Journal of Gerontology: BIOLOGICAL SCIENCES
2006, Vol. 61A, No. 3, 211–217
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Effects of Caloric Restriction and Exercise on Age-Related, Chronic Inflammation Assessed by C-Reactive Protein and Interleukin-6

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Chronic inflammation is associated with the aging process and numerous age-related pathologies. We evaluated the effects of age, caloric restriction (CR), and exercise on plasma C-reactive protein (CRP), interleukin-6, and total antioxidant capacity in Fisher 344 rats. The inflammatory markers were analyzed using enzyme-linked immunosorbent assays (ELISA), while total antioxidant potential was determined by a spectrophotometric method. An increase in circulating levels of CRP with age was attenuated with long-term 40% CR; short-term 40% CR in young animals also reduced CRP concentration compared to age-matched controls. Lifelong exercise with 8% CR showed a marked decrease in CRP levels compared to 8% CR controls and an even greater reduction compared to ad libitum-fed rats. Plasma interleukin-6 levels remained unchanged with age, CR, and exercise, whereas inflammation levels showed an inverse association with plasma antioxidant status. These studies highlight the anti-inflammatory effects of CR and exercise.

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An increase in chronic inflammation has been shown to play a vital role in numerous disease states and has been linked with the aging process (1–3). It has been implicated in a diverse range of diseases including arthritis, cancer, diabetes, and Alzheimer's disease (4–7). Moreover, inflammation has been recognized as playing a major, deleterious role in arteriosclerosis and as an integral component in the pathogenesis of other cardiovascular disease (8–10). Inflammation and cytokine status has also been associated with disability and lower physical function (11–14). C-reactive protein (CRP), an inflammatory biomarker, is increasingly receiving more attention due to its potential in predicting cardiovascular disease (15). It is a nonglycosylated protein of the pentraxin family involved in the acute phase reaction, a nonspecific physiological response to tissue injury, infection, inflammation, and disease activity, which is characterized by an increase in certain cytokines and hormones. CRP primarily functions to recognize and eliminate pathogens and damaged cells by activating the complement system and phagocytic cells (16). Moreover, interleukin (IL)-6, an acute phase cytokine considered to be a primary modulator of hepatic CRP production, has also been implicated in enhancing the inflammatory response persistent in cardiovascular disease (17). Specifically, the primary production of circulating CRP levels is modulated by IL-6 in hepatocytes, although trace amounts of messenger RNA for CRP have been found in lymphocytes and kidneys (18,19). In addition, monokines IL-1 and tumor necrosis factor-α (TNF-α) and interferons are other proinflammatory stimuli associated with increased production of CRP (20). Expression is regulated through activation of transcription factors CCAAT/enhancer-binding protein (C/EBP) β and δ from the C/EBP family, signal transducer and activator of transcription 3 (STAT3), and Rel proteins such as nuclear factor-κB (NF-κB) (20). Hence, the primary objectives of these studies were to determine the relationship between CRP and IL-6 with age and life-prolonging interventions.

Numerous studies have shown that both lifelong exercise and lifelong caloric restriction (CR) extend mean and maximal life span, respectively, in a variety of species (21–23). However, little is known regarding the relationship between either of these interventions and the attenuation of chronic systemic inflammation. Both interventions have been shown to decrease the risk factors and incidence of age-related pathologies, but the mechanisms by which these interventions extend life span remain unclear (23–25). Here, studies were designed to investigate the effect of short-term (2-month) CR, long-term (22-month) CR, as well as lifelong wheel running on plasma levels of inflammatory cytokines (CRP and IL-6) and total antioxidant status in Fisher 344 rats. We hypothesized that CR and exercise would attenuate age-related increases in the plasma levels of both cytokines and that this would be directly associated with improved antioxidant status. These studies provide further insight into the beneficial mechanism of how CR and exercise affect inflammatory response, in addition to establishing a relationship between IL-6 and CRP levels in the plasma of rats.

