

infoaging guides

BIOLOGY OF AGING



# Caloric Restriction

An introduction to aging science brought to you by the  
American Federation for Aging Research

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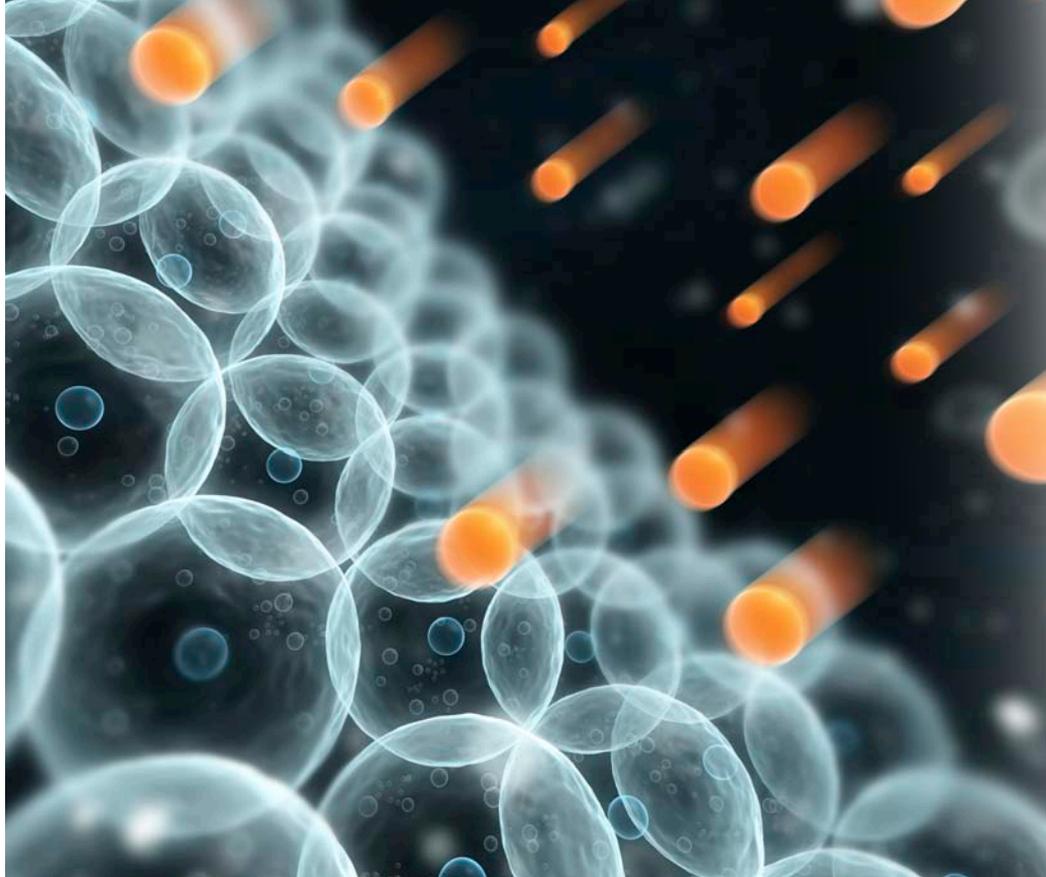
## WHAT IS CALORIC RESTRICTION?

Caloric restriction is an experimental tool that utilizes “undernutrition without malnutrition.” In other words, caloric restriction means lowering typical calorie consumption by 30 to 40 percent, while maintaining all the necessary nutrients and vitamins to support life. Until recently, researchers found this to be the only reliable way to increase longevity in mammals. Two new studies, however, have shown that a diet containing very low levels of an amino acid called methionine can also extend lifespan in mice and rats.

## THE IMPORTANCE OF CALORIC RESTRICTION

Caloric restriction has been shown to increase both the average and the maximal lifespan in paramecia (creatures made of a single cell), worms, spiders, insects, and rodents. Non-human primates are now being tested, but the complete outcome of these tests will not be known for several decades because monkeys have relatively long lifespans compared to other animals. Preliminary results suggest that calorie-restricted monkeys are healthier and tend to live longer than their freely fed counterparts. For example, one new study shows that the immune systems of aged rhesus monkeys on a calorie restricted diet resembles, in several ways, the immune systems of younger animals.

