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Reduced energy intake: the secret to a long and healthy life?

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Abstract

Reduced energy intake, or caloric restriction (CR), is known to extend life-span and to retard age-related health decline in a myriad of species, including nematode worms, flies, fish, mice and rats. The exact mechanism whereby CR exerts its life-extending and health-extending effects is unclear. CR however has been shown to improve insulin sensitivity, reduce oxidative stress and alter neuroendocrine responses and central nervous system (CNS) function in animals. In this review article we provide a comprehensive overview of the effects of CR on animal physiology and we discuss some of the potential molecular mechanisms and pathways whereby reduced energy intake can increase health-span and life-span. A better understanding of how energy intake can influence the aging process could lead to new strategies and therapeutics to reduce age-related decline and increase health-span.

The effect of energy consumption on health-span and life-span

Throughout history, numerous societies have recognized the beneficial effects on health and general wellbeing of limiting food intake for certain periods of time, either for religious beliefs or when food was scarce. More than 70 years ago, the first controlled scientific study of energy restricted diets and their ability to extend life-span was published by McCay and colleagues [38]. McCay showed that feeding rats with a diet containing indigestible cellulose significantly extended both the mean and maximum lifespan of these rats. Since then, numerous other studies have confirmed this observation and the results have been extended to many other species, including mice [54,49], fruitflies [8], nematodes [21], water fleas, spiders and fish [54]. Variations of this basic dietary regime are the most effective way of extending life-span of mammals without genetically altering them. Reductions in energy intake of 25–40% below the *ad libitum* energy intake level, are known to increase both the mean and maximum life-span of rats and mice by 25–40%. Maximum extension of life-span (and health-span) has been shown to be achieved when CR is initiated in young, post-pubertal, animals. The amount by which CR extends life-span in rodents depends upon the baseline energy intake of the control *ad libitum* fed animals and on the magnitude of the CR. Life-span extension in mammals has been shown to increase progressively as caloric intake is reduced, until the point of starvation.

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Rodents maintained on reduced energy diets are generally smaller and leaner and they have less body fat and smaller major organs than *ad libitum* fed animals [53]. Animals on CR diets are generally more active, which may relate to the need to search for food [20,34] and the normal age-related decline in physical activity is markedly reduced in CR animals [39]. See Figure 1 for an overview of some of the effects of CR on laboratory animals.

Immune function

Reducing energy intake has been shown to have beneficial effects on the function of the immune system. Data from numerous studies have shown that both reduced energy and reduced meal frequency diets [24] can reduce inflammatory responses, mainly by reducing the production of tumor necrosis factor (TNF) from macrophage cells [51]. Additionally, allergic reactions to some prevalent allergens, such as dust mite antigen, have been shown to be reduced in rodents on energy restricted diets [9]. In general, the effects of mild and moderate reduced caloric intake on the function of the immune system in rodents has been shown to be beneficial. These beneficial effects of CR on immune function include the eradication of infectious agents while limiting overall tissue damage by reducing the inflammatory response.

Cancer

A number of studies of rodents on caloric restricted dietary regimes have indicated that CR can reduce the incidence of spontaneous tumor formation and can also suppress, to some extent, the further growth and development of induced tumors. CR has been shown to suppress the carcinogenic actions of several types of chemical agents in rodents, including polycyclic hydrocarbons, alkylating and methylating agents, and aromatic amines [50,1,4,25,13]. Additionally, CR has been shown to inhibit several types of radiation-induced cancers [18, 19]. CR dietary regimes can attenuate cell proliferation in most tissues studied [31,22,30]. The reduced pace of DNA replication in normal cells in response to CR could make those cells less susceptible to DNA damage (by exposure to carcinogenic agents) and also suppress the uncontrolled proliferation of transformed cells. Additionally, results from a variety of experimental models suggest that CR enhances the rates of apoptosis concomitant with decreases in DNA synthesis, thereby markedly reducing the number and volume of pre-neoplastic lesions [17,23,43]. CR may exert its actions upon tumor cell growth through the modulation of levels of circulating hormones and growth factors. As CR acts in a very broad manner with respect to species, mode of induction and the type of tumor inhibited, it is possible that the modulation of growth factors that act upon many somatic systems may be the crux of the anti-proliferative and pro-apoptotic effects of CR upon tumors. One of these growth factors affected by CR that has been studied extensively is insulin-like growth factor-1 (IGF-1). IGF-1 acts on the majority of somatic cells and tissues to regulate cell growth, development and cell death [45]. It is presently unknown whether a reduced energy regime will have the same beneficial effects on tumor growth and tumor development in humans as it has been shown to have in laboratory rodents.

