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Caloric restriction prevents age-related decline in skeletal muscle dihydropyridine receptor and ryanodine receptor expression

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Abstract The dihydropyridine receptor (DHPR), a voltage-gated L-type Ca^{2+} channel, and the Ca^{2+} release channel/ryanodine receptor isoform-1 (RyR1) are key molecules involved in skeletal muscle excitation-contraction coupling. We have reported age-related decreases in the level of DHPR expression in fast- and slow-twitch muscles from Fisher 344 cross Brown Norway (F344BNX) rats (Renganathan, Messi and Delbono, J. Membr. Biol. 157 (1997) 247–253). Based on these studies we postulate that excitation-contraction uncoupling is a basic mechanism for the decline in muscle force with aging (Delbono, Renganathan and Messi, Muscle Nerve Suppl. 5 (1997) S88–92). In the present study, we extended our studies to older ages and we intended to prevent or retard excitation-contraction uncoupling by restricting the caloric intake of the F344BNX rats from 16 weeks of age. Three age groups, 8-, 18-, and 33-month old caloric restricted rats, were compared with ad libitum fed animals. The number of DHPR and RyR1 and DHPR/RyR1 ratio (an index of the level of receptors uncoupling) in skeletal muscles of 8-month and 18-month rats was not significantly different in either ad libitum fed or caloric restricted rats. However, the age-related decrease in the number of DHPR, RyR1 and DHPR/RyR1 ratio observed in 33-month old ad libitum fed rats was absent in 33-month old caloric restricted rats. These results suggest that caloric restriction prevents age-related decreases in the number of DHPR, RyR1 and DHPR/RyR1 ratio observed in fast- and slow-twitch rat skeletal muscles.

Key words: Caloric restriction; Aging; Skeletal muscle; Dihydropyridine receptor; Ryanodine receptor; Excitation-contraction coupling; Calcium channel

1. Introduction

The mechanisms underlying age-related decline in skeletal muscle structure and function, termed sarcopenia, are only partially understood. Previous studies reported by our laboratory support the concept that excitation-contraction uncoupling plays an important role in the reduced level of calcium supply to contractile proteins and consequently in muscle weakness associated with aging [1]. Two proteins participate in sarcolemmal excitation-sarcoplasmic reticulum calcium release, namely, dihydropyridine receptor (DHPR), a voltage-gated Ca^{2+} channel, and a Ca^{2+} release channel/ryanodine receptor (skeletal muscle isoform-1, RyR1). DHPR is expressed in the t-tubule and through a hypothetical mechanical interaction with RyR1 elicits Ca^{2+} release from the sarcoplasmic reticulum [2]. The increase in myoplasmic Ca^{2+} concentration triggers muscle contraction.

We reported age-related decrease in the number of DHPR, RyR1 and DHPR/RyR1 ratio in fast- and slow- and mixed-skeletal muscles from Fisher 344 cross Brown Norway rats (F344BNX) [3]. These results provide evidence for the hypothesis that DHPR-RyR1 uncoupling results in alterations in the voltage-controlled sarcoplamic reticulum Ca^{2+} release mechanism [1], decreases in myoplasmic Ca^{2+} elevation in response to sarcolemmal depolarization, reduced Ca^{2+} supply to contractile proteins and reduced contraction force with aging [4].

In this study, young (8-month), middle-aged (18-month) and old (33-month) F344BNX rats were examined to determine whether age-related changes in the number of DHPR, RyR1 and DHPR/RyR1 ratio can be prevented or delayed by caloric restriction. Although caloric restriction is a robust 'anti-aging' intervention [5] with beneficial effects on skeletal muscle structure [6–10], effects of diet on aging skeletal muscle DHPR and RyR1 number and properties are unknown. We report that restricting the calorie intake of the rats to 60% of the control ad libitum fed group from 16 weeks of age prevents the decline in the number of DHPR, RyR1 and DHPR/RyR1 ratio in aged skeletal muscles. These results may be functionally relevant for age-associated muscle weakness.