Methods

CR Animals

For the short-term CR studies we used 6-month-old, ad libitum-fed (6AL, young; $n = 8$) and 6-month-old CR (6CR, young CR; $n = 8$) male, Fisher 344 rats (National Institute

on Aging Colony; Harlan Sprague Dawley, Indianapolis, IN). For the long-term CR studies we used 26-month-old, AL (26AL, old; $n = 8$) and 26-month-old, CR (26CR, old CR; $n = 8$) male, Fisher 344 rats. The 6CR and 26CR animals were subjected to CR starting at 3.5 months of age (10% restriction), increased to 25% restriction at 3.75 months, and maintained at 40% restriction from 4 months throughout the animal's life. CR animals were fed the NIH31-NIA fortified diet to ensure that they were not malnourished, whereas AL animals were fed the NIH31 rat diet. All animals had unrestricted access to water. The rats were individually housed in a temperature- (18–22°C) and light-controlled environment with a 12-hour light/dark cycle. After 1 week of acclimation, the animals were randomly killed (approximately 5 per day) on consecutive days.

Lifelong Exercised Animals

For the wheel-running study, male Fisher 344 rats were purchased from Harlan at 10–11 weeks of age and were housed in our facilities until they were killed at 24 months of age. All animals were singly housed in a temperature- (20 ± 2.5°C) and light-controlled (12-hour light/dark cycle) environment with unrestricted access to water. Upon arrival, rats were randomly assigned to one of three groups: sedentary, AL animals (ad libitum; $n = 20$); sedentary, 8% food restriction (sedentary; $n = 20$), and wheel running, 8% food restriction (runners; $n = 20$). The 8% CR group and the wheel-running group were fed the Harlan Teklad Rodent Diet (#8604). It was decided to kill the rats at 24 months of age because 24 months is the mean life span for this species. Moreover, at the time of death (24 months), 12 animals remained alive within each group, 8 of which were used for plasma biochemical analysis within this study.

Rats fed ad libitum tend to abruptly decrease their running activity, and slight food restriction (8%–10%) has been shown to prevent this decline (26,27). This degree of CR has no significant effect on longevity of the animals (21). Food intake for two groups of rats (sedentary and runners) was therefore restricted by 8% below the ad libitum food intake of a separate group of sedentary, age-matched, male Fisher 344 rats. Throughout the duration of the study, the food intake of these two groups was adjusted accordingly (based on ad libitum food intake). All sedentary rats were housed in standard rodent cages supplied by the University of Florida's Animal Care Services. Rats in the wheel-running group were housed in cages equipped with Nalgene Activity Wheels (1.081 m circumference) obtained from Fisher Scientific (Pittsburgh, PA) and had free access to the wheels. Each wheel was equipped with a magnetic switch and an LCD counter that recorded the number of wheel revolutions. The number of revolutions was recorded daily for each animal. Body weights of all rats were recorded weekly.

Rats were monitored by the veterinary care staff of the University of Florida's Animal Care Facilities. Animals with tumors and animals that became ill during their life span were immediately killed and not used for the study. On the experimental days, killing of animals was randomized, with equal representation of all groups and ages each time.

Plasma Isolation

Animals were killed with isoflurane (administered via inhalation using a precision vaporizer at 5%). Afterwards, the chest was opened and blood removed by cardiac puncture drawn directly into Vacutainer tubes containing ethylenediaminetetraacetic acid (K3EDTA; 8.4 mg per Vacutainer; BD, Franklin Lakes, NJ) for plasma acquisition. Plasma samples that were hemolytic were not included in any analysis of the parameters studied. The blood aliquots were centrifuged at 4°C at 1500 *g* for 10 minutes, and plasma was stored at –80°C until use. All treatment of animals throughout this study conformed fully with the Guiding Principles for Research Involving Animals research, and all experimental procedures were approved by the University of Florida's Institute on Animal Care and Use Committee.

Plasma Levels of CRP

CRP was measured using a solid phase sandwich enzyme-linked immunosorbent assay (ELISA) (BD Biosciences, San Diego, CA) with a minimum detectable CRP concentration of 0.35 ng/ml and inter-assay coefficient of variation <10%. Sample absorbencies were read in triplicate at 450 nm, with wavelength correction at 630 nm off a standard curve and expressed in micrograms per milliliter. CRP concentrations were normalized to total protein content, measured using the Bradford method.

Plasma Levels of IL-6

IL-6 concentrations were measured using an ELISA (Endogen, Rockford, IL). Sample absorbencies were read in triplicate at 450 nm, with wavelength correction at 550 nm off a standard curve and expressed in picograms per milliliter. The sensitivity was <16 pg/ml, and inter-assay coefficient of variation <10%. IL-6 concentrations were normalized to total protein content, measured using the Bradford method.

