Calorie restriction

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Calorie restriction (CR), or **caloric restriction**, or **energy restriction**, is a dietary regimen that reduces calorie intake without incurring malnutrition or a reduction in essential nutrients. "Low" can be defined relative to the subject's previous intake before intentionally restricting calories, or relative to an average person of similar body type. Calorie restriction without malnutrition has been shown to work in a variety of species, among them yeast, fish, rodents and dogs to decelerate the biological aging process, resulting in longer maintenance of youthful health and an increase in both median and maximum lifespan.[1] The life-extending effect of calorie restriction however is not shown to be universal.[2]

In humans the long-term health effects of moderate CR with sufficient nutrients are unknown.[3]

Two main lifespan studies have been performed involving nonhuman primates (rhesus monkeys). One, begun in 1987 by the National Institute on Aging, published interim results in August 2012 indicating that CR confers health benefits in these animals, but did not demonstrate increased median lifespan; maximum lifespan data are not yet available, as the study is still ongoing.[4] A second study by the University of Wisconsin beginning in 1989 issued preliminary lifespan results in 2009,[1][5][6] and final results in 2014.[7] It found that CR primates were only 36.4% as likely to die from age-related causes when compared with control animals, and had only 56.2% the rate of death from any cause.

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Health effects

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Risks of malnutrition

As noted above, the term "calorie restriction" as used in biogerontology refers to dietary regimens that reduce calorie intake without incurring malnutrition.[3] If a restricted diet is not designed to include essential nutrients, malnutrition may result in serious deleterious effects, as shown in the Minnesota Starvation Experiment.[8] This study was conducted during World War II on a group of lean men, who restricted their calorie intake by 45% for 6 months, and composed roughly 90% of their diet with carbohydrates.[8] As expected, this malnutrition resulted in many positive metabolic adaptations (e.g. decreased body fat, blood pressure, improved lipid profile, low serum T3 concentration, and decreased resting heart rate and whole-body resting energy expenditure), but also caused a wide range of negative effects, such as anemia, lower extremity edema, muscle wasting, weakness, neurological deficits, dizziness, irritability, lethargy, and depression.[8]

Musculoskeletal losses

Short-term studies in humans report loss of muscle mass and strength and reduced bone mineral density (BMD).[9] However, whether or not the reduction in BMD actually harms bone health is unclear.[10] In a study in premenopausal women, BMD after weight loss was higher when normalized for body weight;[10] reduced BMD is also observed in humans undergoing long-term calorie restriction with adequate nutrition, but no fractures have been reported[11] and the reduction in BMD was not associated with deleterious changes in bone microarchitecture.[10]

The authors of a 2007 review of the CR literature warned that "[i]t is possible that even moderate calorie restriction may be harmful in specific patient populations, such as lean persons who have minimal amounts of body fat."[12]

Lower-than-normal BMI, high mortality

CR diets typically lead to reduced body weight, yet reduced weight can come from other causes and is not in itself necessarily healthy. In some studies, low body weight has been associated with increased mortality, particularly in late middle-aged or elderly subjects. Low body weight in the elderly can be caused by pathological conditions associated with aging and predisposing to higher mortality (such as cancer, chronic obstructive pulmonary disorder, or depression) or of the cachexia (wasting syndrome) and sarcopenia (loss of muscle mass, structure, and function).[13] One of the more famous of such studies linked a body mass index (BMI) lower than 18 in women with increased mortality from noncancer, non−cardiovascular disease causes.[14] The authors attempted to adjust for confounding factors (cigarette smoking, failure to exclude pre-existing disease); others argued that the adjustments were inadequate.[15]

> "epidemiologists from the ACS (American Cancer Society), American Heart Association, Harvard School of Public Health, and other organizations raised specific methodologic questions about the recent Centers for Disease Control and Prevention (CDC) study and presented analyses of other data sets. The main concern ... is that it did not adequately account for weight loss from serious illnesses such as cancer and heart disease ... [and] failed to account adequately for the effect of smoking on weight ... As a result, the Flegal study underestimated the risks from obesity and overestimated the risks of leanness."[16]