2. Materials and methods

2.1. Animals, diets and tissue collection

Young (8-month), middle-aged (18 month) and old (33-month) Fisher 344 cross Brown Norway F1 hybrid female rats were obtained from SPF Aging colony at the National Center for Toxicological Research (Bionetics, Jefferson, AR, USA). Ad libitum rats consumed NIH-31 pellets without dietary restriction. Rats on caloric restriction were fed ad libitum with NIH-31 pellets till 13 weeks, switched to 10% calorie reduction at 14 weeks, 25% calorie reduction at 15 weeks, 40% calorie reduction at 16 weeks and maintained at that level for the rest of their life-span. Caloric restricted animals were fed on NIH-31 vitamin supplemented pellets. The body weights for ad libitum fed and caloric restricted rats were (mean ± S.D.) 218 ± 15 and 175 ± 5 g for 8-month, 287 ± 34 and 216 ± 6 g for 18-month and 347 ± 54 and 221 ± 6 g for 33-month old animals, respectively. Rats were housed in a pathogen-free area at Wake Forest University School of Medicine (WFUSM). Animal handling and procedures followed an approved protocol by the Animal Care and Use Committee of WFUSM. Extensor digitorum longus (EDL) muscle, soleus muscle and a pool of mixed fiber-type skeletal muscles were removed after sacrificing the animal by decapitation. Fresh muscles were used immediately for radioligand binding assays.

2.2. Muscle homogenate and radioligand binding to DHPR and RyR1

EDL, soleus and whole hindlimb leg muscles were used. Muscles were homogenized as described previously [3]. Protein concentration

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was determined by Coomassie protein assay with bovine serum albumin as the protein calibration standard. DHPR and RyR1 concentration were determined using the radioligands [^{3}H]PN200-110 and [^{3}H]ryanodine, respectively, as described previously [3]. Homogenates (1–2 mg protein/ml) were incubated with 0.05–5 nM [^{3}H]PN200-110 for 1 h at 23°C in 50 mM Tris-HCl, pH 7.5, 10 μM Ca^{2+}, 1 mM diisopropyl fluorophosphate (DIFP) and 5 μM leupeptin. [^{3}H]Ryanodine binding was determined by incubating the homogenate at 1–2 mg protein/ml in 0.5–80 nM [^{3}H]ryanodine for 24–48 h at 10°C in 20 mM PIPES-NaOH, pH 7.0, 1.0 mM NaCl, 100 μM Ca^{2+}, 5 mM AMP, 1 mM DIFP, and 5 μM leupeptin. Membrane bound [^{3}H]PN200-110 and [^{3}H]ryanodine were determined by filtration through Whatman GF/B filters using a Millipore unit (XX2702250, Millipore, Bedford, MA, USA). Filters were rinsed three times with 5 ml of ice cold 200 mM choline chloride, 20 mM Tris-HCl, pH 7.5. Non-specific [^{3}H]PN200-110 and [^{3}H]ryanodine binding was assessed in the presence of 10 μM unlabeled nifidepine (Sigma, St. Louis, MO, USA) and 10 μM unlabeled ryanodine (Calbiochem, San Diego, CA, USA), respectively. Radioligand concentrations used resulted in occupancy of $>95\%$ of the high-affinity binding sites [11].

2.3. Data analysis

Linear regression and non-linear least square analysis were used to calculate non-specific and total binding of the radioligands to the receptors. Specific binding of [^{3}H]PN200-110 and [^{3}H]ryanodine at each concentration were calculated by subtracting the non-specific binding from the total binding obtained from the above analysis.The following equation:

$$Y = (x{\cdot}a)/((x+b)+(x{\cdot}c)) \quad (1)$$

where a = receptor number (B_{max}); $b = K_d$, dissociation constant; c = the non-specific binding or the low affinity site, was used to fit the binding isotherm. Data were also given in a graphical representation of the Scatchard plot. All values were analyzed for statistical significance using unpaired Student's t-test or a two-factor analysis of variance (ANOVA).