Total Antioxidant Status

Total antioxidant potential was assayed using a commercially available kit (Calbiochem, La Jolla, CA). The rationale behind using the total antioxidant potential capacity was to determine the totality of all low-molecular-weight antioxidants—such as vitamin C, glutathione, and uric acid—in the plasma. This temperature-dependent spectrophotometric assay relies on the ability of the sample antioxidants to inhibit the oxidation of ABTS (2,2′-Azino-di-[3-ethylbenzthiazoline sulphonate]) to $ABTS^{\bullet+}$. The amount of $ABTS^{\bullet+}$ produced was monitored by reading the absorbance at 600 nm. The degree of suppression of the absorbance at 600 nm by the antioxidants in the sample is proportional to their concentration. Samples were measured in triplicate, and the inter-assay coefficient of variation was <15%.

Statistical Analysis

Two-tailed, unpaired *t* tests were used to determine significant differences between groups. Significance was set at $p < .05$. Due to the separate studies and separate biochemical analyses, statistical comparisons were performed between: (i) the young AL and CR rats; (ii) the young, old,

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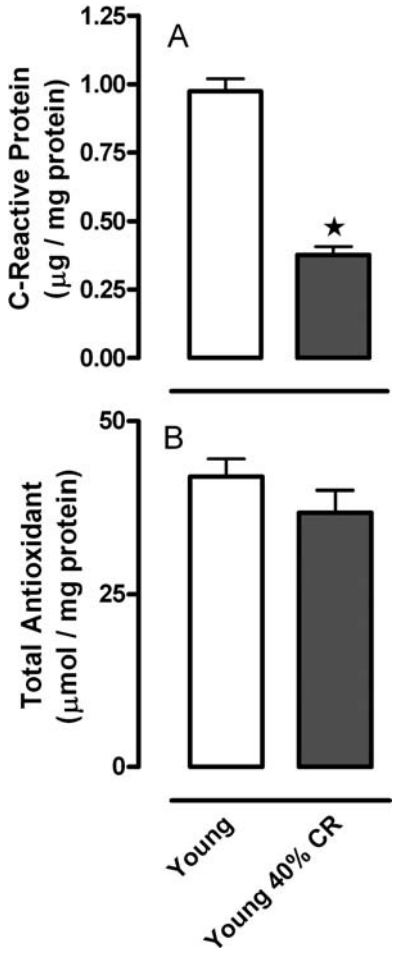

Figure 1. Effects of short-term calorie restriction (CR) on plasma concentration of C-reactive protein (CRP) and total antioxidant capacity in young (6-month-old) and age-matched CR Fisher 344 male rats. CR was started at 4 months of age at 40% compared to ad libitum-fed animals (see Methods). Values are means ± standard error of the mean. ★ Significant ($p < .0001$) differences from young animals. Young rats $n = 8$, for CR group $n = 8$.

and old CR rats; and (iii) the old AL, old runners (+8% CR), and old 8% CR controls.

Results

Body Weights of Calorie Restriction Studies

There was a significant difference in body weights between the 6-month-old, CR animals (310.0 g ± 4.5, $N = 8$) and the 6-month-old ad libitum-fed (AL) group of animals (364.0 g ± 7.3, $N = 8$; $p < .0001$). A significant difference in body weights was also observed in the 26CR animals (304.4 g ± 4.5, $N = 8$) in comparison to their age-matched counterparts, the 26AL (350.6 g ± 17.4, $N = 8$) group ($p = .031$).

Body Weights and Running Activity of Exercise Study

Running wheel activity and body weight were carefully monitored during the animals' life span. Complete running activity profile, daily energy expenditure, and mitochondrial function are being published elsewhere (28). In brief, the average distance run per day was recorded daily throughout the duration of the study. Although peak running activity occurred at 6 months of age (~2500 m/day), running activity was maintained at an average of 1145 ± 248 m/day for the remainder of the study. This is in contrast to previous studies that show a continual decline in the average distance run per day after approximately midlife, as the animals age (male Long Evans) (26,29). Daily energy expenditure was estimated in the two groups of rats at 10 months of age. Runners exhibited significantly higher energy expenditure than the pair-fed sedentary controls (approximately 70% more energy per day than the sedentary rats). This activity level, in terms of wheel revolutions per day, remained relatively constant throughout their life span, and potential adaptations (such as a reduction of systemic inflammation) were determined at 24 months of age. At this age there were no significant differences in body weight between the 24AL animals (381.2 g ± 21.28, $N = 8$) and their same-age counterparts whose diet was restricted by 8% (383.1 g ± 8.564, $N = 8$). Wheel-running animals' body weight (339.2 g ± 7.568, $N = 8$) tended to be significantly lower than that of their sedentary counterparts ($p = .084$); however, changes were not statistically significant.

