Monkey caloric restriction study shows big benefit, contradicts earlier study

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Rhesus monkeys 27-year-old Canto, on a restricted diet (left), and 29-year-old Owen, a control subject on an unrestricted diet (right), were photographed at the Wisconsin National Primate Research Center at the University of Wisconsin-Madison on May 28, 2009. Canto and Owen were among the subjects in a pioneering long-term study of the links between diet and aging in rhesus macaque monkeys. Credit: Jeff Miller, University Communications, UW-Madison

The latest results from a 25-year study of diet and aging in monkeys shows a significant reduction in mortality and in age-associated diseases

among those with calorie-restricted diets. The study, begun at the University of Wisconsin-Madison in 1989, is one of two ongoing, long-term U.S. efforts to examine the effects of a reduced-calorie diet on nonhuman primates.

The study of 76 rhesus monkeys, reported Monday in *Nature Communications*, was performed at the Wisconsin National Primate Research Center in Madison. When they were 7 to 14 years of age, the monkeys began eating a diet reduced in calories by 30 percent. The comparison monkeys, which ate as much as they wanted, had an increased risk of disease 2.9 times that of the calorie-restricted group, and a threefold increased risk of death.

"We think our study is important because it means the biology we have seen in lower organisms is germane to primates," says Richard Weindruch, a professor of medicine at the School of Medicine and Public Health, and one of the founders of the UW study. "We continue to believe that mechanisms that combat aging in caloric restriction will offer a lead into drugs or other treatments to slow the onset of disease and death."

Restricting the intake of calories while continuing to supply essential nutrients extends the lifespan of flies, yeast and rodents by as much as 40 percent. Scientists have long wanted to understand the mechanisms for caloric restriction. "We study caloric restriction because it has such a robust effect on aging and the incidence and timing of age related disease," says corresponding author Rozalyn Anderson, an assistant professor of geriatrics. "Already, people are studying drugs that affect the mechanisms that are active in caloric restriction. There is enormous private-sector interest in some of these drugs."

Still, the effects of caloric restriction on primates have been debated. An influential 2012 report on 120 monkeys being studied at the National

Institute of Aging (NIA) reported no differences in survival for caloric restriction animals and a trend toward improved health that did not reach statistical significance.

The discrepancy may be a result of how the feeding was implemented in control animals in the NIA study, say the Wisconsin researchers. Ricki Colman, a senior scientist at the Wisconsin Primate Center, who presently co-leads the project, suggests that NIA's control monkeys were actually calorie-restricted. "In Wisconsin, we started with adults. We knew how much food they wanted to eat, and we based our experimental diet on a 30 percent reduction in calories from that point." In contrast, the NIA monkeys were fed according to a standardized food intake chart designed by the National Academy of Science.

Through their own experience in monkey research, and by reference to an online database recording the weight of thousands of research monkeys, the Wisconsin researchers concluded that the NIA controls were actually on caloric restriction as well, says Colman. "At all the time points that have been published by NIA, their control monkeys weigh less than ours, and in most cases, significantly so."

Weindruch also points to some results from the NIA that seem to contradict the "no significant result" analysis. Twenty monkeys entered the NIA study as mature adults, 10 in the test group and 10 in the control group, and five of these (four test monkeys and one control monkey) lived at least 40 years. "Heretofore, there was never a monkey that we are aware of that was reported to live beyond 40 years," Weindruch says. "Hence, the conclusion that caloric restriction is ineffective in their study does not make sense to me and my colleagues."

Furthermore, he says, it could be that the small caloric restriction in the NIA control animals had its own benefits, suggesting that a reduction of as little as 10 percent could meaningfully retard aging.

Each of these studies cost millions of dollars and took decades to perform, and they are unlikely to be repeated, says Anderson—so all involved are trying to extract the maximum science from them. "We are now working with the NIA scientists to perform a comprehensive analysis of all of our data, taking into consideration the differences in study design, genetics, time of origin and composition of the diet. It's possible that insights we could not get from the individual studies will emerge from this aggregate data."

Caloric restriction became something of a fad two decades ago, when a few individuals set out to cut their calories by 30 percent to slow the diseases of aging, but the Wisconsin and NIA studies have a much broader focus. "We are not studying it so people can go out and do it, but to delve into the underlying causes of age-related disease susceptibility," says Anderson. "It's a research tool, not a lifestyle recommendation, but some people get caught up: 'What if I did caloric restriction?'"

Many of the benefits of caloric restriction are linked to regulation of energy, Anderson says. "It affects how fuel is utilized. Caloric restriction essentially causes a reprogramming of the metabolism. In all species where it has been shown to delay aging and the diseases of aging, it affects the regulation of energy and the ability of cells and the organism to respond to changes in the environment as they age."

Chief among the metabolic deficits is diabetes, which can be seen as "an inability to properly respond to nutrients," Anderson says. Diabetes damages fat, muscles, blood vessels and even brain functioning, and the growing epidemic of diabetes is a leading cause of death and disability in the United States.

The Wisconsin scientists began to see diabetes among the control animals while they were still in the prime of life, within six months after beginning their study. The contrast with the restricted animals could not

have been more dramatic, Colman says. "Until two years ago, we did not have evidence of diabetes in any caloric-restriction animal, but we had a significant numbers of diabetes, or pre-diabetes, metabolic syndrome, in the control animals."

Very few people can tolerate a 30 percent reduction in calories, yet Weindruch insists the Wisconsin study carries an optimistic message. "The basic biology of caloric restriction in rodents, worms, flies and yeast seems to carry over to primates, so we have a real opportunity to dissect that mechanism, look at how we can work with that basic biology, and benefit all those human primates who are so closely related to our rhesus monkeys."

Provided by University of Wisconsin-Madison