3. Results

The aim of this study is to determine the influence of caloric restriction on age-related decrease in the proteins involved in skeletal muscle excitation-contraction coupling, namely, DHPR, RyR1 and the decrease of DHPR/RyR1 ratio, which is an indicator of the uncoupling between these two receptors [3]. Groups of five 8-, 18-, 33-month-old rats fed either ad libitum or on 60% caloric restriction were used in this study. The concentration of DHPR and RyR1 and their dissociation constant for high-affinity radioligands for each animal were determined in a pool of skeletal muscles consisting of both fast- and slow-twitch muscle fibers. Two measurements were made from the muscle pool isolated from each animal. The DHPR was assessed using the high affinity probe [^{3}H]PN200-110. The sarcoplasmic reticulum RyR1 was quantitated by radioligand analysis using the neutral plant alkaloid [^{3}H]ryanodine as a high affinity probe in the same muscle homogenates.

3.1. DHPR and RyR1 in mixed fiber-type skeletal muscles from ad libitum fed rats

Fig. 1 is a representative of [^{3}H]PN200-110 and [^{3}H]ryanodine binding done in 18-month old and 33-month old ad libitum fed rats. The inset for both figures is the Scatchard analysis of ligand binding to DHPR and RyR1, respectively. [^{3}H]PN200-110 and [^{3}H]ryanodine B_{max} and K_d, and DHPR/RyR1 ratio values are calculated from Scatchard analyses of the binding assay for 8-month and 18-month and 33-month age groups and are given in the upper panel of Table 1. The B_{max} and K_d, and DHPR/RyR1 ratio values

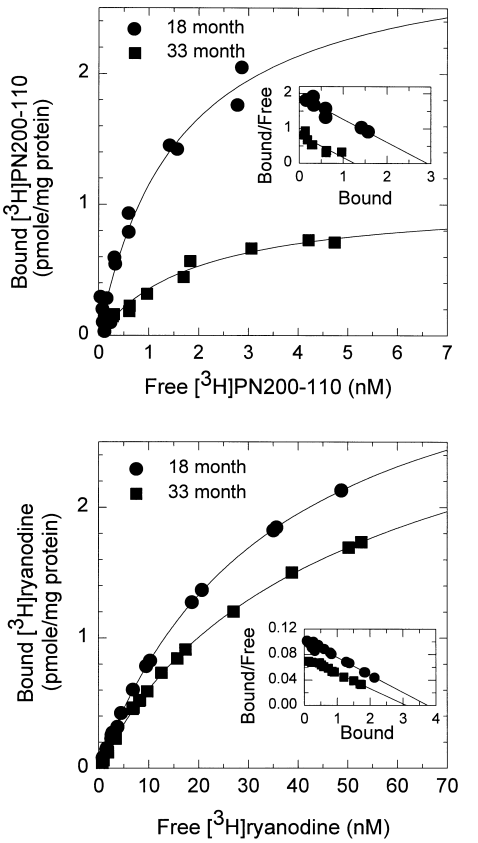

Fig. 1. [^{3}H]PN200-110 (top) and [^{3}H]ryanodine (bottom) binding to skeletal muscle homogenates in an 18-month and 33-month old ad libitum fed rat. B_{max} and K_d values were obtained from Scatchard analysis and fitting of Eq. 1 to binding data (inset). The best fit parameters for all the experiments are included in Table 1.