Although caloric restriction diets are so difficult to maintain that they are unlikely to be a practical approach to delayed aging for people, studying the mechanisms of calorie restriction is still very important. Caloric restriction seems to prevent or delay many age-as-



Caloric restriction has been observed to retard and even reverse oxidative damage in aging animals. Oxidative damage is caused when free radicals and peroxides bombard cells.

sociated diseases and conditions, such as heart disease, dementia, and cancer. If scientists can figure out how it works, they might be able to develop drugs that mimic its effects without requiring people to drastically reduce their calorie intake and risk potentially dangerous side effects.

Caloric restriction may or may not extend the total number of years a human can expect to live, but of equal or greater importance, perhaps, is the possibility of adding to the number of years we can expect to remain healthy. Reducing or delaying age-related diseases until the very end of life would represent an enormous improvement in quality of life for many, if not most, older adults.

## THE ROLE OF CALORIC RESTRICTION IN AGING

### Overview

Caloric restriction seems to slow down some of the destructive processes that take place in cells and tissues as they age. Scientists don't yet know exactly how or why it works, but they have developed several theories.

First, caloric restriction seems to reduce damage from chemical metabolic processes, particularly oxidative and glycation damage, thought to be leading causes of cell aging and death.

On a larger scale, caloric restriction slows the effects of aging on the nervous system, the reproductive organs, and the production

of hormones in some animals. It has also been shown to delay the onset of certain age-related cancers. However, whether or not CR enhances or decreases immune function has not been resolved.

### **Reducing cellular damage**

Oxidative damage results when free radicals, the potentially toxic byproducts of cell energy production, break down DNA; cell membranes; and mitochondria, the energy factories of cells. Caloric restriction has been observed to retard and even reverse oxidative damage in aging animals.

Glycation is the addition or insertion of sugar molecules into DNA and proteins, which takes place in a variety of physiological reactions. Glycation causes damage to proteins and DNA and is thought to be a major cause of degeneration associated with diabetes and other diseases. Caloric restriction also reduces glycation damage in tissues.

### **Hormonal effects**

#### *Insulin*

Caloric restriction in animals also has potent effects on glucose and insulin regulation. Glucose is a simple sugar that serves as a major source of energy for mammals and assists in the formation of biologically important molecules. Insulin plays an important regulatory role in these metabolic processes. With age and obesity, mammals such as mice, monkeys, and humans develop insulin resistance, which is a reduction in the ability of insulin to carry out its regulatory functions. With insulin resistance, blood glucose (blood sugar) levels rise, blood insulin levels rise, and cells and tissues are damaged. Diabetes, high blood pressure, hardening of the arteries, heart

disease, and stroke are all consequences of insulin resistance in humans.

Caloric restriction protects against insulin resistance. The tissues of an animal whose total calorie (and thus energy) intake is limited become more sensitive to insulin for driving glucose into cells. This has been observed in numerous species of laboratory mice and rats; recent studies in non-human primates have also demonstrated caloric restriction's beneficial effects on reducing insulin resistance.

#### *Glucocorticoids*

Caloric restriction has been shown to increase the ability of aging rodents to produce glucocorticoids, which are natural steroids produced when the body is under stress. They help stop glucose from being stored and instead redirect it into tissues that need it. As mammals age, the neuro-transmission of signals between the brain and the adrenal gland is altered and the release of these stress hormones falters.

Caloric restriction also increases the daily peak free-glucocorticoid concentration in plasma, but has little or no effect during most of the remainder of the day. Although many scientists have suggested potential functional roles for this daily increase in peak concentration, there is no evidence that it exerts any effect on the extension of lifespan or any other anti-aging action of caloric restriction.

### **Protection against temperature effects**

Another interesting cellular change noted in aging rodents subjected to caloric restriction is their ability to resist the damaging effects of hyperthermia, or elevated body temperature.

Calorie restricted rodents are harder to kill by hyperthermia, but why this should be true isn't yet clear. Some scientists speculate that this protection occurs because older mammals are less likely to produce protective substances called heat shock proteins. Others say that a rodent's ability to cope with hyperthermia may not involve heat shock proteins at all. Instead, it might be related to weight. Calorie restricted rats are extremely lean and this helps them to stay cooler, even in a hot room. Control rats, in contrast, are obese. Obesity interferes with heat loss in a hot environment.

### **Downsides**

Caloric restriction leads to reduced ability to deal with hypothermia (lowered body temperature)—possibly associated with the individual's lower body fat content. Another problem is that wounds don't heal as quickly in calorie-restricted animals as in normal-fed laboratory animals.

