The Evolution of the Antiaging Action of Dietary Restriction: A Hypothesis

Edward J. Masoro¹ and Steven N. Austad²

¹Aging Research and Education Center, University of Texas Health Science Center, San Antonio.
²Department of Biological Sciences, University of Idaho.

Reducing the intake of dietary energy by laboratory rodents to well below that of animals allowed to eat ad libitum slows the rate of aging. This phenomenon, which is robust and reproducible, is known as the antiaging action of dietary restriction (DR). We hypothesize that this DR response arose because of its evolutionary advantage with respect to survival during periods of unpredictable, short-term food shortage. In our evolutionary scenario, food shortage led to an adaptive redirection of resources away from reproduction toward somatic maintenance via an enhanced heat shock protein response and/or invertebrates. In vertebrates, an additional involvement of the hypothalamic–adenohypophysial–adrenal glucocorticoid system was necessitated to protect against excessive systemic defense responses. We suggest several general implications of our hypothesis.

Restricting the food intake by laboratory mice and rats by 20 to 60% below that eaten by ad libitum-fed animals increases the mean and maximum life span of these rodent populations (Weindruch and Walford, 1988). This dietary manipulation also slows the postmaturational rate of increase in age-specific mortality resulting in a marked increase in the mortality rate doubling time of the population (Masoro, 1995). In addition to its effects on mortality, restricting food intake also maintains the physiological processes in a youthful state (Yu, 1995) and retards many (most) age-associated disease processes in a variety of mouse and rat strains (Masoro, 1993). Notably, these phenomena, which are often referred to by gerontologists as the antiaging action of dietary restriction (DR), are primarily due to a reduction in the intake of energy (calories) rather than of a specific nutrient or adventitious contaminant (Masoro, 1988) and occur without a reduction in mass-specific metabolic rate or level of physical activity (McCarter and Palmer, 1992).

Evolutionary Considerations

A question arises as to whether the slowing of aging by DR has an adaptive evolutionary basis. Harrison and Archer (1988) suggested that the antiaging response to DR evolved because of the selective advantages of the slowing of the reproductive aging of females during DR. They envisioned the periodic lack of food availability in nature as commonplace due to drought and other environmental fluctuations and postulated great selective advantage for those genotypes still capable of reproduction when food again became available. However, Phelan and Austad (1989) challenged this line of reasoning on the grounds that reproductive senescence is largely irrelevant to life in the wild because it is rare to find postreproductive individuals in nature. Holliday (1989) also proposed that the antiaging action of DR evolved in nature in response to periods of scant food supply but explained its evolution in terms of the Disposable Soma Theory of Aging (Kirkwood, 1990). Holliday pointed out that DR increases life span but decreases fecundity and suggested that the reduction in reproduction enables the animals to invest resources in the maintenance of the adult body. As a result, there is an increase in the probability to produce viable offspring during an extended life span, an evolutionary adaptation.

We wish to propose a view of the antiaging action of DR which embraces and expands the view of Holliday. Our view is also based on the likelihood of unpredictable periods of food scarcity in the wild. We further propose that fitness, in the form of increased survival, during unpredictable short-term food shortages will be enhanced in individuals with genomes that direct resources away from reproduction, thereby providing additional resources for successfully coping with environmental challenges (stressors). Thus, individuals with genomes of this sort are more likely to survive a period of food shortage and reproduce when food is once again abundant — clearly a selective advantage — than individuals with less plastic genomes.

Periodic episodes of food shortage and abundance are ubiquitous in nature, and animals have evolved a well-known variety of physiological tactics usually involving selective inactivity, such as seasonal reproductive cessation, and/or short- or long-term torpor or hibernation for managing predictable shortages associated with annual weather patterns. We focus here on physiological adaptation to more unpredictable, short-term (i.e., other than seasonal) food shortages during times of typical food abundance. An evolutionary advantage would presumably accrue to individuals with genomes that allowed rapid and reversible alterations in reproduction and the ability to manage environmental stress in response to these shortages without becoming physically inactive. Remaining physically active during these periods would facilitate the finding of new, richer feeding areas and/or the potential to take immediate reproductive advantage of a new flush of resources in the immediate area.