for 8-month old rats are similar to the values reported for rabbit muscles [11], fast-twitch rat EDL muscles [12] and mice muscles [13] at similar age. These values are not significantly different from our earlier report [3]. A two-fold increase in [^{3}H]PN200-110 binding affinity is seen in 18-month old rats compared to 8-month old rats ($P<0.05$); however, no significant change in [^{3}H]PN200-110 B_{max} value is observed. A two-fold decrease in [^{3}H]ryanodine binding affinity is seen in 18-month old rats ($P<0.05$); however, no significant decrease in [^{3}H]ryanodine B_{max} value is observed. These changes in the K_d do not affect the B_{max} value. A 63% decrease in [^{3}H]PN200-110 B_{max} value and a 25% decrease in [^{3}H]ryanodine B_{max} value is observed in 33-month old rats compared to 18-month old rats. These decreases in the number of DHPR and RyR1 are not due to changes in the binding affinity to [^{3}H]PN200-110 and [^{3}H]ryanodine because the K_d for [^{3}H]PN200-110 and [^{3}H]ryanodine is not significantly different between 18-month and 33-month old rats. Furthermore, in an earlier study using the same animal model (Fisher 344 cross Brown Norway Rats), we have shown that the decrease in the B_{max} value of [^{3}H]PN200-110 and [^{3}H]ryanodine in 28-month old rats is not due to changes in their binding affinity [3]. The age-related decrease in the number of DHPR is higher than the results (51%) reported earlier because the animals used in the present study are 5 months older than in the earlier study [3]. Consequently a higher age-related reduction in DHPR/RyR1 ratio (see below) is observed in the present work than the results

(20%) obtained in the earlier study [3]. The B_{max} values correspond to a PN200-110/ryanodine binding ratio of 1.00 ± 0.22 for 8-month, 1.09 ± 0.15 for 18-month and 0.52 ± 0.13 for 33-month old rats.

3.2. DHPR and RyR1 in mixed fiber-type skeletal muscles from caloric restricted rats

Fig. 2 is a representative of [^{3}H]PN200-110 and [^{3}H]ryanodine binding done in 18-month old and 33-month old caloric restricted rats. A Scatchard analysis of ligand binding to the DHPR and RyR1 is shown as the inset. Analysis of [^{3}H]PN200-110 and [^{3}H]ryanodine binding to skeletal muscle homogenate from 8-month, 18-month and 33-month old rats on 60% caloric restriction are given in the bottom panel of Table 1. The B_{max} and K_d, and DHPR/RyR1 ratio values for 8-month old rats on caloric restriction are similar to the values from 8-month old ad libitum fed rats. The number of DHPR and RyR1 and the respective K_d of 18-month old caloric restricted rats are not statistically different compared to respective values obtained in 8-month or 33-month old caloric restricted rats (Table 1). The B_{max} values of DHPR and RyR1 corresponded to a PN200-110/ryanodine binding ratio of 0.88 ± 0.21 in 8-month, 0.85 ± 0.16 in 18-month and 0.83 ± 0.13 in 33-month old rats. For each age group 10 determinations were made from 5 rats. The DHPR/RyR1 ratio is not significantly different between 8-month, 18-month and 33-month old caloric restricted rats (Table 1). These results indicate that the age-related decrease in the number of DHPR, RyR1 and DHPR/RyR1 ratio observed in 33-month old ad libitum fed rats is absent in 33-month old caloric restricted rats.