Table 1. Effects of Short-Term Calorie Restriction (CR) on Plasma Concentration of Interleukin-6 in Young (6-Month) and Age-Matched CR Fisher 344 Male Rats

	6-Month	6-Month CR
Interleukin-6 (pg/mg protein)	1.78 ± 0.23	1.40 ± 0.18

Notes: Values are means ± standard error of the mean. For all groups of rats, $n = 8$.

Effect of Short-Term CR

First we determined the effects of 2-month CR (40% less than for the AL animals) on cytokine levels (Figure 1 and Table 1) in young (6-month-old) animals. Short-term CR dramatically reduced CRP levels (Figure 1A; 61%) in comparison to those in their age-matched, AL controls, but had no significant effect on IL-6 concentrations (Table 1). Total plasma antioxidant status tended to decrease in the short-term CR rats, but changes were not significant (Figure 1B; 8%).

Long-Term CR

Circulating levels of CRP are shown to increase with age (Figure 2A). The old 26AL rats had substantially higher plasma levels of CRP than did the young 6AL group (258%). In contrast, the old 26CR rats had significantly lower levels (60%) of CRP compared to the 26AL group. Plasma levels of IL-6 did not change significantly with age or lifelong CR (Table 2). Total plasma antioxidant levels were significantly decreased in the old 26AL animals compared to the young 6AL (Figure 2B) (27% decrease), whereas the old 26CR group tended to show an increase compared to the old 26AL animals (23%). Taken together, lifelong CR is a potent intervention to halt inflammation and tended to attenuate the age-associated decrease in antioxidant potential.

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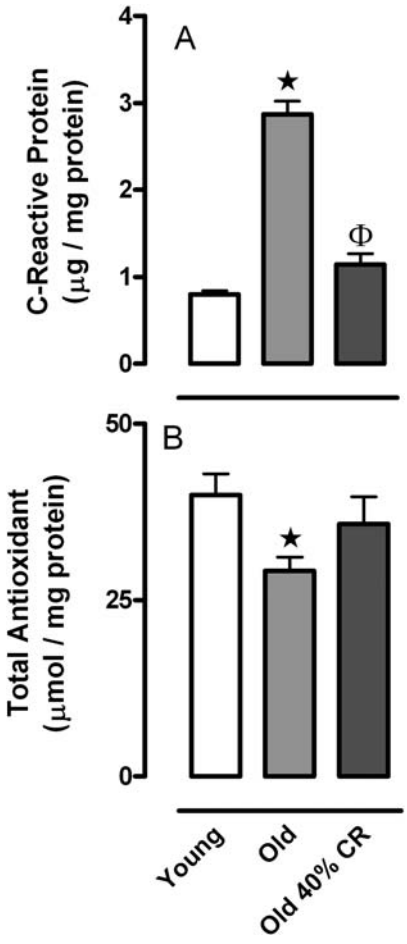

Figure 2. Effects of long-term calorie restriction (CR) on plasma concentration of C-reactive protein (CRP) and total antioxidant capacity in young (6-month-old), old (26-month-old), and old (26-month-old) age-matched CR Fisher 344 male rats. CR was started at 4 months of age at 40% compared to ad libitum-fed animals (see Methods). Values are means ± standard error of the mean. For CRP: ★ = significant ($p < .0001$) differences from young animals; Φ = significant ($p < .0001$) differences from old animals. For total antioxidant capacity: ★ = significant ($p = .0113$) differences from young animals. Total antioxidant capacity was not different ($p = .1472$) between old CR and old rats. For all groups of rats, $n = 8$.