Such epidemiological studies of body weight are not about CR as used in anti-aging studies; they are not about caloric intake to begin with, as body weight is influenced by many factors other than energy intake. Moreover, "the quality of the diets consumed by the low-BMI individuals are difficult to assess, and may lack nutrients important to longevity."[3] Typical low-calorie diets rarely provide the high nutrient intakes that are a necessary feature of an anti-aging calorie restriction diet.[17][18][19] As well, "The lower-weight individuals in the studies

are not CR because their caloric intake reflects their individual ad libitum set-points, and not a reduction from that set-point."[3]

Triggering eating disorders

In those who already suffer from a binge-eating disorder, calorie restriction can precipitate an episode of binge eating, but it does not seem to pose any such risk otherwise.[20]

Young or pregnant

Long-term calorie restriction at a level sufficient for slowing the aging process is generally not recommended in children, adolescents, and young adults (under the age of approximately 21), because this type of diet may interfere with natural physical growth, as has been observed in laboratory animals. In addition, mental development and physical changes to the brain take place in late adolescence and early adulthood that could be negatively affected by severe calorie restriction.[21] Pregnant women and women trying to become pregnant are advised not to practice calorie restriction, because low BMI may result in ovulatory dysfunction (infertility), and underweight mothers are more prone to preterm delivery.[21]

Miscellaneous concerns

It has also been noted that people losing weight on such diets risk developing cold sensitivity, menstrual irregularities, and even infertility and hormonal changes.[22]

Mechanisms

Even though there has been research on CR for over 70 years, the mechanism by which CR works is still not well understood.[1] Some explanations include reduced core body temperature,[23] reduced cellular divisions, lower metabolic rates, reduced production of free radicals,[24] reduced DNA damage[25][26] and hormesis.[27]

Temperature

Caloric restriction lowers the core body temperature, a phenomenon believed to be an adaptive response to reduce energy expenditure when nutrients availability is limited. Lowering the temperature may prolong the lifespan of cold blooded animals. Mice, which are warm blooded, have been engineered to have a reduced core body temperature which increased the lifespan independently of calorie restriction.[23]

Hormesis

Some research has pointed toward hormesis as an explanation for the benefits of CR. Southam and Ehrlich (1943) reported that a bark extract that was known to inhibit fungal growth actually stimulated growth when given at very low concentrations. They coined the term "hormesis" to describe such beneficial actions resulting from the response of an organism to a low-intensity biological stressor. The word "hormesis" is derived from the Greek word "hormaein", which means "to excite". The (mito)hormesis hypothesis of CR proposes that the diet imposes a low-intensity biological stress on the organism, which elicits a defensive response that helps protect it against the causes of aging. In other words, CR places the organism in a defensive state so that it can survive adversity, resulting in improved health and longer life. Such responses include enhanced expression of heat shock proteins and antioxidant enzymes.[28] This switch to a defensive state may be controlled by longevity genes (see below).[29]

Mitochondrial hormesis

Mitochondrial hormesis was a purely hypothetical concept until late 2007, when work by Michael Ristow's group on a small worm named Caenorhabditis elegans suggested that the restriction of glucose metabolism extends life span primarily by increasing oxidative stress to stimulate the organism into having an ultimately increased resistance to further oxidative stress.[30] This is probably the first experimental evidence for hormesis being the reason for extended life span following CR.