That these sorts of shortages frequently occur is demonstrated by field experiments in which supplemental food is
provided to wild populations. Food supplementation increased reproduction by some measure (larger litters and/or longer breeding season and/or higher proportion of females breeding) in 91% (of 35) experiments with birds and small mammals (Boutin, 1990) and typically increases reproduction in primates as well (Asquith, 1989). These experiments are not similarly informative with respect to the effects of food abundance on survival potential (defined as the probability of survival under standardized conditions), because food shortage in nature is likely to lead to increased risk-taking behavior (e.g., exposure to predators, intraspecific aggression, infectious disease, willingness to sample novel, potentially toxic, food items) while foraging.

How does this concept link to the antiaging action of DR? Before addressing this question, our view of the nature of aging and its general cause should be presented. By aging we are not merely referring to the passage of time but also to the deterioration of the organism (i.e., senescence), which underlies the decreasing ability to survive as chronological age increases. We envision the basis of this deterioration to be the many harmful processes which occur during life; some are intrinsic to living processes, such as the damaging substances generated during oxidative metabolism; others are of extrinsic origin, such as the action of toxic substances in food and damage caused by infectious agents. Aging occurs because protective and repair processes are not fully able to prevent the progressive accumulation of damage with increasing chronological age. Although, in our view, the antiaging action of DR evolved to protect rodents against acute challenges (stressors) during periods of food shortage, in the laboratory setting these same mechanisms protect against the long-term, low intensity harmful processes that cause aging and thus are considered to be (and indeed they are) antiaging processes.

Is there evidence that DR protects laboratory rodents against damage from acute stressors? Several studies indicate that such is the case. DR has been found to protect male F344 rats, both young and old, from the damage caused by the surgical implantation of jugular canulae (Masoro, 1994); specifically, dietary restricted rats lose a much lower percentage of body weight during the 48 hours following this surgical procedure than ad libitum-fed rats. Klebanov et al. (1995) reported that foot pad edema in response to carrageenan injection, an inflammatory response, is delayed and of shorter duration in dietary restricted compared to ad libitum-fed young BALB/C mice. Heydari et al. (1993) have shown that the ability of 20-month-old male F344 rats to survive an acute increase in environmental temperature is markedly enhanced by DR. Duffy et al. (1995) have shown that DR protects rats from the damaging action of toxic drugs.

**Role of Glucocorticoid System**

By what mechanism does DR protect rodents against stressors? The glucocorticoid system is known to broadly enable mammals to successfully cope with a variety of damaging challenges (Munck et al., 1984). Is there evidence that the glucocorticoid system is influenced by DR? Sabatino et al. (1991) measured the diurnal pattern of plasma corticosterone levels in ad libitum-fed and dietary restricted male F344 rats in a life-span longitudinal study. They also measured plasma levels of corticosteroid-binding globulin, hereby enabling estimation of plasma concentrations of free corticosterone, the biologically active fraction of the circulating hormone (Mendel, 1989). Although the early morning levels of plasma free corticosterone were nondetectable in both ad libitum-fed and dietary restricted rats, the afternoon peak levels were greater in dietary restricted rats throughout the life span, ranging from two- to eightfold higher. This elevation of free levels has recently been confirmed by the direct measure of plasma free corticosterone by centrifugal ultrafiltration (Nelson, 1994a). Also, suggestive evidence that plasma free corticosterone levels may be elevated in rats and mice by DR has been published earlier by several investigators (Armario et al., 1987; Stewart et al., 1988; Filteau et al., 1992).

Is this daily period of elevated plasma free corticosterone concentration by DR evidence of a functional hyperadrenocorticism in these animals? Plasma and pituitary levels of ACTH are decreased by DR in male F344 rats (Han et al., 1995), which indicates that the elevated plasma concentration of free corticosterone is having a negative feedback action. Also, thymic weight relative to body weight is decreased and adrenal weight relative to body weight is increased by DR (Nelson, 1994b). These findings are consistent with the view that DR is causing daily periods of moderate hyperadrenocorticism, but further research is needed to establish it as a fact.