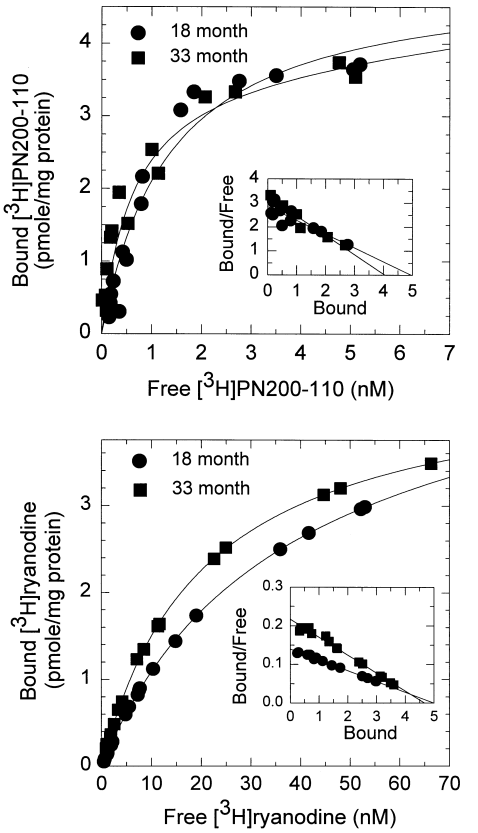

Fig. 2. [^{3}H]PN200-110 (top) and [^{3}H]ryanodine (bottom) binding to skeletal muscle homogenates in an 18-month and 33-month old caloric restricted rat. B_{max} and K_d values were obtained from Scatchard analysis and fitting of Eq. 1 to binding data (inset). The best fit parameters for all the experiments are included in Table 1.

3.3. The age-related effects on the number of DHPR depend on the diet

A two-factor analysis of variance (ANOVA) was used to see whether the number of DHPR, RyR1 and the ratio of DHPR/RyR1 are affected by the interaction of two different factors, namely aging and caloric restriction. The age-related effects on the number of DHPR and RyR1 (Table 1) depend on whether the animals were fed ad libitum or caloric restricted. There was a statistically significant interaction between the age and the dietary status (ad libitum or caloric restriction) of the rats in the number of DHPR ($P < 0.05$). In the case of RyR1 and DHPR/RyR1 ratio no statistically significant interaction between age and caloric status of the rat was observed because the age-related changes in these two parameters were only seen in rats fed ad libitum and not in caloric restricted rats.

Table 1
High-affinity [^{3}H]PN200-110 and [^{3}H]ryanodine binding to skeletal muscles of F344BNF1 rats fed either ad libitum or on 60% caloric restriction

Age	DHPR		RyR1		DHPR/RyR1
	B_{max}	K_d	B_{max}	K_d	
Ad libitum					
8-month	2.80 ± 0.47	2.98 ± 0.78	2.82 ± 0.27	19 ± 8	1.00 ± 0.22
18-month	3.52 ± 1.53 (ns)	1.54 ± 0.60 ($P < 0.05$)	3.37 ± 0.66 (ns)	51 ± 26 ($P < 0.05$)	1.09 ± 0.15 (ns)
33-month	1.30 ± 0.25 ($P < 0.01$)	1.67 ± 0.67 (ns)	2.55 ± 0.29 ($P < 0.05$)	39 ± 16 (ns)	0.52 ± 0.13 ($P < 0.01$)
Caloric restriction					
8-month	2.56 ± 0.21 (ns)	2.39 ± 1.63 (ns)	2.85 ± 0.63 (ns)	18 ± 7 (ns)	0.88 ± 0.21 (ns) (ns)
18-month	4.42 ± 1.95 (ns) ($P = 0.05$)	2.62 ± 0.81 (ns) (ns)	4.52 ± 1.95 (ns) (ns)	22 ± 14 (ns) (ns)	0.85 ± 0.16 (ns) (ns)
33-month	3.63 ± 0.56 ($P < 0.001$) (ns)	1.50 ± 1.25 (ns) (ns)	4.40 ± 0.36 ($P < 0.001$) (ns)	38 ± 12 (ns) (ns)	0.83 ± 0.13 ($P < 0.05$) (ns)

B_{max} and K_d are mean ± S.D. and expressed in pmol/mg protein and nM, respectively. Statistical significance within 8-, 18-, and 33-old month rats is given below the data, and between ad libitum fed rats and rats fed on caloric restriction is given next to the data. ns = not significant.