Although aging can be conceptualized as the accumulation of damage, the more recent determination that free radicals participate in intracellular signaling has made the categorical equation of their effects with "damage" more problematic than was commonly appreciated in the past. It was previously proposed on a hypothetical basis that free radicals may induce an endogenous response culminating in more effective adaptations that protect against exogenous radicals (and possibly other toxic compounds).[31] Recent experimental evidence strongly suggests that this is indeed the case, and that such induction of endogenous free-radical production extends the life span of a model organism and mitohormetically exerts life-extending and health-promoting effects. Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction.[32][33][34]

Evolution

It has been recently argued that during years of famine, it may be evolutionarily desirable for an organism to avoid reproduction and to up-regulate protective and repair enzyme mechanisms to try to ensure that it is fit for reproduction in future years. This argument seems to be supported by recent work studying hormones.[35] Prolonged severe CR lowers total serum and free testosterone while increasing sex hormone binding globulin (SHBG) concentrations in humans; these effects are independent of adiposity.[36]

Lowering of the concentration of insulin and substances related to insulin, such as insulin-like growth factor 1 and growth hormone, has been shown to up-regulate autophagy, the repair mechanism of the cell.[37] A related hypothesis suggests that CR works by decreasing insulin levels and thereby up-regulating autophagy,[37][38] but CR affects many other health indicators, and it is still undecided whether insulin is the main concern.[39] Calorie restriction has been shown to increase DHEA in primates, but it has not been shown to increase DHEA in post-pubescent primates.[40][41] The extent to which these findings apply to humans is still under investigation.

Chromatin and PHA-4

Evidence suggests that the biological effects of CR are closely related to chromatin function.[42] A study conducted by the Salk Institute for Biological Studies and published in the journal *Nature* in May 2007 determined that the gene PHA-4 is responsible for the longevity behind calorie restriction in roundworms, "with similar results expected in humans".[43]

Free radicals and glycation

Two very prominent proposed explanations of aging that have a bearing on calorie restriction are the free radical theory and the glycation theory. With high amounts of energy available, mitochondria do not operate very efficiently and generate more superoxide. With CR, energy is conserved and there is less free radical generation. A CR organism will have less fat and require less energy to support the weight, which also means that there does not need to be as much glucose in the bloodstream.

Less blood glucose means less glycation of adjacent proteins and less fat to oxidize in the bloodstream to cause sticky blocks resulting in atherosclerosis. Type 2 diabetics are people with insulin insensitivity caused by long-term exposure to high blood glucose. Type 2 diabetes and uncontrolled type 1 diabetes are much like "accelerated aging", due to the above effects. There may even be a continuum between CR and the metabolic syndrome.

Reduced DNA damage

Calorie restriction reduces production of reactive oxygen species (ROS).[24][44] ROS causes several types of DNA damage including 8-hydroxy-2'-deoxyguanosine (8-OHdG). The level of 8-OHdG is often used as an indicator of the general level of oxidative damage in DNA.

Sohal et al. observed that caloric restriction decreased 8-OHdG damages in the DNA of mouse, heart, skeletal muscle, brain, liver and kidney. The levels of 8-OHdG in the DNA of these organs in 15 month old mice were reduced to an average of 81% of that in the DNA of mice fed an unrestricted diet.[25] Kaneko et al. observed that, in rats, dietary restriction retarded the onset of age-related increases in 8-OHdG in nuclear DNA of brain, heart, liver and kidney. The level of 8-OHdG in these organs of the calorie restricted rats at 30 months averaged 65% of the level in rats fed an unrestricted diet.[45] Hamilton et al. found that dietary restriction in both mice and rats reduced the age-related levels of 8-OHdG. In rats aged 24–26 months that had been fed a calorie restricted diet, the level of 8-OHdG in heart, skeletal muscle, brain and kidney DNA was, on average, 62% of the level in rats fed an unrestricted diet. In mice, after a calorie restricted diet for 24–26 months, the level of 8-OHdG in heart, brain, liver and kidney DNA averaged 71% of the level in mice fed an unrestricted diet.[46] Also, Wolf et al. observed that, in the rat, calorie restriction reduced 8-OHdG in the DNA of heart, skeletal muscle, brain and liver. After 24 months, the levels of 8-OHdG in these organs averaged 64% of those in the rats fed an unrestricted diet.[47]