Non-Insulin dependent diabetes and cardiovascular disease

The risk of developing non-insulin dependent (type 2) diabetes or cardiovascular disease is greatly increased by excessive food intake and obesity. Multiple studies have shown that CR is effective at promoting euglycemia and increasing insulin sensitivity [2,52,55]. A longitudinal study on male rats demonstrated that CR decreased the mean 24-hour plasma glucose concentration by approximately 15 mg/dl and the circulating insulin levels by approximately 50%. Thus, the rats on the CR dietary regime utilized glucose at the same rate as did the rats fed the *ad libitum* diet, despite the lower plasma glucose and insulin levels [36]. Therefore, it has been proposed that the significant effects of CR on circulating levels of glucose and insulin could play a role in the beneficial and life-extending actions of CR.

Atherosclerosis is now widely recognised as an inflammatory disorder [46] and the initiating event in the progression of atherosclerosis is thought to be the development of endothelial dysfunction. Some of the potential causative factors of endothelial dysfunction and atherosclerosis include the generation of free radicals, increased circulating levels of oxidatively modified LDL, hypertension, diabetes and elevated circulating levels of homocysteine. A recent study in humans showed that long-term CR can reduce the risk of atherosclerosis [15]. Reduced energy intake has been shown to decrease blood pressure in obese humans, and CR is also associated with a decrease in plasma norepinephrine levels, decreased excretion of catecholamines and evidence of diminished sympathetic activity [26, 27].

Neurodegenerative disorders

Accumulating evidence suggests that dietary energy intake can affect both cognitive performance and neuronal health. Similarly to other organ systems in the body, brain cells encounter a cumulative burden of oxidative stress and metabolic stress that may be a universal feature of the aging process. Increased levels of oxidative stress and damage can be found in each of the major classes of cellular molecules, including proteins, lipids and nucleic acids. Some oxidative modifications of proteins that have been observed in neuronal cells during aging include carbonyl formation [6,7,12] covalent modifications of cysteine, lysine and histidine residues by the lipid peroxidation product 4-hydroxynonenal [42], nitration of proteins on tyrosine residues [47], and glycation [41]. Additionally, a common oxidative modification of DNA that is observed during brain aging is the formation of 8-hydroxydeoxyguanosine [48]. Each of these modifications of proteins, lipids and nucleic acids are also exacerbated in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). Dietary regimes whereby caloric intake is reduced have been shown to ameliorate and attenuate neuronal damage and to improve functional outcome in animal models of neurodegenerative disorders, such as Huntington's disease (HD) and PD [11,10]. The exact mechanism whereby reduced energy intake offers neuronal protection and improved functional outcome in neurodegenerative disorders is unclear. Some of the potential mechanisms include increased resistance to oxidative, metabolic and excitotoxic insults, the upregulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) and the upregulation of heat shock proteins such as heat-shock protein-70 (HSP-70) and glucose-regulated protein-78 (GRP-78) [32,56, 11,10].

Potential molecular mechanisms of caloric restriction

The acquisition of food and energy sources is one of the most important and vital behavioral traits and therefore the removal or limitation of food and energy sources will cause a certain degree of physiological and emotional stress in the organism. The exact mechanisms whereby a dietary regime of reduced caloric intake can increase both health-and life-span are presently still unclear. A vast array of potential mechanisms are thought to be involved in the beneficial actions of CR and these include: alteration in stress responses (*i.e*. CR can induce a mild stress response, presumably due to reduced glucose availability, which protects cells from oxidative stress and excitotoxic insults), increased formation of ketone bodies, alterations in glucose and insulin signalling, alterations in cytokine signalling and immune function, alterations in satiety and adipose-generated hormones, sirtuin signalling, peroxisome proliferators-activated receptor (PPAR) signalling, and FoxO transcription factor activation and signalling [for review see 33].

