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Caloric Restriction and Aging: Eat Less, Live Longer

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Introduction

The commonly used phrase "you are what you eat" has recently been shadowed by a new saying, "eat less, live longer." Caloric restriction (CR), also termed dietary restriction (DR) is defined as undernutrition without malnutrition. In experimental studies, this means reducing animal diets by a certain percent of calories as compared to ad libitum (AL) but keeping the diet approximately unchanged in total protein, vitamins, and minerals. Caloric restriction is the only experimental manipulation known to retard aging and increase survival of mammals (1). Caloric restriction has been shown to extend mean and maximum life span, decelerate the rate of aging, and inhibit the onset of a number of life-shortening diseases in laboratory animals. The extent to which life span is increased is significant. Mice who were subject to 55-65% DR were found to exhibit 35-65% greater mean and maximal life spans than mice on an unrestricted diet (2).

The objective of many studies has been the causal factors in CR's effect on the rate of aging. CR is believed to reduce oxidative stress, inhibit mitochondrial oxidative damage to DNA, decrease pathologic fat deposition, and prevent carcinogenesis. The specific mechanisms through which CR extends life span and prevents aging are not completely understood. However, through understanding the physiological and molecular changes that CR causes, we can get a more complete picture of how CR produces its beneficial effects.

Oxidative Damage Reduction

9;It is believed that aging is the result of oxidative damage to tissues. The free radical theory of aging predicts that caloric restriction, which extends life span, should reduce oxidative damage. In mammals, the oxidative processes centered in the liver are a major source of free radicals. Antioxidants are produced in the liver to neutralize the effects of free radicals, but these levels have been shown to decrease with age. Because CR has been shown to increase antioxidant production, it is hypothesized that one mechanism through which CR inhibits aging is by limiting oxidative damage. Several studies looked at changes in liver antioxidant levels which in normal ad libitum rats and mice, steadily decreased with age. Rats calorically restricted to 50-60% of AL were able to maintain copper/zinc superoxide dismutase, catalase, cytochrome oxidase, GSH, uric acid, malondialdehyde, and glutathione peroxidase mRNA and activity levels as they got older (3, 4). Mice with CR to 75-80% of AL showed no decrease of manganese-superoxide dismutase or catalase mRNA with age (5). These antioxidant enzymes help protect against oxidative damage in the liver, thus CR maintenance of levels found at youth prevent liver hypertrophy and disease. Antioxidants are known to neutralize the protein, lipid, and DNA damage to cells done by free radicals. It is interesting to note that carbohydrate restriction, but not caloric restriction could not prevent liver antioxidant decline and liver degeneration with age (4).

CR also reduces age-associated fiber loss and change in fiber type composition in skeletal muscle. In old rats, skeletal muscle shows cytochrome c and succinate dehydrogenase activity - indices of skeletal muscle degeneration. The skeletal muscle of CR rats not only

contained significantly fewer numbers of these types of muscle fibers, but also a greater number of skeletal muscle fibers (6). CR also prevents age-associated accrual of oxidative damage to mouse skeletal muscle mitochondria which is believed to be the cause of senescence-related decline in skeletal muscle mass and performance. Mice who were restricted to 40% fewer calories did not experience the oxidative damage to mitochondrial proteins, measured as amounts of protein carbonyls and loss of protein sulfhydryl content that the ad libitum mice did. The ad libitum fed mice also had an increase in rate of superoxide anion radical generation by submitochondrial particles as they got older. However, the CR mice did not show any age related increases in this destructive free radical (7). In both skeletal and cardiac muscle, o,o.-dityrosine, a free radical which contributes to the deterioration of cardiac and skeletal muscle function with advancing age, was found to increase in ad libitum mice, but not in mice restricted calorically to 60% (8). This caloric restriction was also found to extend the average and maximum life span of mice by approximately 40%.

CR also appears to retard oxidative damage to the brain. Senescence has been associated with loss of brain function. One study found that dietary restriction retarded senescence associated decline of sensorimotor coordination and improve the performance of aged mice on an avoidance learning problem. In the normal mouse brain, protein carbonyl concentration, one measure of protein oxidation was found to increase as the mouse aged. This increase in oxidative protein damage is associated with senescence-related functional loss of brain function. CR resulted in the reversal of age-associated regional increases of carbonyl and sulfhydryl concentration, with the largest changes occurring within the striatum (9). Also, CR is found to decrease the transcription of glial fibrillary acidic protein (GFAP), an intermediate filament of astrocytes. GFAP shows increased expression during aging and brain injury as a result of oxidative stress (10). Therefore, CR attenuates the aging process of the brain through changes in brain protein transcription. Many studies looking at different organs - heart, kidneys, liver, and brain - found that the protein carbonyl content, mitochondrial superoxide, and mitochondrial hydrogen peroxide generation increases associated with age cause oxidative damage of cells (11). The levels of these indices of protein and mitochondrial oxidation were unchanged over time in mice with CR. By protecting against the damaging actions of acute oxidative stressors, CR maintains most physiological processes in a youthful state and delays the occurrence and progression of age-associated disease processes.

