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OPINION

Health span extension by later-life caloric or dietary restriction: a view based on rodent studies

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Abstract In spite of the potential benefit of lifelong food restriction to retard aging and extend life span, it is unrealistic in human. The restriction late in life may be more practical. There are, however, only limited studies on the effect of late onset caloric or dietary restriction. We and other investigators have shown that the late life restriction rejuvenates some parameters that decline with age in rats and mice. Although such studies may provide a basis for human application of late-life caloric or dietary restriction, the prolongation of maximum life span would not be expected in view of the current status of the long-lived population in which maximum life span potential appears to have already been achieved. The late life caloric restriction, however, could extend the health span if the extent were appropriate.

Keywords Caloric restriction · Dietary restriction · Late life · Health span · Longevity · Rodent · Human

Introduction

Caloric restriction (CR) or dietary restriction (DR) has been well recognized as a robust non-genetic means to extend mean and/or maximum life span of a variety of animal species in a wide range of taxa from yeast, water flea, fish, nematode, insect and rodents as well as monkey (Weindruch 1996). It is therefore conceivable that CR/DR interferes in general or ''public'' mechanisms of biological aging or life maintenance processes that are common to these organisms although the definition of aging is not necessarily the same in all models. Studies on the mechanisms of anti-aging effects of CR/DR may thus shed light on basic mechanisms of aging (Masoro 2000; Sinclair 2005). Many studies on aging and CR/DR have been conducted on laboratory rodents that appear to provide more information that may be translated into human compared with studies on non-mammalian models. In a majority of previous studies CR/DR was initiated soon after weaning or early in life, in which animals are generally fed 30–40% less food than ad libitum feeding for life. Numerous studies have reported that such regimen retards age-associated harmful or potentially harmful changes (Masoro 2003), resulting in extension of both mean and maximum life spans since McCay reported the seminal paper 70 years ago (McCay et al. 1935).

Beneficial effects of CR/DR late in life in rodents

Weindruch and Walford (1982) were the first to show convincingly that late life CR initiated at 12 months of age can reduce tumorigenesis associated

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with advancing age and extend life span in mice, albeit to a lesser extent than in lifelong CR. Studies on late life CR/DR have been limited since then, however, perhaps because the life span extension by the late life regimen is not as remarkable as that by lifelong CR.

In view of difficulties of practicing significant CR/DR from childhood or adolescence in human even if such life style would be proved beneficial for later life, studies on late life CR in rodents that could provide the basis for possible human application for better quality of life appear of value although life span extension would be limited if any. We have, therefore, conducted studies on late life DR in mice and rats in protein and protein metabolism as well as DNA and DNA repair, focusing on oxidative mechanisms of these macromolecules, starting the regimen from ages of about 23–28 months in mice and rats, which may be roughly equivalent to 60–70 years of age in human. Two-months of DR (daily feeding of 60% of ad libitum consumption of food) in mice reduced accumulation of altered enzymes in the brain and liver of 23.5 month-old mice to the level of young (11 month-old) animals (Takahashi and Goto 1987). Half-lives of proteins were extended in hepatocytes in primary culture of ad libitum fed old mice but were shortened to the young level in the cells of the old animals (23 month-old) after about 2 months of DR (Ishigami and Goto 1990). In rats subjected to DR (every-other-day feeding) from 26.5 to 30 months of age, the proteasome activity of the liver that declines with age was increased to the level of ad libitum fed young animals (10 month-old), suggesting that the upregulation of this activity is responsible for the reduction of altered proteins and increase in protein turnover by DR in old animals described above (Goto et al. 2001, 2002). The reduction of protein carbonylation and increase in proteasome activity were also observed in the skeletal muscle and tendon in these animals (Radak et al. 2002). The mitochondrial protein carbonyls were reduced in rat livers by the late onset DR (Nagai et al. 2000). Additionally, DR can partially restore impaired metabolism of apolipoprotein A-IV and C-III in aged mice so that lipoprotein lipase is likely upregulated to promote lipid immobilization, suggesting improvement of reduced lipid metabolism (Araki and Goto 2004). More recently, the carbonylation of rat liver histones that is paradoxically decreased in old rats increased to the young level by DR from the age of 28–30 months (Sharma et al. 2006). Biological significance of this finding is not clear but it could have implication in age-related reduction in transcription and repair activities since decreased carbonylation of basic histones likely augments histone–DNA interaction thus suppressing the gene functions. We also found that oxidative modification to nuclear DNA can be significantly reduced by 2 months of DR in late life with concomitant reduction of the repair enzyme (OGG1) activity, probably due to adaptation to the reduced damage (our unpublished results). CR regimen in rats during 1 year starting at 24 months of age is reported to reduce brain mitochondrial H_2O_2 production by 24% and oxidative damage to the mitochondrial DNA by 23% compared with unrestricted counterparts (Sanz et al. 2005). Spindler's group has reported that 8 weeks of CR initiated at 19 months of age reduced incidence of liver and other tumors, resulting in a significant average and maximum life span extension in mice (Spindler 2005). They also reported that the regimen caused similar changes of hepatic gene expression as seen in lifelong CR (Dhahbi et al. 2004).