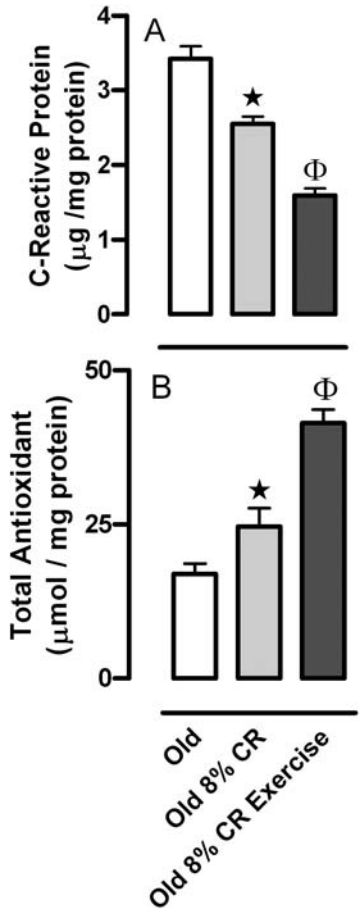

Figure 3. Effects of long-term calorie restriction (CR) combined with exercise on plasma concentration of C-reactive protein (CRP) and total antioxidant capacity in old (24-month-old) ad libitum-fed, old (24-month-old) CR (CR 8%), as well as old (24-month-old) lifelong wheel-running CR (8%) Fisher 344 male rats. CR was started at 4 months of age at 8% compared to ad libitum-fed animals (see Methods). Values are means ± standard error of the mean. For CRP: ★ = significant ($p = .0010$) differences from old animals; Φ = significant ($p < .0001$) differences from old 8% CR rats. For total antioxidant capacity: ★ = significant ($p = .0276$) differences from old animals; Φ = significant ($p = .0004$) differences from old 8% CR rats. For all groups of rats, $n = 8$.

Long-Term Exercise

Lifelong exercise (and 8% CR) showed a marked decrease (38%) in CRP levels compared to the 8% CR sedentary control rats, and an even greater reduction (53%) was observed comparing them with the AL rats (Figure 3A). 8% CR reduced circulating CRP levels by 25% compared to those levels in the age-matched, AL rats. In contrast, plasma antioxidant levels were the highest in the lifelong exercising 8% CR group compared to 8% CR and AL animals (Figure 3B). No changes were found in IL-6 levels between these treatment groups (Table 3). In summary, in 24-month-old animals, lifelong 8% CR reduced CRP levels and increased total antioxidant status compared to old 24AL animals. The addition of exercise to 8% CR had an additional beneficial effect in reducing CRP and showed the highest total plasma antioxidant status of all three groups.

Discussion

The objective of these studies was to examine the effects of age, CR, and chronic exercise on the plasma levels of CRP and IL-6 and the effect on total antioxidant potential. We found that short-term CR in young animals (2 months old) was already highly effective in reducing plasma CRP levels by 61%. Lifelong 40% CR and 8% CR in old animals also led to significantly lower levels of plasma CRP compared to age-matched AL control animals (reductions of 60% and 25%, respectively). Moreover, lifelong exercise (and 8% CR) was able to reduce the level of CRP by 38% (compared to the 8% CR sedentary controls) and by 53% (compared to the AL rats). On the contrary, circulating IL-6 levels were not affected by age, diet, or exercise. Taken together, interventions known to extend maximum and mean life span in rodent studies were effective in reducing a general systemic biomarker of inflammation (CRP),

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Table 2. Effects of Long-Term Calorie Restriction (CR) on Plasma Concentration of Interleukin-6 in Young (6-Month), Old (26-Month), and Old (26-Month) Age-Matched CR Fisher 344 Male Rats

	6-Month	26-Month	26-Month CR
Interleukin-6 (pg/mg protein)	0.70 ± 0.034	0.74 ± 0.045	0.73 ± 0.056

Notes: Values are means ± standard error of the mean. For all groups of rats, $n = 8$.

increasing total antioxidant capacity (Table 4), but had no effect on the cytokine IL-6 (Tables 1, 2, and 3).