Adverse effects of caloric restriction

Although CR can increase life-span and reduce the incidence of many major diseases, several adverse consequences of CR have been reported. Wound healing is impaired in rats maintained on a CR diet, which is associated with decreased collagen production by skin cells [44]. Some aspects of immune function may also be compromised by CR. For example, the ability of deer mice to generate an immune response on re-exposure to an antigen (immunological memory) was impaired when they were maintained on a CR diet [35]. In another study it was shown that CR increases the mortality of old mice caused by exposure to influenza virus [16].

Thus, while CR improves the function and longevity of most tissues and organs, there are some exceptions. Interestingly, even different subpopulations of cells within a tissue can be differentially affected by CR. For example, many types of neurons within the brain are positively affected by CR in ways that may increase their resistance to Alzheimer's, Parkinson's and Huntington's disease [33]. However, motor neurons in the spinal cord may be adversely affected by CR in ways that increase their vulnerability to amyotrophic lateral sclerosis [37]. Finally, there is considerable evidence that CR can impact negatively on reproductive and neuroendocrine systems of females. Thus, females subjected to CR can develop amenorrhea and may greatly increase their spontaneous exercise resulting in anorexia nervosa [14,34]. A better understanding of how the magnitude of CR, including meal size and frequency, impact on specific cell types and organ systems will be necessary to develop specific CR regimes that are tailored for individuals depending upon their age, sex and activity level.

Caloric restriction in humans – Would it work and is it feasible?

In humans, overeating promotes disease in multiple organs systems (for example, type 2 diabetes and cardiovascular disease) and is known to shorten both life-span and health-span. In the United States, overeating and obesity is now considered a leading cause of morbidity and mortality [3,5]. Obesity is a public health and policy problem because of its prevalence, costs and burdens and the prevalence of obesity has been continually rising throughout the world. Caloric restriction reduces disease risk in overweight individuals and could potentially also have beneficial effects in individuals with a normal, healthy bodyweight. Presently, it seems unlikely that we will ever establish with certainty whether CR increases maximum life-span in humans. Additionally, the form of CR that might work best in humans is also unknown and perhaps short-term fasts might be easier than the continuous daily grind of CR. Multiple studies are underway to determine whether CR would be beneficial in primates. There are currently two major studies of CR in Rhesus monkeys (non-human primates) in progress, one at the University of Wisconsin at Madison and the other at the National Institute on Aging's Intramural Research Program that could, within the next 15–20 years, determine whether CR indeed increases maximum life-span in non-human primates. Data collected from these two important studies have shown that CR offers protection against the development of insulin resistance and type 2 diabetes, reduces the risk of developing atherosclerosis and cardiovascular disease, reduces circulating levels of triidothyronine, lowers metabolic rate and core body temperature, reduces oxidative stress and damage, lowers circulating levels of IGF-1 and IL6, and improves overall immune function [40,28,29,57].

One caveat that needs to be taken into account when examining data from CR studies is that the majority of energy restricted animals are compared to *ad libitum* fed animals. Laboratory rats and mice that are fed *ad libitum* amounts of standard rodent food tend to overeat and become overweight or obese. Additionally laboratory animals experience a lack of both mental and physical activity. Hence, it is not entirely surprising that an animal that has a lower body weight and exerts more physical and mental activity (as animals will attempt to search for food in their home cage) has a longer health- and lifespan than an overweight *ad libitum* fed

laboratory animal. It still remains unclear whether reducing energy intake in an animal that already has a healthy bodyweight and sufficient amounts of physical and mental activity will increase its health- and maximum life-span. This remains an important issue to be addressed by the current CR research community.