Is there any reason to believe that a moderate increase in the plasma concentration of glucocorticoids could play a role in the antiaging action of DR? Conditions involving long-term stress of moderate intensity, i.e., damage from and/or responses to stressors (damaging agents or processes), are known to increase longevity (Sacher, 1977), and such conditions are likely to sustain moderately elevated plasma levels of glucocorticoids. For example, mice subjected to daily exposure to electric shock or to intermittent exposure to low environmental temperatures or to both were found to live somewhat longer than mice not subjected to these stressors (Ordy et al., 1967). Also, rats immersed for 4 hours each day in cool water starting at 6 months of age ate more but lived longer and had fewer neoplasms than rats not so treated (Holloszy and Smith, 1986). Although conditions of chronic severe stress are clearly deleterious (Pare, 1965), it appears that prolonged moderate intensity stressors or possibly moderate intensity but intermittent stressors may well retard aging processes. Unfortunately, in the two studies just mentioned, the plasma levels of glucocorticoids were not measured, and it is possible that another factor such as the effect of the stressors on body weight (a factor suggested by Turturro et al., 1995) is responsible for the antiaging actions.

However, it is noteworthy that chronic treatment of a short-lived mouse strain with prednisolone phosphate increased life span (Bellamy, 1968), but such treatment did not do so with longer lived mouse strains (Hochschild, 1971; Forbes, 1975). Chronic treatment of Drosophila melanogaster with hydrocortisone acetate increases the mean length of life of both sexes (Hochschild, 1973).

The strongest evidence that the antiaging action of DR may relate to the elevated plasma concentration of glucocorticoids comes from cancer studies. Cancer is predominantly...
a disease of the aged (Dix, 1989). DR markedly retards the occurrence of spontaneous tumors (Weindruch and Walford, 1982). It also protects against the chemical induction of tumors (Klurfeld et al., 1987). Pashko and Schwartz (1992) have found that DR inhibits 12-0-tetradecanoylphorbol-13-acetate (TPA) promotion of skin papillomas in CD-1 mice, and that adenectomy prior to initiating DR completely reverses the inhibition of tumor development. Since glucocorticoids block TPA promotion of skin tumors (Schwarz et al., 1977), Schwartz and Pashko (1994) postulate that elevated plasma adrenocortical steroids in response to DR mediate its tumor inhibitory action. Indeed, the possibility that elevated plasma glucocorticoids broadly mediate the antiaging actions of DR in addition to its action on neoplastic disease deserves further study. In line with this possibility, Sparrow et al. (1993) have reported, in a longitudinal study, that men with morning plasma cortisol levels one standard deviation below the mean exhibit a greater age-associated decline in pulmonary function than do men with plasma cortisol levels one standard deviation above the mean.

Role of Heat Shock Protein System

Another general protective mechanism that may be involved in the antiaging action of DR is the heat shock protein system. This system protects cells against the damaging action of a broad spectrum of agents in addition to heat (Lindquist, 1986). Heydari et al. (1993) have found that the ability of hepatocytes to express the heat shock protein 70 (hsp 70) gene after a mild heat stress decreases with age, and that at all ages DR increases its expression. At least in part, this action of DR is due to its ability to maintain an active heat shock transcription factor. Aly et al. (1994) have observed that DR enhances the induction of heat shock proteins (hsp/ hsp70) 27, 70, and 90 in the hypothalamus of old rats.

Evolutionary Pathway of Antiaging Action of DR

In addition to increasing the life span of rodents, DR also extends life and retards reproduction in a variety of invertebrate species (Austad, 1989; Finch, 1990) that do not have the hypothalamic-adenohypophyseal-adrenal cortical system. Invertebrates and other poikilotherms commonly vary their mass-specific metabolic rate enormously in response to environmental temperature changes and may therefore respond to DR by simply reducing mass-specific metabolic rate. This, in turn, would curtail the rate at which damaging substances such as reactive oxygen species are being produced, and could prolong their lives for rather trivial reasons. Alternatively, and consistent with our hypothesis, we propose that DR enhances the primitive invertebrate heat shock protein system as an evolved protective response against agents directly damaging to cells such as heat and other protein denaturants during periods of food scarcity.