Elevated inflammatory milieu are among the physiological changes deemed synonymous with the aging process, and have been cited as significant indicators of mortality in older populations (10,30,31). Given the social and economic impact of inflammation and cardiovascular heart disease and subclinical inflammation with age (10,30), our research attempted to elucidate potential mechanisms driving these outcomes. A recently emerging and important area of aging research closely associated with inflammation is biological redox status. The presence of an aging effect on systemic levels of inflammation was confirmed by increased levels of the CRP in the plasma of old animals, and a reduced plasma total antioxidant redox status. Plasma contains several key cellular thiols (i.e., glutathione), vitamin C, and uric acid, which are important in maintaining the plasma redox potential, and largely reflect the total antioxidant capacity (25,32). The observed reduction of the plasma antioxidant potential reflects either an increased consumption of antioxidants by oxidants or a decreased synthesis of low molecular antioxidants. The plasma sample obtained from rats is small, and future studies will have to explore the numerous other antioxidants that may be affected by these treatments. A significant implication of our study is the need to study the mechanistic relationships between oxidative stress and inflammation.

Inflammatory cell types are sensitive to reactive oxygen species and regulate their function based on the presence of oxidants (33,34). In other words, specific proinflammatory enzymes (inducible nitric oxide synthase [iNOS], cyclooxygenase-2 [COX 2], and xanthine oxidase [XOD]) can be activated by gene regulators (NF-κB activation) in response to the formation of oxidants. This presents the possibility that a proinflammatory state may become more chronic in association with advancing age. Key mediators of inflammatory pathways, i.e., TNF-α and NF-κB, have been extensively studied by laboratories (including ours) with regard to a possible role in aging (2,35–40). Specifically, several laboratories have explored the attenuation of inflammation through the use of lifelong CR. Indeed, an overall chronic inflammation present in rodents was blunted with this intervention (2,35). Their postulate (2) centers on the increased signaling to NF-κB accompanying aging and the ability of CR to counter this occurrence. These researchers formulated the inflammation theory of aging, which complements two other theories of aging: the free radical oxidative stress theory and the glycooxidation theory (41). However, whether IL-6 and CRP are molded by interplay between oxidative stress and inflammatory mediators has not been investigated in animal models used for aging.

Table 3. Effects of Long-Term Calorie Restriction (CR) and Exercise on Plasma Concentration of Interleukin-6 in Old (24-Months) Ad Libitum-Fed, and Old CR (24-Month 8% CR), and Old (24-Month) Lifelong Wheel-Running CR Fisher 344 Male Rats

	24-Month	24-Month 8% CR	24-Month 8% CR Exercise
Interleukin-6 (pg/mg protein)	1.31 ± 0.14	1.41 ± 0.12	1.39 ± 0.09

Notes: Values are means ± standard error of the mean. For all groups of rats, $n = 8$.

CRP is an important innate immune system molecule and has received vigorous attention due to its potential as a predictive marker for the risk of experiencing cardiovascular events (42). IL-6 is a cytokine with both anti- and proinflammatory effects on many cell types, and is known to induce the synthesis of all the acute phase proteins by the liver (43). We assessed the CRP and IL-6 levels and antioxidant status in the plasma and observed an age-associated increase in CRP levels (and reduction in antioxidant status), which CR (40%) attenuated. Even in rats with short-term CR at the age of 6 months, there is a 60% decrease in CRP levels compared to the same age rats, which were fed an ad libitum diet. Future studies will need to determine if short-term CR at an older age is also effective in attenuating inflammation. Surprisingly, 8% CR was also highly effective in reducing circulating CRP levels. Recent studies showed that long-term CR is highly effective in reducing the risk for atherosclerosis in humans; this reduction was strongly associated with a reduction in plasma CRP levels (31). Hence, CR is exceptionally effective in reducing inflammation, which may contribute to the aging process.

Wheel running (combined with 8% CR) was also very effective in modulation of CRP concentration in the plasma compared to 8% CR only. We found that plasma CRP levels were decreased by CR (8%) and were even lower when 8% CR was combined with exercise. Combining both 8% CR and chronic exercise shows a decrease of the levels of CRP by approximately 53%. Previous studies (44–46) have been conducted to investigate whether exercise can modulate inflammatory responses. It has also been shown that physical activity and exercise decrease levels of inflammatory markers, achieved by a decrease in the inflammatory response (47,48). For example, in humans the higher levels of exercise were associated with lower levels of CRP (e.g., CRP = 1.95 mg/L for sedentary humans and 1.72 for >180 min/wk