Another factor to consider with the direct translation of a CR dietary regime from laboratory rodents to humans is compliance. Adhering to a CR dietary regime, such as a 20% or 40% decrease in overall caloric intake, would require major dietary and lifestyle changes. These changes might not be practical in the high-stress, fast-paced environment that we live in today. Considering that the incidence of obesity is rapidly increasing in both industrialized and developing nations, it remains to be seen whether many people would be able to comply with such a strict dietary regime as 20% or 40% CR. Perhaps by encouraging healthy eating and physical and mental activity by providing wide-spread access to healthy eating education programs, low-cost and readily available healthy and nutritious food, and sufficient time for daily physical activity and exercise, we could potentially increase health-span and reduce the risk of diseases, such as type 2 diabetes, dietary related cancers and cardiovascular disease, significantly more so in a larger number of people than any strict caloric restriction or energy restriction dietary regime would be able to do.

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References

1. Andreou KK, Morgan PR. Effect of dietary restriction on induced hamster cheek pouch carcinogenesis. Arch Oral Biol 1981;26:525–31. [PubMed: 6797392]
2. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci USA 2003;100:6216–20. [PubMed: 12724520]
3. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002;3:565–74. [PubMed: 12217794]
4. Boissonneault GA, Elson CE, Pariza MW. Net energy effects of dietary fat on chemically induced mammary carcinogenesis in F344 rats. J Natl Cancer Inst 1986;76:335–38. [PubMed: 3080637]
5. Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab 2004;89:2583–89. [PubMed: 15181027]
6. Butterfield DA, Howard BJ, Yatin S, Allen KL, Carney JM. Free radical oxidation of brain proteins in accelerated senescence and its modulation by N-tert-butyl-alpha-phenylnitrone. Proc Natl Acad Sci USA 1997;94:674–78. [PubMed: 9012843]
7. Cakatay U, Telci A, Kayali R, Tekeli F, Akcay T, Sivas A. Relation of oxidative protein damage and nitrotyrosine levels in the aging rat brain. Exp Gerontol 2001;36:221–29. [PubMed: 11226738]
8. Chapman T, Partridge L. Female fitness in Drosophila melanogaster and interaction between the effect of nutrition and of encounter rate with males. Proc R Soc Lond Ser B Biol Sci 1996;263:755–59.
9. Dong W, Kari FW, Selgrade MK, Gilmour MI. Attenuated allergic responses to house dust mite antigen in feedrestricted rats. Environ Health Perspect 2000;108:1125–31. [PubMed: 11133391]
10. Duan W, Guo Z, Jiang H, Ware M, Li XJ, Mattson MP. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc Natl Acad Sci USA 2003;100:2911–16. [PubMed: 12589027]
11. Duan W, Mattson MP. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. J Neurosci Res 1999;57:195–206. [PubMed: 10398297]
12. Dubey A, Forster MJ, Lal H, Sohal RS. Effect of age and caloric intake on protein oxidation in different brain regions and on behavioral functions of the mouse. Arch Biochem Biophys 1996;333:189–97. [PubMed: 8806770]

13. Dunn SE, Kari FW, French J, et al. Dietary restriction reduces insulin like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. Cancer Res 1997;57:4667–72. [PubMed: 9354418]

14. Exner C, Hebebrand J, Remschmidt H, Wewetzer C, Ziegler A, Herpertz S, Schweiger U, Blum WF, Preibisch G, Heldmaier G, Klingenspor M. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Mol Psychiatry 2000;5:476–81. [PubMed: 11032380]

15. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci USA 2004;101:6659–63. [PubMed: 15096581]

16. Gardner EM. Caloric restriction decreases survival of aged mice in response to primary influenza infection. J Gerontol A Biol Sci Med Sci 2005;60:688–94. [PubMed: 15983169]

17. Grasl-Kraupp B, Bursch W, Ruttkay-Nedecky B, et al. Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. Proc Natl Acad Sci USA 1994;91:9995–99. [PubMed: 7937932]

18. Gross L, Dreyfuss Y. Reduction in the incidence of radiation-induced tumors in rats after restriction of food intake. Proc Natl Acad Sci USA 1984;81:7596–98. [PubMed: 6594701]

19. Gross L, Dreyfuss Y. Prevention of spontaneous and radiation-induced tumors in rats by reduction of food intake. Proc Natl Acad Sci USA 1990;87:6795– 97. [PubMed: 2395873]