All these findings suggest that DR initiated even late in life can restore youthful cellular functions, thus possibly promoting quality of life.

Could CR/DR extend maximum human life span?

Human life span or longevity is obviously not limited directly as a result of biological aging but mostly by diseases, famine and injuries. The situation is different from life span or longevity limitation in laboratory animals in which causes of death are usually unclear. In industrialized societies, diseases due to both genetic and environmental factors are major determinants of the life span although biological aging surely affects increased susceptibility to diseases in old age. The heritability of life span in a species is reported to be some 20–30%, the rest being environmental factors and chance in human as well as in experimental animals (Finch and Tanzi 1997). This estimation, however, cannot be applied to the contribution of genes to the rate of biological aging. It is therefore not unexpected to find that elimination of major causes of death such as cancer, cardiovascular

diseases and stroke in elderly people in industrialized countries would not dramatically increase the maximum life expectancy, although it is true that average life span has increased tremendously in the last half century mainly by virtue of the development of medical care and general hygienic improvement that have greatly reduced death from major diseases.

In Japan, for example, where average life expectancy at birth in 2005 is 78.64 and 85.59 years for male and female, respectively, having increased from 63.60 to 67.75 in 1955, that of 65 year-old male and female in 2005 would increase by 3.18 and 2.08 years to 18.21 and 23.28 years, respectively, if cancer could be cured or prevented, and only 1.21 and 1.62 years for cardiovascular diseases and 0.99 and 1.26 years for cerebrovascular diseases (Ministry of Health, Labor and Welfare, Japan 2004). These estimates suggest that modern development of medicine and public health care has already achieved major life span extension in developed countries. In rodents CR/DR reduces cancer incidence that is a leading cause of death and hence its reduction is a major factor in life span extension (Weindruch 1992; Hursting et al. 1994). This should not, however, be the case in human since the elimination of cancer would not extend longevity remarkably as described above. One prediction of human maximum life span potential based on statistics of over 20,000 Japanese centenarians is about 115 and 122 years for male and female, respectively (Gondo 2002). The maximum life span potential is longer than those based on statistics of the whole population, consistent with the view that the mortality rate decelerates in the very old population (Vaupel et al. 1998). Assuming that the estimated maximum life span potential noted above is the limit of human life span, it is unlikely that the life span increases further in human by CR/DR because the average daily energy supply per person in Japan (2761 kcal) has been 17% lower than the average value of developed countries (3314 kcal), and 27% less than that in the US (3774 kcal) in particular (FAOSTAT 2002). This suggests that the caloric intake has already been ''restricted'' to some extent in Japan where the world's longest average life span has been attained, if we assume the energy supply per person parallels caloric intake. In fact, available data on caloric intake show that it has not changed since 1950 or even somewhat reduced in recent years in Japan (Shibata 2002, and his personal communication). Lowering caloric intake has been proven to reduce the risk of atherosclerosis and inflammation and thus decrease the incidence of cardiovascular diseases and cancer in western countries where obesity is an epidemic problem (Walford et al. 2002; Fontana et al. 2004). It is therefore reasonable for Westerners to expect lowering of the incidence of diseases such as atherosclerosis and type II diabetes by CR/DR but perhaps not for Japanese and other people in some Asian countries where the energy supply is already substantially lower. I would therefore argue that CR/DR will not extend maximum life span but possibly prolong health span with better quality of life by reducing the risk of age-related diseases and thereby increasing mean life span, apart from the potential risk of diseases such as sarcopenia and osteoporosis.

Conclusions

It appears that the maximum life span is reaching its limit in industrialized countries in view of the prediction from maximum attainable age of centenarians. In Okinawa prefecture where the average life span at birth was the longest in Japan at least until recently the calorie intake is substantially lower than mainland Japan. Nevertheless, the maximum life span of the centenarians has never been over 116, the longest documented record of Japanese centenarians. It is therefore unlikely that the maximum life span will increase further by DR/CR in human as it is in the case of rodents.

In view of rodent studies showing that CR/DR initiated late in life equivalent to 60–70 years in human is beneficial in ''rejuvenating'' a variety of parameters such as protein damage and turnover, and DNA repair, it may be possible that the same is true for human elderly in increasing health span but perhaps not extending maximum life span by stopping eating before you feel full, say, a little bit less than the satisfactory amount—as an old Japanese proverb says: ''hara (=stomach) hachibu (=80%)''.

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