## **EXTENDING LIFE: BEHIND THE SCENES**

In 1935, Clive McCay, a nutritionist at Cornell University, made the stunning discovery that rats fed fewer calories (just enough to maintain a steady body weight) than their littermates lived considerably longer. This discovery opened the door to a new field of medicine dedicated to understanding the fundamental biology of aging. In the intervening years, scientists have come to understand that a calorie-restricted diet postpones death and disease in many laboratory animals, including nematodes, fruitflies, and rodents. Moreover, it decelerates many age-related changes in nearly

every body system and cell type tested. A review published in the *Milbank Quarterly* explains that lifespan is extended because the diet delays whatever diseases are the key causes of death in each species tested. Notably, animals on calorie-restricted diets remain healthy and active long after their control littermates have died — a finding that has a tremendous bearing on public health and preventive medicine.

Researchers at the University of Texas Health Science Center at San Antonio learned, for example, that when rodents in a control group are given access to a running wheel, they typically run about 1,000 meters a day [.62 miles] until they are about eight months old, when they gradually

cut back to about 200 meters a day [.12 miles]. In contrast, calorie-restricted rodents may run 4,000 to 5,000 meters a day [2.5 to 3 miles] until they are about two years old, when they begin to slow down. They are still running about 1,000 meters a day at three years of age — a year beyond the median lifespan for the control rodents.

Evidence of the calorie-restricted effect — meaning a longer, healthier life — is exciting and consistent. These basic observations have been repeated in more than 100 rigorous scientific investigations in dozens of independent laboratories over many years. For the first 50 years or so after its initial discovery, the calorie-restricted regimen was the only known way

to produce very old, but vital rodents. More recently, an association between deficient production or utilization of growth hormones and longer lifespan has been observed in a variety of studies with mutant mice. The restriction of the amino acid methionine has also been shown to extend longevity. Recently, researchers have demonstrated that caloric restriction doesn't benefit all strains of inbred rodents. The beneficial effects are dependent on an animal's genetic constitution. In fact, caloric restriction has proven harmful in some strains of mice.

#### *Obstacles to Progress*

The goal of caloric restriction research is to recognize the precise mechanisms by which it slows

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aging. If this mechanism were understood, a simple intervention, such as a pill, might induce these same changes without restricting the number of calories in one's diet. Such a discovery would constitute a huge landmark in medical research. However, a number of impediments have hindered progress.

Some of these obstacles are scientific. Aging experiments in mammals take years, rather than weeks, to complete. Young scientists must write many peer-reviewed journal articles to advance, to get promoted, and finally, to attain tenure. The relatively slow pace required for aging research in mammals interferes with a young professional's career goals, limiting the number of researchers willing to commit their careers to this kind of work.

The absence of a validated tool to accurately measure biological age is yet one more impediment to the testing of agents believed to slow aging, and the fact that the precise biochemical pathways involved in aging remain undiscovered is another.

Most obstacles are political, however. Despite the obviously improved mental and physical



health in laboratory animals on calorie-restricted diets, many scientists, including those who set national research priorities, shun research into the biological control of aging. Instead, they allocate funding to doing research on individual diseases, such as heart disease and cancer—and receive a great deal of emotional support from the public in doing so. If research funding narrowly targets individual health conditions, it obviously cannot also target the broader field of aging research. The fact remains, however, that progress in aging research has the potential to improve public health to a far greater extent than doing research on one lethal disease at a time.

Finally, there exists a subtle public predisposition against longevity research, which is viewed by some to be unethical, because of concerns that progress in this field might create a world with too many healthy old people and not enough room for the young. Pointing out that such an argument could also be used against past research on antibiotics and current research on cancer does little to dispel this belief.

These obstacles and others must be overcome before such aging research can defer the onset of late life illnesses and prolong the period of healthy active lives for millions of Americans.

## **FUTURE OF CALORIC RESTRICTION RESEARCH**

The major goals of future caloric restriction research should be to learn the basic mechanism(s) underlying its anti-aging actions and to identify more palatable procedures for accomplishing these actions. Caloric restriction might work at the level of the individual cell. Alternatively, it may work by stimulating the nervous system in some fashion, which can affect cells throughout the body, or it may produce its benefits by inducing our bodies to express protective hormones.

**American Federation for Aging Research (AFAR)**  
55 West 39th Street, 16th Floor  
New York, NY 10018

Phone: (212) 703-9977  
Toll-free: (888) 582-2327  
Fax: (212) 997-0330  
Email: [info@afar.org](mailto:info@afar.org)

### **Websites:**

[www.afar.org](http://www.afar.org)  
[www.beeson.org](http://www.beeson.org)  
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