Thus in rodents, calorie restriction slows aging, decreases ROS production and reduces the accumulation of oxidative DNA damage in multiple organs. These results link reduced oxidative DNA damage to slower aging. The consistent observation that calorie restriction reduces oxidative DNA damage lends support to the proposal of Holmes et al. that oxidative DNA damages are a prominent cause of aging.[26] This is also discussed in detail by Bernstein et al.[48]

Sirtuin-mediated mechanism

Situins, specifically Sir2 (found in yeast) has been implicated in the aging of yeast[49] and is a highly conserved, NAD^+ - dependent histone deacetylase.[50] Sir2 homologs have been identified in a wide range of organisms, from bacteria to humans.[51] Yeast has 3 SIR genes (SIR2, SIR3, and SIR4) that are responsible for silencing mating type loci, telomeres, and rDNA.[52] Although all three genes are required for the silencing of mating type loci and telomeres, only SIR2 has been implicated in the silencing of rDNA.[53] In addition, SIR2 related genes also regulate formation of some specialized survival forms, such as spores in yeast[54] and daher larvae in *C. elegans*.[55] A study done by Kaeberlein et al. (1999) in yeast found that deletions of Sir2 decreased lifespan, and additional copies increased lifespan.[51] All these studies implicate the role of SIR2 in survival and longevity.

In many calorie restriction studies, it is believed that Sir2 mediates the longevity effects from calorie restriction for several reasons. First, it was found that in yeast without SIR2, calorie restriction did not impart longevity in yeast;[56] second, in Sir2 mutants an abundance of extra-chromosomal ribosomal DNA circles (that typically limit lifespan) has been observed, and that mitigation of these circles restore regular life span, but still are resistant to calorie restriction-mediated longevity;[57][58] third, that caloric restriction increases the activity of Sir2 *in vivo*.[59] Although Sir2 has been implicated in calorie restriction-mediated longevity, the method by which Sir2 is regulated under caloric restriction is still debated.

Two hypotheses of Sir2/caloric restriction -mediated longevity is the NADH mechanism and the NAD salvage pathway mechanism. In the NADH hypothesis, it is believed that caloric restriction causes an increase in respiration,[59] which in turn causes a reduction in the levels of NADH.[50] This decrease in the concentration of NADH would up regulate SIR2, since NADH functions as a competitive inhibitor of SIR2.[58] In addition, it has been shown that overexpression of NADH hydrogenase increased longevity and knocking out the electron transport chain blocked caloric restriction-mediated longevity. The NAD salvage pathway mechanism relies on

the a study by Anderson et al., in which they showed that caloric restriction causes an up regulation of PCN1 (an enzyme responsible for synthesizing NAD from nicotinamide and ADP-ribose) decreases the levels of nicotinamide, which in turn upregulates SIR2 and thus increases lifespan.[60] Although these models are not mutually exclusive, no experiment has been conducted linking the two.[58]

Caloric restriction mimetics

Work on the mechanisms of CR has given hope to the synthesizing of future drugs to increase the human life span by simulating the effects of calorie restriction. In particular, the large number of genes and pathways reported to regulate the actions of CR in model organisms represent attractive targets for developing drugs that mimic the benefits of CR without its side effects.[61][62][63] However, MIT biologist Leonard Guarente cautioned that "(treatment) won't be a substitute for a healthy lifestyle. You'll still need to go to the gym."[64]

Sir2, or "silent information regulator 2", is a sirtuin, discovered in baker's yeast cells, that is hypothesized to suppress DNA instability.[65] In mammals, Sir2 is known as SIRT1. David Sinclair at Harvard Medical School in Boston is a leading proponent of the view that the gene Sir2 may underlie the effect of calorie restriction in mammals by protecting cells from dying under stress.[66] It is suggested that a low-calorie diet that requires less Nicotinamide adenine dinucleotide to metabolize may allow SIRT1 to be more active in its life-extending processes. An article in the June 2004 issue of the journal *Nature* showed that SIRT1 releases fat from storage cells.[67]

