issue of Proceedings of the National Academy of Sciences, Ames and his colleagues report the surprising results. Not only did the older rats do better on memory tests, they had more pep, and the energy-producing organelles in their cells worked better.

"With the two supplements together, these old rats got up and did the Macarena," said Ames, also a researcher at Children's Hospital Oakland Research Institute (CHORI). "The brain looks better, they are full of energy - everything we looked at looks more like a young animal."

"The animals seem to have much more vigor and are much more active than animals not on this diet, signaling massive improvement to these animals' health and well-being," said former UC Berkeley post-doctoral fellow Tory M. Hagen, now an assistant professor at the Linus Pauling Institute at Oregon State University, Corvallis. "And we also see a reversal in loss of memory. That is a dual-track improvement that is significant and unique. This is really starting to explode and move out of the realm of basic research into people."

Based on the group's earlier studies, the University of California patented use of the combination of the two supplements to rejuvenate cells. Ames, through the Bruce and Giovanna Ames Foundation, and Hagen founded a company in 1999 called Juvenon to license the patent from the university. Juvenon currently is engaged in human clinical trials of the combination.

One of the three PNAS articles probes the reasons behind this rejuvenation, concluding that the two chemicals "tune up" the energy-producing organelles that power all cells, the mitochondria. Both chemicals are normally used in mitochondria.

Ames calls mitochondria the "weak link in aging." Evidence has been piling up, he said, that deterioration of mitochondria is an important cause of aging. A significant cause of this deterioration, he believes, is the accumulation of destructive free radicals - byproducts of normal metabolism - that disable enzymes and other chemicals.

The combination therapy targets mitochondria to get rid of destructive radicals and to boost the activity of a damaged enzyme, carnitine acetyltransferase, that plays a key role in burning fuel in mitochondria. The researchers hoped that the anti-oxidant alpha-lipoic acid would do the former, and that flooding the cell with acetyl-L-carnitine, one of two proteins that the enzyme acts on, would achieve the latter.

Experiments showed that this regimen worked. Associate researcher Jiankang Liu of CHORI, UC Berkeley postdoctoral fellow David W. Killilea and Ames demonstrated that the enzyme carnitine acetyltransferase is less active in old rats than in young rats, and that it binds less tightly to acetyl-L-carnitine in older rats.

Supplementation with acetyl-L-carnitine or a combination of acetyl-L-carnitine and alpha-lipoic acid restored the enzyme's activity nearly to that found in young rats and substantially restored binding to acetyl-L-carnitine.

"The acetyl-L-carnitine is protecting the protein and the higher levels are enabling the protein to work, while alpha-lipoic acid knocks down oxygen radicals," Ames said. "Each chemical solves a different problem - the two together are better than either one alone."

Ames and Hagen have long had an interest in mitochondria as they relate to aging, and they were intrigued by a 1999 Italian study that showed acetyl-L-carnitine, when fed to old rats, improved mitochondrial activity.

The two thought this might be a way to reverse the effects of aging on mitochondria, and in various trials found it to work to some degree. Free radicals were still damaging the cell, however, so they decided to pair it with one of the few antioxidants that gets into mitochondria, alpha-lipoic acid. Lipoic acid is produced by mitochondria and boosts levels of other antioxidants.

In the second of the PNAS studies, Hagen, Ames and colleagues compared 2- to 4-month-old rats to 24- to 28-month-old rats, all fed acetyl-L-carnitine in their water and alpha-lipoic acid in their chow.

After as much as a month on the supplements, the old and lethargic rats became more peppy, Ames said.

"We significantly reversed the decline in overall activity typical of aged rats to what you see in a middle-aged to young adult rat 7 to 10 months of age," Hagen said. "This is equivalent to making a 75- to 80-year-old person act middle-aged. We've only shown short-term effects, but the results give us the rationale for looking at these things long term."

They found also that the combination of lipoic acid and acetyl-carnitine improved mitochondrial activity and thus cellular metabolism, and increased levels of various chemicals known to decline with age, including ascorbic acid, an antioxidant.

In a third study, Liu, Hagen, Ames and colleagues fed old rats a similar diet of the two supplements and looked at memory function as measured by the Morris water maze test and a peak procedure for assessing temporal or time-based memory developed by Seth Roberts, professor of psychology at UC Berkeley. They found that supplementation improved both spatial and temporal memory, and reduced the amount of oxidative damage to RNA in the brain's hippocampus, an area important in memory. In electron microscope pictures of cells from the hippocampus, mitochondria showed less structural decay in old rats that had a supplemented diet.

"We did two different tests for cognitive activity in rats, and in both it made a big difference to feed them this mixture," Ames said. "Memory degenerates with age, and this makes them better."

The analysis of nucleic acid damage in the brain was performed with post-doctoral researcher Elizabeth Head and Carl W. Cotman, professor of neurobiology and behavior, at the Institute for Brain Aging and Dementia at UC Irvine. UC Berkeley psychology graduate student Afshin M. Gharib worked with Liu to conduct the peak performance tests.

"In aging, you're oxidizing the proteins in mitochondria and they lose activity," Ames explained. "If some of that lost activity is due to binding for substrate or coenzyme - like binding of acetyl-L-carnitine by carnitine acetyltransferase - and you can raise the level of those, then you can reverse some of the loss.

"We showed, in fact, that that is what's happening with acetyl-L-carnitine. Aldehydes from lipid oxidation are glomming onto that protein, and that is what appears to cause the reduction in binding activity. But if you raise the level of acetyl-L-carnitine, now it works."

Hagen added, "With aging, we see so many different things that are occurring to mitochondria that then lead to consequences in the cell. If you tune up mitochondria you may have a means of at least delaying the onset of a number of age-related problems that we encounter, or we can in some ways, hopefully, reverse what has already taken place."

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