3.4. DHPR and RyR1 in soleus and EDL muscles from ad libitum fed and caloric restricted rats

To determine whether the prevention of age-related decrease in the number of DHPR by caloric restriction is due to changes in fast- and/or slow-twitch muscles, binding assays on these muscles were performed on ad libitum fed and caloric restricted 8-month, 18-month and 33-month old rats. The B_{max} values of DHPR and RyR1 in soleus and EDL muscles of the ad libitum fed rats were determined by a single saturating concentration of [^{3}H]PN200-110 and [^{3}H]ryanodine and are similar to values reported by us earlier [3,13] (Table 2). The B_{max} values of DHPR and RyR1 in soleus and EDL muscles of younger rats were similar to middle-aged rats. Aged rats (33-month) showed a decline in the number of DHPR and RYR1 in both soleus and EDL muscles similar to those reported in our earlier study [3]. In the present work we found a significant decrease in the number of RyR1 in soleus muscles that was not recorded before [3]. An explanation for this difference can be that 5-month older rats have been used in the present study. Because of an equivalent decrease in the number of DHPR, the decrease in DHPR/RyR1 ratio of the 33-month old rats is similar to the results obtained earlier in 28-month old rats [3]. The number of DHPR in soleus and EDL muscles isolated from caloric restricted 8-month, 18-month and 33-month old rats are given in the bottom panel of Table 2. These results indicate that there are no significant age-related changes in the number of DHPR, RyR1 and DHPR/RyR1 ratio in soleus and EDL muscles from caloric restricted rats. Furthermore, these results suggest that caloric restriction modulates equally both receptors in muscles consisting almost exclusively of slow- or fast-twitch muscle fibers.

4. Discussion

The present study reports that a 40% restriction in caloric intake from 16 weeks of age prevents age-related decrease in the number of DHPR, RyR1 and DHPR/RyR1 ratio observed in 33-month old rat skeletal muscles. 33-month old ad libitum fed rats show a decrease in the number of DHPR and RyR1 compared to 18-month old rats. This decrease in [^{3}H]PN200-110 and [^{3}H]ryanodine B_{max} is not due to changes in the binding affinity for [^{3}H]PN200-110 and [^{3}H]ryanodine because no significant change in their respective K_d is observed between 18-month and 33-month old rats. These results are consistent with our earlier study involving ad libitum fed F344BNX rats [3]. In this study we reported that the age-related decrease in the number of DHPR and RyR1 is not due to decrease in the binding affinity to [^{3}H]PN200-110 and [^{3}H]ryanodine.

The DHPR is a voltage-gated Ca^{2+} channel and its activation by *t*-tubule membrane depolarization evokes Ca^{2+} release from sarcoplasmic reticulum through RyR1 into the myoplasm [14]. Contractile proteins on binding Ca^{2+} initiate muscle contraction and force development. Hence, DHPR and RyR1 play a central role in the mechanism of excitation-contraction coupling in skeletal muscle. The reduction in the number of DHPR and RyR1 alters the electromechanical transduction leading to muscle force development, resulting in muscle weakness in the elderly [4]. In young EDL muscle, the DHPR/RyR1 ratio of $\sim$1 indicates that every DHPR is coupled to one RyR1. In older EDL muscle, the DHPR/RyR1 ratio of 0.83 indicates that there is a number of RyR1 unlinked to DHPR. In young soleus muscle, the DHPR/RyR1 ratio of 0.52 indicates that every other RyR1 is coupled to DHPR and in older soleus muscle the ratio decreases to 0.3 suggesting further RyR1 uncoupling to DHPR. Chronic restriction prevents the uncoupling of RyR1 from DHPR by preventing decline in the number of DHPR supporting the concept that the structural elements involved in the signaling cascade of the muscle force development are better preserved.

Skeletal muscle in the resting state utilizes a large share of the body's total oxygen consumption, due to its large mass, and most of the oxygen consumption during intense muscular activity. Approximately 2–3% of oxygen consumed is converted into reactive oxygen species as a by-product of the normal operation of the electron transport system [15]. These reactive molecules are believed to create a state of 'oxidative stress', which produces oxidative changes to proteins. It is

Table 2
High-affinity [^{3}H]PN200-110 and [^{3}H]ryanodine binding to soleus and EDL muscles of F344BNF1 rats fed either ad libitum or on 60% caloric restriction