Sirtuins

Attempts are being made to develop drugs that act as CR mimetics, and much of that work has focused on a class of proteins called sirtuins.[68] Resveratrol has been reported to activate SIRT1 and extend the lifespan of yeast,[69] nematode worms, fruit flies,[70] vertebrate fish,[71] and mice consuming a high-caloric diet.[72] However, resveratrol does not extend life span in normal mice[73] and the effect of resveratrol on lifespan in nematodes and fruit flies has been disputed.[74]

There are studies that indicate that resveratrol may not function through SIRT1[75][76] but may work through other targets.[77][78] A clinical trial of the resveratrol formulation SRT501 was suspended.[79]

There is some evidence from mice that caloric restriction may be mediated through SIRT3[80] or SIRT6.[81]

History

The first person to promote calorie restriction as a means of prolonging life was Luigi Cornaro, a 15th-century Venetian nobleman who adopted a calorie restricted diet at age 35 to address his failing health. It is said his restricted diet cured him of all of his ailments in less than a year, and he went on to live to be 102 years old.[82] His book *Discorsi della vita sobria* (Discourses On the Temperate Life (http://www.soilandhealth.org/02/0201hyglibcat/020105cornaro.html)) described his regimen, which centered on the "quantifying principle" of restricting himself to only 350 grams of food daily (including bread, egg yolk, meat, and soup) and 414 milliliters of wine. The book was extremely successful, and "was a true reconceptualization of old age. As late as the Renaissance it was largely the negative aspects of this phase of life which were emphasized ... Cornaro's method offered the possibility for the first time not only of a long but also a worthwhile life."[83]

In 1934, Mary Crowell and Clive McCay of Cornell University observed that laboratory rats fed a severely reduced calorie diet while maintaining micronutrient levels resulted in life spans of up to twice as long as otherwise expected. These findings were explored in detail by a series of experiments with mice conducted by Roy Walford and his student Richard Weindruch. In 1986, Weindruch reported that restricting the calorie intake of laboratory mice proportionally increased their life span compared to a group of mice with a normal diet. The calorie-restricted mice also maintained youthful appearances and activity levels longer and showed delays in

age-related diseases. The results of the many experiments by Walford and Weindruch were summarized in their book *The Retardation of Aging and Disease by Dietary Restriction* (1988) (ISBN 0-398-05496-7).

The findings have since been accepted and generalized to a range of other animals. Researchers are investigating the possibility of parallel physiological links in non-human and human primates. In response to these results, a small number of people have independently adopted the practice of calorie restriction in some form as a potential anti-aging intervention.[84][85]

Two randomized controlled studies on the effects of CR in non-human primates have been conducted: the Wisconsin National Primate Research Center and the National Institute on Aging CR monkey studies. In 1989, scientists at University of Wisconsin started a study involving 46 adult male and 30 female rhesus monkeys.[1][5] The National Institute on Aging CR monkeys study, started in 1987, involves 60 male and 60 female rhesus monkeys. Monkeys in both studies have been randomized with a 1:1 ratio to 30% CR or to a control diet. Results are being periodically published.

Luigi Fontana and other scientists at Washington University in St. Louis have studied long-term physiologic, metabolic, and molecular effects of CR in a small group of healthy lean men and women.[84][85]

In May 2007 a multi-center clinical trial called the CALERIE (Comprehensive Assessment of the Long-term Effects of Reducing Energy Intake) study was begun, to examine the effect of 2 years of sustained 25% CR on: a) slowing aging as assessed by proxy indicators and b) protecting against age-related disease processes. 220 healthy volunteers across 3 sites (Tufts University, Pennington Biomedical Research Center, and Washington University School of Medicine) were recruited.[86]

A study at UCSF called "CRONA" was started in December 2010, and studied 28 long-term CR practitioners over a few months.[87] The study was completed on September 20, 2011.[88] As of August 2012 the results had not yet been published.