Hsp70 induction and protection against stress

All living organisms show a reduced ability to respond to stress with increasing age. These stresses can range from hyperthermia, ischemia, to other kinds of physiological and environmental stresses placed on the body. The ability of cells to express heat shock proteins in response to stress is universal to all organisms and is believed to play a critical protective role. The most extensively studied heat shock protein in relation to aging is HSP70. Cells transfected with hsp70 become resistant to injury induced by glucose deprivation and inhibition of mitochondrial respiration, providing direct evidence for a cytoprotective function of hsp70 during metabolic stress (12). The induction of hsp70 expression as well as its nuclear transcription and mRNA expression by stress is reduced

approximately 50% with age in a variety of tissues from rats as well as mononuclear cells from human subjects (13). CR reverses the decline in the induction of hsp70 expression in various organs. In a study of rat hepatocytes, induction of hsp70 synthesis, nuclear transcription, and mRNA levels by heat shock was 40-50% higher in old rats fed with a CA of 60% than old rats fed ad libitum(1). In another study, hsp70 mRNA levels were found to be significantly increased in the stomach and duodenum of aged CR rats compared with ad libitum controls in response to the stress of fasting (14). Because CR has been shown in replication to maintain high HSP70 levels in response to stress even in old age, the cytoprotective actions of CR can be expanded to other organ systems that have not been specifically tested. HSP70 is induced by acidosis in cultured astrocytes and in ischemic brain damage, protecting the brain against many types of injury (15). Hsp70 expression is also induced in the spleen lymphocytes from rats and rhesus monkeys in response to heat stress (16). Across species and organ systems, HSP70 induction, transcription, and mRNA expression decreases with age thus making the body less able to protect itself from environmental or pathological stresses. Maintenance of youthful HSP70 levels as the body ages is a way in which CR preserves the integrity of the body and organs in opposition to aging.

Metabolism

CR has also been shown to affect body and brain metabolism. It was noted that CR rodents had altered neurobehavioral functions, increases in motor activity, serum corticosterone, and a decrease in the basal setpoint for body temperature and brain metabolism (17). These changes strongly suggest that many beneficial effects of CR are controlled by the hypothalamic-pituitary-adrenal axis via hormonal regulation.

Another study showed that CR of 60% caused a three-fold increase in plasma corticosterone levels. Experimentally induced injury to the hind foot pad of the same mice showed that edema was reduced and fell earlier in CR mice (18). Therefore, these results suggest that a CR induces an increase in potentially protective glucocorticoid activity in response to injury.

Age dependent changes in glucose homeostasis are believed to affect aging. CR is believed to lower the nutritionally derived level of insulin exposure and to oppose changes in body metabolism associated with aging. A study comparing the circulating levels of glucose, insulin, C-peptide, and free fatty acids of 60% CR rats with ad libitum rats found that CR rats had 85% less fat pad mass, 15% lower glucose levels, 50-60% lower insulin levels, and a significant decrease in insulin secretion, determined by C-peptide levels (19). Another study found that CR decreased intra-abdominal fat and increased insulin sensitivity. Therefore CR has a marked effect on a pathologic fat depot, a change associated with significant improvement in tissue insulin sensitivity (20). The CR induced changes in body composition is supported by work done on rhesus macaques which found that CR animals have a significant decrease in body weight, total body fat tissue mass, and total body percent fat tissue mass (21). Therefore, by inducing decrease of insulin exposure, CR reduces pathologic body fat, thus opposing the unhealthy effects of adipose accumulation over time.

Cancer Prevention

CR appears to affect aging by inhibiting specific chronic diseases that occur at increasing frequency with age. The maintenance of cell number homeostasis in normal tissues requires a highly regulated balance between the rates of cell proliferation and cell death. With exposure to pathologic conditions, an imbalance in these rates increases risk of carcinogenesis. Apoptotic cell death, as opposed to necrotic cell death eliminates aged, injured, or superfluous cells, maintains this balance, and protects tissues from developing abnormal function or composition. One study established that chronic CR induced an increase in spontaneous apoptotic rate and a decrease in cell proliferation rate in hepatocytes of mice relative to ad libitum fed mice. This diet induced shift in cell death rate was associated with a marked reduction in subsequent development of spontaneous hepatoma and a marked increase in disease-free life span in CR rats (22). Apoptosis reduced the number of putative pre-carcinogenic hepatocytes and thus decreased the risk of permanent genetic error and carcinogenesis. CR, by limiting exposure to endogenous growth factors, altering physiological characteristics, and limiting exposure to food toxicants, inhibits the onset of cancer.

Conclusion

The mechanisms through which CR causes its beneficial effects to the body to prevent aging and increase life-span are far from understood. However, the significant number and reproducibility of experiments correlating CR with a longer, healthier life makes one wonder why we all do not practice some degree of CR. Though there have been no clinical experiments performed on live humans, we would expect that the cross-species mammalian results would be applicable to humans. Reversal of oxidative damage by increasing antioxidant production, pathological stress protection, alteration of pathological fat depositing metabolism, and prevention of cancer are the experimentally supported mechanisms through which CR prevents aging. There are most likely many other CR affecting factors that contribute to senescence retardation. This is an appropriate time for an ethical discussion on CR as applied to humans. Careful considerations must be taken to perform CR studies on humans and the epidemiological implications must be considered if the human population were to increase life-span by 35-60%. However, based on the evidence that CR reduces the incidence of life-threatening disease, it would be a wise suggestion that we all practice moderation in our caloric intake to improve the quality of life.

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