20. Hart RW, Turturro A. Evolution and dietary restriction. Exp Gerontol 1998;33:53–60. [PubMed: 9467716]

21. Houthoofd K, Braeckman BP, Lenaerts I, Brys K, De Vreese A, Van Eygen S, Vanfleteren JR. Axonic growth up-regulates mass-specific metabolic rate, stress resistance, and extends life-span in Caenorhabditis elegans. Exp Gerontol 2002;37:1371–78. [PubMed: 12559406]

22. Hursting SD, Perkins SN, Phang JM. Calorie restriction delays spontaneous tumorigenesis in p53-knockout transgenic mice. Proc Natl Acad Sci USA 1994;91:7036–40. [PubMed: 8041741]

23. James SJ, Muskhelishvili L. Rates of apoptosis and proliferation vary with caloric intake and may influence incidence of spontaneous hepatoma in C57BL/6 × C3H F1 mice. Cancer Res 1994;54:5508–10. [PubMed: 7923185]

24. Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, Dixit VD, Pearson M, Nassar M, Tellejohan R, Maudsley S, Carlson O, John S, Laub DR, Mattson MP. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med 2007;42:665–74. [PubMed: 17291990]

25. Lagopoulos L, Stalder R. The influence of food intake on the development of diethylnitrosamine-induced liver tumours in mice. Carcinogenesis 1987;8:33–37. [PubMed: 3802392]

26. Landsberg, L.; Young, JB. Diet-induced changes in sympathetic nervous system activity. In: Bassett, EG., editor. Nutritional factors: modulating effects on metabolic processes. New York: Raven Press; 1981. p. 155-74.

27. Landsberg L, Young JB. The role of the sympathetic nervous system and catecholamines in the regulation of energy metabolism. Am J Clin Nutr 1983;38:1018–24. [PubMed: 6359855]

28. Lane MA, Baer DJ, Rumpler WV, Weindruch R, Ingram DK, Tilmont EM, Cutler RG, Roth GS. Calorie restriction lowers body temperature in rhesus monkeys, consistent with a postulated anti-aging mechanism in rodents. Proc Natl Acad Sci USA 1996;93:4159–64. [PubMed: 8633033]

29. Lane MA, Ingram DK, Roth GS. Calorie restriction in nonhuman primates: effects on diabetes and cardiovascular disease risk. Toxicol Sci 1999;52:41–48. [PubMed: 10630589]

30. Lev-Ran A. Mitogenic factors accelerate later-age diseases: insulin as a paradigm. Mech Ageing Dev 1998;102:95–113. [PubMed: 9663795]

31. Lok E, Nera EA, Iverson F, et al. Dietary restriction, cell proliferation and carcinogenesis: a preliminary study. Cancer Lett 1998;38:249–55. [PubMed: 3349445]

32. Lowenstein DH, Chan PH, Miles MF. The stress protein response in cultured neurons: characterization and evidence for a protective role in excitotoxicity. Neuron 1991;7:1053–60. [PubMed: 1764242]

33. Martin B, Mattson MP, Maudsley S. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. Ageing Res Rev 2006;5:332–53. [PubMed: 16899414]

34. Martin B, Pearson M, Kebejian L, Golden E, Keselman A, Bender M, Carlson O, Egan J, Ladenheim B, Cadet JL, Becker KG, Wood W, Duffy K, Vinayakumar P, Maudsley S, Mattson MP. Sex-

Dependent Metabolic, Neuroendocrine and Cognitive Responses to Dietary Energy Restriction and Excess. Endocrinology. 2007Epub ahead of print