Research

Primates

Several studies have been conducted on calorie restriction in non-human primates. One found positive effects on lifespan and a variety of aging-related diseases.[6][7] Another found reductions in several age-related diseases, but no difference in median lifespan; maximum lifespan has not been reported as the study is still ongoing.[89] One hypothesis is that the animal's genetics and the quality of the food are more important than the quantity.[90]

Rodents

Seventy years ago, C. M. McCay et al. discovered that reducing the amount of calories fed to rodents nearly doubled their life spans. The life extension varied for each species, but on average there was a 30–40% increase in life span in both mice and rats.[39]

Yeast

Fungi models are very easy to manipulate, and many crucial steps toward the understanding of aging have been made with them. Many studies were undertaken on budding yeast and fission yeast to analyze the cellular mechanisms behind increased longevity due to calorie restriction. First, calorie restriction is often called dietary restriction because the same effects on life span can be achieved by only changing the nutrient quality without changing the amount of calories. Data from Dr Guarente, Dr Kennedy, Dr Jazwinski, Dr Kaeberlein, Dr Longo, Dr Shadel, Dr Nyström, Dr Piper, and others showed that genetic manipulations in nutrient-signaling pathways could mimic the effects of dietary restriction. In some cases, dietary restriction requires mitochondrial

respiration to increase longevity (chronological aging), and in some other cases not (replicative aging). Nutrient sensing in yeast controls stress defense, mitochondrial functions, Sir2, and others. These functions are all known to regulate aging. Genes involved in these mechanisms are TOR, PKA, SCH9, MSN2/4, RIM15, SIR2, etc.[91][92][93][94][95] Importantly, yeast responses to CR can be modulated by genetic background. Therefore, while some strains respond to CR with increased lifespan, in others CR shortens it [96]

Humans

Studies have been conducted to examine the effects of CR with adequate intake of nutrients in humans; however, long-term effects are unknown.[3]

Biomarkers for cardiovascular risk

A review of the effects of CR on the aging heart and vasculature concluded that "Data from animal and human studies indicate that [beyond the effects of "implementation of healthier diets and regular exercise"], more drastic interventions, i.e., calorie restriction with adequate nutrition (CR), may have additional beneficial effects on several metabolic and molecular factors that are modulating cardiovascular aging itself (e.g., cardiac and arterial stiffness and heart rate variability)."[97] Studies of long-term practitioners of rigorous CR show that their risk factors for atherosclerosis are substantially improved in a manner consistent with experimental studies in rodent models of atherosclerosis and nonhuman primates.[97] Risk factors such as c-reactive protein; serum triglycerides, low-density lipoprotein, high-density lipoprotein; blood pressure; and fasting blood sugar, are substantially more favorable than persons consuming usual Western diets and comparable or better than long-term endurance exercisers.[97] Similar effects were also seen during a "natural experiment" in Biosphere 2,[97] and in subjects in the “Minnesota Starvation Experiment” during World War II.[8] Cardiac "diastolic function was better in subjects who practiced strict CR for 3–15 years than that in healthy age- and sex-matched control subjects ... CR subjects had less ventricular stiffness and less viscous loss of diastolic recoil, both of which would be consistent with less myocardial fibrosis.[97] "These effects, in combination with other benefits of CR, such as protection against obesity, diabetes, hypertension, and cancer, suggest that CR may have a major beneficial effect on health span, life span, and quality of life in humans."[97]