In vertebrates, with their more elaborate immune system, an additional enhancement of the adrenocortical system by DR evolved to protect animals from excessive responses of systemic defense processes (such as immune processes and inflammatory processes) during food scarcity. In this regard, it is noteworthy that inflammatory processes have been implicated in the pathogenesis of many age-associated diseases such as Alzheimer's disease, arthritis, colorectal cancer, and ischemic heart disease (Nelson, 1995). We feel that these two protective mechanisms are sufficient to explain the ability of DR to retard the occurrence and progression of a broad spectrum of aging processes.

General Implications of the Hypothesis

There are several rather straightforward predictions from our hypothesis, some of which could be tested using common laboratory rodent models; others would require novel animal models.

Common laboratory rodents could be used to test the prediction that, in addition to food restriction, other environmentally relevant (e.g., heat, cold) stressors which moderately stimulate the glucocorticoid system would also be expected to retard aging and the development of disease without necessarily reducing body mass. Second, disabling the glucocorticoid system by, for instance, knocking out genes required for its stimulation (Muglia et al., 1995) would be predicted to reduce or eliminate the antiaging effects of DR.

Looking to novel animal models, a significant implication of our hypothesis is that the antiaging effects of DR will be tied to a particular mode of food availability (sporadic, short-term shortages) in nature such that species with differing patterns of food availability may not exhibit a similar physiological response to chronic food restriction. That is, some populations or species depending upon their dietary mode or environment will experience short-term unpredictable food shortages rarely or never. In such cases, we expect that the protective effect induced by food shortage will have been lost.

Vegetation-consuming animals inhabiting the moist tropics where vegetation is continuously abundant may represent such species. Thus, we do not find it surprising that monkey species living in tropical forests (e.g., squirrel monkeys) respond differently to DR than do monkeys such as rhesus macaques, that live in more temperate and variable environments (Weindruch et al., 1995).

It is apparent that there is a wide range of interspecific variability in the physiological response to acute short-term food shortage. For instance, in humans a 24–36-hour fast is associated with substantially decreased exercise endurance capacity (Loy et al., 1986), whereas in rats, similar fasting enhances endurance capacity (Dohm et al., 1983). Similarly, some species, such as rats, respond to reduced food availability without reducing spontaneous activity levels (McCarter and Palmer, 1992) and only marginally reducing body temperature (Duffy et al., 1990); others, such as house mice, drop into brief periods of shallow torpor associated with daily inactivity and a substantially greater reduction in body temperature (Duffy et al., 1991); and still others, such as the little pocket mouse (Perognathus longimembris), enter deep torpor, consisting of complete dormancy lasting up to a week and a body temperature falling by as much as 30°C (Lyman et al., 1982). With such a range of response to acute food restriction, a similar range of response to chronic DR, including variation in its antiaging effect, would not be surprising.

In sum, our hypothesis suggests that an evolutionary history of short-term, unpredictable food shortages has pro-
duced the antiaging effect of DR found among at least some species in the laboratory. We also hypothesize that this effect will be mediated by upregulation of the heat shock protein system and by moderate stimulation of the glucocorticoid system. Critically evaluating the hypothesis is in principle straightforward and will suggest the extent to which DR’s antiaging effect is expected to be general among species.

ACKNOWLEDGMENTS

The authors acknowledge support by National Institutes of Health grants AG-11534 to Dr. Steven N. Austad and AG-00469 to Dr. Edward J. Masoro.

Address correspondence to Dr. Edward J. Masoro, Department of Physiology, The University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-7756.

REFERENCES


Schwartz, A.G., Pashko, L.L. Role of adrenocortical steroids in mediating...
EVOLUTION OF ANTIAGING OF DR

1997 Gordon Research Conference on the Biology of Aging

Genetics of Aging, Longevity and Stress
January 5th through 10th, 1997
Doubletree Hotel in Ventura, California

The meeting will include sessions on a wide variety of topics and will cover extensively recent studies in this area employing model systems. Also covered will be genetic advances in osteoporosis, heart disease, Alzheimer's disease, and Werner's disease.

Applicants will need to apply through the Gordon Conference office.

There will be opportunity for presenting posters and some short oral presentations. Some funding to supplement travel expenses of more junior applicants is anticipated. Applicants for either presentation or travel supplements should submit an abstract with their application.

For a detailed program see the Oct. 11, 1996 issue of Science or look at our URL: http://ibgwww.colorado.edu/~shaie/gordon.html