Table 4. Summary of Percent Change in C-Reactive Protein (CRP) and Total Antioxidant Status Between the Different Treatment Groups

Intervention	% Change CRP	% Change Total Antioxidant Status
6AL vs 6CR	61% ↓ ($p < .0001$)	8% ↓ ($p = .4989$)
6AL vs 26AL	258% ↑ ($p < .0001$)	27% ↓ ($p = .0113$)
26AL vs 26CR	60% ↓ ($p < .0001$)	23% ↑ ($p = .1472$)
24AL vs 24CR-8%	25% ↓ ($p = .0010$)	11% ↑ ($p = .7144$)
24CR-8% vs 24CR-8%-WR	38% ↓ ($p < .0001$)	68% ↑ ($p = .0007$)

Note: 6AL = young ad libitum-fed; 6CR = young short-term CR; 24AL or 26AL = old ad libitum-fed; 26CR = old lifelong CR; 24CR-8% = old 8% restricted compared to ad libitum-fed; 24CR-8%-WR = old 8% restricted and lifelong wheel running.

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of exercise) (47). Taken together, studies show beneficial effects due to a reduction in iNOS activity and/or several cytokines expression (i.e., TNF-α, CRP, and IL-6). Exercise can also reduce the risk of numerous chronic diseases including cardiovascular disease, hypertension, diabetes, metabolic syndrome, and several forms of cancer, all of which have an inflammatory component (24). We have used the phrase ''chronic exercise'' to mean exercise throughout the life span of the individual. A limitation of our studies is the absence of an exercise without 8% CR group; thus, it is not possible to determine whether the effect of exercise is additive, potentiating, or synergestic to the effect of 8% CR.

IL-6 levels in the plasma did not change to a significant degree with age, CR, or exercise. We found this data very interesting because CRP levels were altered by treatments, and plasma CRP is considered to be mainly under the transcriptional control of IL-6 produced by hepatocytes. Hence, no quantitative relation between the circulating levels of the two markers was found. There are conflicting data in the literature showing an increase or no change with age. However, our data are in strong agreement with those of Beharka and colleagues (49), who showed that IL-6 production does not increase with age. These authors suggest that previous contradicting results in the literature may be due to the health status of persons investigated (49). Other cytokines may have a more significant role in regulating CRP production with age, CR, and exercise. Monokines, IL-1 and TNF-α, and interferons are other proinflammatory stimuli associated with increased production of CRP (20), and TNF-α has been shown to increase with age (40). Therefore, future studies need to determine if these proteins are responsible for the changes observed in CRP levels.

CRP has been shown to be a good clinical marker in predicting cardiovascular disease and other diseases strongly associated with chronic inflammation. Moreover, effective strategies in attenuating and maintaining inflammation that should be considered are CR and chronic exercise. Lifelong (40%) CR may always remain the most robust intervention to extend maximum life span; however, moderate (8%) CR combined with exercise may be more easily achieved in humans and is worthy of further investigation in human populations for reducing inflammation and maintaining good health.

Acknowledgments

This research was supported by grants to C.L. from the National Institute on Aging (AG17994 and AG21042). R.K. is a University Scholar, and funding was provided by The University of Florida Scholar's Program.

We are very grateful to Asimina Hiona for her technical assistance in this study.

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Received April 30, 2005
Accepted August 10, 2005
Decision Editor: James R. Smith, PhD

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Editor Nominations

The Gerontologist

The Gerontological Society of America's Publications Committee is seeking nominations for the position of Editor-in-Chief of *The Gerontologist*, the Society's multidisciplinary journal.

The position will become effective January 1, 2007. The Editor-in-Chief makes appointments to the journal's editorial board and develops policies in accordance with the scope statement prepared by the Publications Committee and approved by Council (see the journal's General Information and Instructions to Authors page). The Editor-in-Chief works with reviewers and has the final responsibility for the acceptance of articles for his or her journal. The editorship is a voluntary position. Candidates must be dedicated to developing a premier scientific journal.

Nominations and applications may be made by self or others, but must be accompanied by the candidate's curriculum vitae and a statement of willingness to accept the position. **All nominations and applications must be received by March 31, 2006.** Nominations and applications should be sent to the Publications Committee, Attn: Patricia Walker, The Gerontological Society of America, 1030 15th Street, NW, Suite 250, Washington, DC 20005-1503.