Biomarkers for cancer risk

Long-term CR in humans results in a reduction of several metabolic and hormonal factors that have been associated with increased risk of some of the most common types of cancer in developed countries, consistent with similar shifts in CR rodents and nonhuman primates, in whom CR affords substantial protection against cancer morbidity and mortality.[98][98][85] These include lower levels of total and abdominal fat, circulating insulin, testosterone, estradiol, and inflammatory cytokines linked to cancer.[85] Long-term CR can also reduce levels of serum Insulin-like growth factor 1 in humans, and increase levels of IGFBP-3; however, unlike in rodents, this effect can be blocked if dietary protein is not reduced to the Dietary Reference Intake.[85]

Concerns and confounders

Activity levels

Calorie restriction preserves muscle tissue in nonhuman primates[99][100] and rodents.[101][102] Mechanisms include reduced muscle cell apoptosis and inflammation;[101] protection against[102] or adaptation to[99] age-related mitochondrial abnormalities; and preserved muscle stem cell function.[103] Muscle tissue grows when stimulated, so it has been suggested that the calorie-restricted test animals exercised more than their companions on higher calories, perhaps because animals enter a foraging state during calorie restriction. However, studies show that overall activity levels are no higher in CR than ad libitum (AL) animals in youth,[104] while CR animals are more active at middle age and beyond due to a protective effect against the decline in

activity observed in middle-aged and older animals.[105]

Amino acids for exercise

Exercise has also been shown to increase health and life span and lower the incidence of several diseases (relative to sedentary and obese controls, but not to energy-restricted sedentary controls of matching body weight).[106] Calorie restriction comes into conflict with the high caloric needs of athletes, and may not provide them sufficient energy levels or amino acids for repair. Moreover, in experiments comparing CR to exercise, CR animals lived much longer than exercised animals.[107]

Age of onset

There is some evidence suggesting that the benefit of CR in rats might only be reaped in early years. A study on rats that were gradually introduced to a CR lifestyle at 18 months showed no improvement over the average life span of the AL group.[108] This view, however, is disputed by Spindler, Dhahbi, and colleagues, who showed that in late adulthood, acute CR partially or completely reversed age-related alterations of liver, brain and heart proteins, and that mice placed on CR at 19 months of age showed increases in life span.[109] The Wisconsin rhesus monkey study showed increased survival rates and decreased diseases of aging from caloric restriction even though the study started with adult monkeys.[110]

Larger organisms

Another objection to CR as an advisable lifestyle for humans is the claim that the physiological mechanisms that determine longevity are very complex, and that the effect would be small to negligible in our species.[111] Several of the biological changes observed in animals with longer life spans on CR have already been observed in humans which proponents argue suggests that the life-extending properties of CR will extend to humans.[112]

Activity level

Laboratory rodents placed on a CR diet tend to exhibit increased activity levels (particularly when provided with exercise equipment) at feeding time. Monkeys undergoing CR also appear more restless immediately before and after meals.[113] Despite this brief daily period of increased activity overall activity is no higher in CR than AL animals in youth after an initial period of adaptation to the diet.[104] On the other hand, CR has been found to retard the *decline* in activity that occurs during normal aging: in one study, animals on a conventional diet "showed little activity" by early middle age, while those on CR "were observed to run around the cage and climb onto and hang from the wire cage tops throughout their life spans. In fact, the longest surviving [CR] mouse was observed hanging from the top of his cage only 3 days before he became moribund."[105]

Stereotyped behavior

Observations in some accounts of animals undergoing CR have noted an increase in stereotyped behaviors.[113] For example, monkeys on CR have demonstrated an increase in licking, sucking, and rocking behavior.[114]

Aggression

A CR regimen may also lead to increased aggressive behavior in animals.[113]

Critique

The concept that caloric restriction universally prolongs longevity has been contested. Increased longevity is measured only relative to control animals, but a review of the evidence indicates that the lives of these control animals are artificially shortened by weight-gain from unnatural ad libitum feeding in the laboratory.[115]

See also

- CR Society International
- Fasting
- Very low calorie diet
- Okinawa diet
- Mitohormesis
- Intermittent fasting

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