35. Martin LB 2nd, Navara KJ, Weil ZM, Nelson RJ. Immunological memory is compromised by food restriction in deer mice Peromyscus maniculatus. Am J Physiol Regul Integr Comp Physiol 2007;292:R316–320. [PubMed: 16902185]
36. Masoro EJ, McCarter RJM, Katz MS, McMahan CA. Dietary restriction alters the characteristics of glucose fuel use. J Gerontol Biol Sci 1992;47:B202–208.
37. Mattson MP, Cutler RG, Camandola S. Energy intake and amyotrophic lateral sclerosis. Neuromolecular Med 2007;9:17–20. [PubMed: 17114821]
38. McCay CM, Crowell MF, Maynard LA. The effect of retarded growth upon the length of life-span and upon the ultimate body size. J Nutr 1935;10:63–79.
39. Means LW, Higgins JL, Fernandez TJ. Midlife onset of dietary restriction extends life and prolongs cognitive-functioning. Physiol Behav 1993;54:503–508. [PubMed: 8415944]
40. Messaoudi I, Warner J, Fischer M, Park B, Hill B, Mattison J, Lane MA, Roth GS, Ingram DK, Picker LJ, Douek DC, Mori M, Nikolich-Zugich J. Delay of T cell senescence by caloric restriction in aged long-lived nonhuman primates. Proc Natl Acad Sci USA 2006;103:19448–453. [PubMed: 17159149]
41. Munch G, Thome J, Foley P, Schinzel R, Riederer P. Advanced glycation end products in ageing and Alzheimer's disease. Brain Res Rev 2000;23:134–43. [PubMed: 9063589]
42. Papaioannou N, Tooten PC, van Ederen AM, Bohl JR, Rofina J, Tsangaris T, Gruys E. Immunohistochemical investigation of the brain of aged dogs. I. Detection of neurofibrillary tangles and of 4-hydroxynonenal protein, an oxidative damage product, in senile plaques. Amyloid 2001;8:11–21. [PubMed: 11293821]
43. Poetschke HL, Klug DB, Perkins SN, et al. Effects of calorie restriction on thymocyte growth, death and maturation. Carcinogenesis 2000;21:1959–64. [PubMed: 11062154]
44. Reiser K, McGee C, Rucker R, McDonald R. Effects of aging and caloric restriction on extracellular matrix biosynthesis in a model of injury repair in rats. J Gerontol A Biol Sci Med Sci 1995;50A:B40–47. [PubMed: 7814778]
45. Resnicoff M, Abraham D, Yutanawiboonchai W, et al. The insulin-like growth factor I receptor protects tumor cells from apoptosis in vivo. Cancer Res 1995;55:2463–69. [PubMed: 7758000]
46. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–26. [PubMed: 9887164]
47. Sloane JA, Hollander W, Moss MB, Rosene DL, Abraham CR. Increased microglial activation and protein nitration in white matter of the aging monkey. Neurobiol Aging 1999;20:395–405. [PubMed: 10604432]
48. Sohal RS, Agarwal S, Candas M, Forster MJ, Lal H. Effect of age and caloric restriction on DNA oxidative damage in different tissues of C57BL/6 mice. Mech Ageing Dev 1994;76:215–224. [PubMed: 7885066]
49. Sprott RL. Diet and calorie restriction. Exp Gerontol 1997;32:205–214. [PubMed: 9088917]
50. Tannenbaum A. The genesis and growth of tumors. II. Effects of caloric restriction per se. Cancer Res 1942;2:57–70.
51. Vega VL, De Cabo R, De Maio A. Age and caloric restriction diets are confounding factors that modify the response to lipopolysaccharide by peritoneal macrophages in C57BL/6 mice. Shock 2004;22:248–53. [PubMed: 15316395]
52. Wang ZO, Bell-Farrow AD, Sonntag W, Cefalu WT. Effect of age and caloric restriction on insulin receptor binding and glucose transporter levels in aging rats. Exp Gerontol 1997;32:671–84. [PubMed: 9785093]
53. Weindruch R, Sohal RS. Seminars in medicine of the Beth Israel Deaconess Medical Center: caloric intake and aging. N Engl J Med 1997;337:986–94. [PubMed: 9309105]
54. Weindruch, R.; Walford, RL. The Retardation of Aging and Disease by Dietary Restriction. Thomas Charles, C., editor. Springfield; IL: 1988. 1998
55. Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. Diabetes Care 1994;17:30–36. [PubMed: 8112186]

56. Yu ZF, Mattson MP. Dietary restriction and 2-deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. J Neurosci Res 1999;57:830–839. [PubMed: 10467254]