Age	Soleus muscle			EDL muscle		
	DHPR	RYR1	DHPR/RyR1	DHPR	RyR1	DHPR/RyR1
Ad libitum						
8-month	1.81 ± 0.49	3.38 ± 0.54	0.52 ± 0.09	3.45 ± 0.65	3.55 ± 0.74	0.95 ± 0.10
18-month	1.78 ± 0.48 (ns)	3.89 ± 0.72 (ns)	0.47 ± 0.05 (ns)	4.51 ± 1.53 (ns)	4.42 ± 2.10 (ns)	1.04 ± 011 (ns)
33-month	0.84 ± 0.52 ($P < 0.01$)	2.62 ± 0.59 ($P < 0.02$)	0.31 ± 0.16 ($P < 0.05$)	2.86 ± 0.67 ($P < 0.03$)	3.57 ± 0.88 ($P < 0.01$)	0.83 ± 0.19 ($P < 0.05$)
Caloric restriction						
8-month	2.30 ± 1.17 (ns)	3.51 ± 0.79 (ns)	0.67 ± 0.32 (ns)	4.24 ± 0.73 (ns)	4.82 ± 0.97 (ns)	0.88 ± 0.04 (ns)
18-month	2.19 ± 0.68 (ns)	4.3 ± 1.83 ($P < 0.02$) (ns)	0.55 ± 0.21 (ns) (ns)	4.70 ± 0.85 (ns) (ns)	4.98 ± 1.72 (ns) (ns)	0.98 ± 0.14 (ns) (ns)
33-month	1.9 ± 0.68 ($P < 0.02$) (ns)	3.61 ± 0.96 ($P < 0.05$) (ns)	0.53 ± 0.17 ($P < 0.05$) (ns)	5.95 ± 1.26 ($P < 0.05$) (ns)	5.59 ± 1.00 ($P < 0.001$) (ns)	1.08 ± 0.28 ($P < 0.005$) (ns)

The values of B_{max} are mean ± S.D. and expressed in pmol/mg protein. Statistical significance within 8-, 18-, and 33-old month rats is given below the data, and between ad libitum fed rats and rats on caloric restriction is given next to the data. ns = not significant.

postulated that oxidative stress in skeletal muscle may contribute to the development of muscle loss and weakness [16,17].

Caloric restriction has beneficial effects on skeletal muscle structure. Caloric restriction delays the decline of gastrocnemius muscle mass and reduces the age-related loss of hindlimb skeletal muscle mass in Fisher 344 rats [6]. Caloric reduction has been found to reduce the rate of age-related skeletal muscle mass loss in soleus, anterior tibialis, EDL and hindlimb muscle of rats [7,8]. The secondary or delayed onset injury induced by the free radicals in EDL muscle was alleviated by treatment with a free radical scavenger, polyethylene glycol-superoxide dismutase [9]. Furthermore, 50% caloric restriction initiated at 17 months of age preserved the fiber number and fiber type composition in the vastus lateralis muscle of the aged rat [10]. Of all the interventions used to stop the aging process, namely, anti-oxidant supplementation, deprenyl drug therapy, hypophysectomy, dehydroepiandrosterone drug therapy, and caloric restriction, caloric restriction has proved to be the most effective and reproducible procedure [5]. The molecular mechanism(s) by which caloric restriction prevents the decrease in the number of DHPR and RyR1 has yet to be elucidated. However, caloric restriction can maintain the level of these proteins in old animals by preventing (i) the decline of plasma IGF-I concentration [18]; (ii) decrease in protein synthesis [19]; or by (iii) oxidative-stress induced protein oxidation and degradation [20], further studies are needed to evaluate these points.

In summary, the present work demonstrates that age-related changes in the number of DHPR, RyR1 and DHPR/RyR1 ratio in fast- and slow-twitch muscle fibers can be prevented by caloric restriction. The molecular mechanisms leading to preservation of DHPR and RyR1 levels in aging muscles are currently under investigation.

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