57. Zainal TA, Oberley TD, Allison DB, Szweda LI, Weindruch R. Caloric restriction of rhesus monkeys lowers oxidative damage in skeletal muscle. FASEB J 2000;14:1825–36. [PubMed: 10973932]

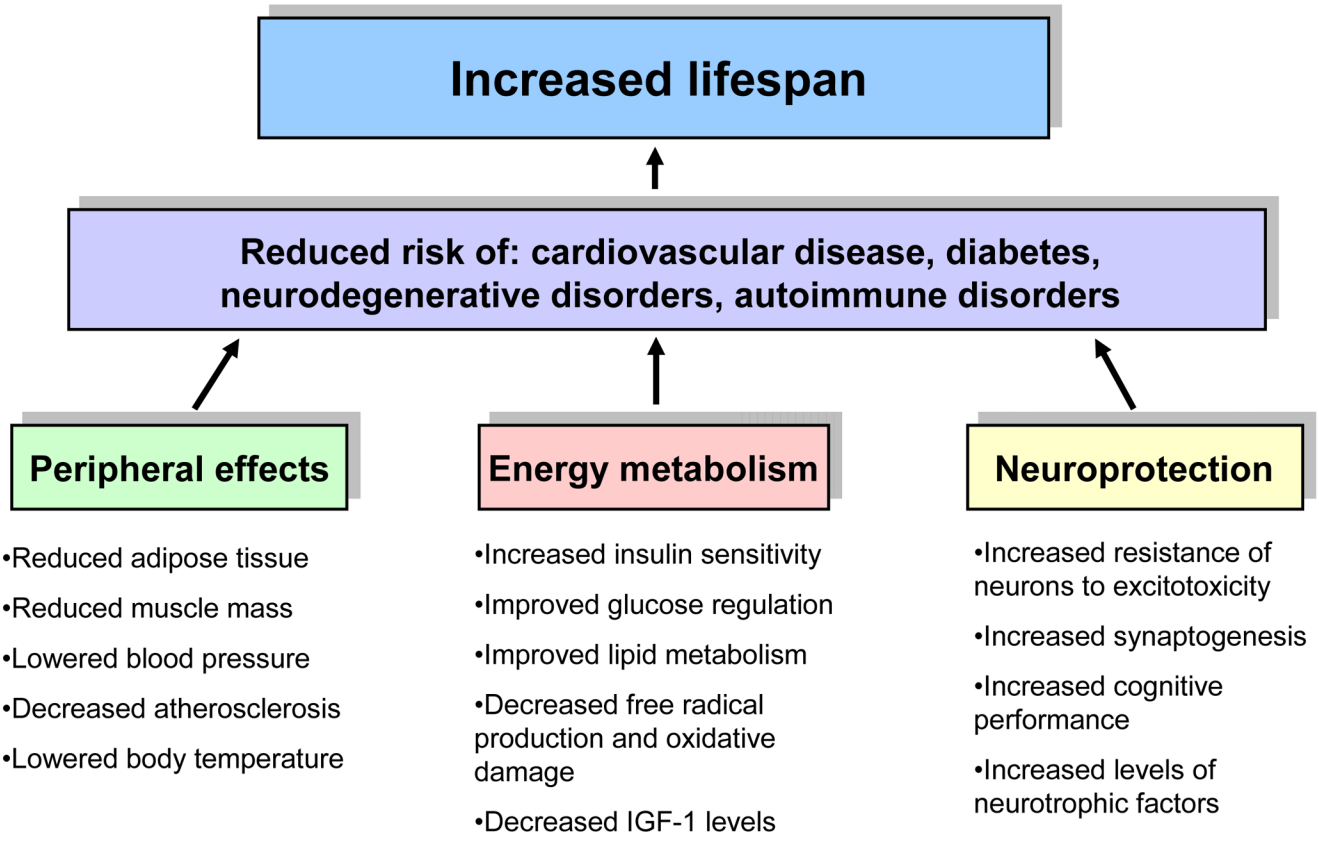

Figure 1.
Some of the physiological changes associated with energy restriction in mammals.