Angiotensin-Converting Enzyme Inhibition, Body Composition, and Physical Performance in Aged Rats

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This study was designed to test the effects of angiotensin-converting enzyme (ACE) inhibition on body composition and physical performance in aged rats. Male Brown Norway × Fischer 344 rats were randomized to receive daily injections of enalapril (40 mg/kg or 80 mg/kg) or saline from 24 to 30 months of age. Body composition was determined using dual-energy X-ray absorptiometry (DXA), and physical performance was assessed using the grip strength and inclined plane procedures. Performance measures were assessed at baseline and monthly thereafter. DXA was performed at baseline, 3 months, and 6 months of follow-up. Compared with the enalapril groups, the saline group experienced a greater 6-month decline in the physical performance measures. Lean body mass declined in both groups; however, the enalapril groups also experienced a significant loss of fat mass. These results suggest that ACE inhibition may prevent age-related declines in physical performance, which may be mediated by a reduction in body fat mass.

OBSERVATIONAL studies suggest that angiotensin-converting enzyme (ACE) inhibition may help to prevent age-related declines in physical performance. We previously reported a positive association between use of ACE inhibitors and muscle strength and walking speed in a subpopulation of individuals from the Women’s Health and Aging Study (WHAS) (1). Our results suggest that ACE inhibitor treatment could decrease long-term decline in physical function in elderly women. Other evidence from a recent cross-sectional study using a sample of healthy elderly men and women from the Health and Aging Body Composition Study (Health ABC) demonstrated a significant positive association between use of ACE inhibitors and skeletal muscle mass (2). However, it remains to be determined in prospective randomized controlled trials whether ACE inhibitors may prevent the progression of disability in older persons and whether this effect is mediated by remodeling body composition.

Several genetic studies suggest that the renin-angiotensin system (RAS) modulates the function of skeletal muscle tissue and is a determinant of visceral adiposity. Enhanced responsiveness to exercise, mediated by an increase in muscle strength, is associated with the insertion (I) rather than the deletion (D) allele of the ACE gene, which, in turn, results in higher levels of ACE (3). There is also a higher prevalence of the ACE I/I allele among elite endurance athletes relative to the general population (4,5). Results from the Olivetti Prospective Heart Study reported that, in men aged 25–75 years, over a 20-year follow-up, the D/D genotype was a significant predictor of becoming overweight and increased abdominal adiposity (6). Although no functional outcomes were measured in this study, several studies have demonstrated that increased obesity is positively associated with declining physical performance and disability (7–10).

We have recently reported on the validity of an assessment method for evaluating declining physical performance in adult rats that is conceptually similar to that used in humans (11). Evaluating the therapeutic effects of ACE inhibitors on both changes in body composition and physical function in rodents may have future applications in randomized clinical trials in humans and help explain the biological mechanisms by which the changes occur. Thus, the purpose of this study was to assess the effects of ACE inhibition on body composition and physical performance in aged rats.

METHODS

Subjects

Brown Norway × Fischer 344 (F1) male rats (n = 92) were obtained from the National Institute on Aging colony at Harlan Industries (Indianapolis, IN) at 22 months of age. Male rats were chosen as subjects based on previous data from our laboratory characterizing declining function in aged male rats, over this same time span. Animals were housed in a specific pathogen-free facility throughout testing, which was accredited by the American Association for Accreditation of Laboratory Animal Care. Testing began at 24 months of age and continued for 6 months. Rats were housed 2 per cage (24 × 9 × 12 inches), were maintained on a 12-hour light/12-hour dark cycle with food (Purina standard lab chow; Nestle Purina, St. Louis, MO) and water available ad libitum, and were assessed on a monthly basis for signs of overt health problems using a standardized form. Measures included, but were not limited to, checking
for sudden decline in body weight, redness around the eyes and nostrils, ruffled coat, open sores on tail, and hunched posture. Animals were also palpated during these assessments to monitor for symptoms of disease and gross tumors. A total of 70 rats survived and were healthy at the end of the study. All animals were necropsied for gross pathologies whether they died spontaneously or were killed at the completion of the study. The causes of mortality in these animals ranged from indeterminate cause (n = 4), pituitary tumor (n = 1), neck tumor (n = 1), mammary tumor (n = 7), chest tumor (n = 1), intestinal tumor (n = 1), open tumor on testicle (n = 2), possible stroke (n = 2), anesthesia associated with dual-energy X-ray absorptiometry (DXA) scans (n = 2), and hind paw infection (n = 1).

Physical performance measures were assessed at baseline and monthly through the end of the study. DXA was performed at baseline, and at 3 months and 6 months follow-up.

Enalapril Administration and Treatment Monitoring

When animals reached 24 months of age, they were randomized to daily subcutaneous injections of 40 mg/kg or 80 mg/kg of enalapril maleate (enalapril, n = 30 in each group) mixed in a phosphate buffer saline solution or saline control (saline, n = 32) and were followed for 6 months. These doses were chosen based on pilot data from our laboratory showing that doses equal to or less than 20 mg/kg had little effect on physical performance (unpublished data). At the time of euthanasia, a subset of blood samples were taken for analyses of angiotensin I (ANGI)/angiotensin II (ANGII) ratio (n = 6 in each enalapril group and n = 5 in the saline group). Blood pressure, heart rate, and physical activity were monitored in a subset of animals (n = 3 in each dosing group) across a 30-day time period (24 to 25 months of age) using telemetry probes (TL11M2-C50-PXT: Data Science International, Arden Hills, MN) to ensure that the drug treatment was effective. Animals were anesthetized with a combination of ketamine/xylazine (ketamine 100 mg/kg given IM) and subsequently implanted with a sterile catheter attached to the telemetry probe, in the descending aorta. Lean and fat mass was determined for the total body.

Body Composition

Body composition was determined by DXA (Delphi A; Hologic, Inc., Bedford, MA), using the small animal software (n = 23 saline; n = 21 in each enalapril group). This software allows for whole body and subregion analysis of body composition. At our Center, the percent coefficients of variation (%CV) are 0.54% for BMC, 0.58% for BMD, 0.40% for lean mass, and 1.66% for fat mass. Prior to the scan, animals were anesthetized as described above for the telemetry surgery. Lean and fat mass was determined for the total body.

Muscle Weight, Cell Number, and Area

At the time of euthanasia, the soleus was excised, weighed, and immediately placed in formalin (n = 8, saline; n = 8, 40 mg/kg; n = 9, 80 mg/kg enalapril). The muscle was subsequently embedded in paraffin, cut into 8 μm sections, and stained with hematoxylin and eosin (H&E). Fiber cross-sectional area was analyzed using an inverted microscope (Axiovert 100; Zeiss, Oberkochen, Germany) and a PXL-EEV-37 CCD camera (Photometrics, Tucson, AZ)-based imaging system. Isee software (Inovision, Raleigh, NC) running in a Silicon Graphics O2 (Mountain View, CA) workstation was used for data acquisition and image processing. A 100 × 100 μm area was selected for analysis and cell number and individual area of each cell was determined using the Isee software.

Physical Performance Measures

Inclined plane.—This test is a measure of muscle tone and stamina. The rat was placed facing upward on a 60° tilted 1 cm mesh screen. The time taken for the animal to fall onto two 7.6 cm foam pads was divided by the animal’s weight and recorded with a maximum latency of 30 minutes.

Grip strength.—Forelimb grip strength was determined using an automated grip strength meter (Columbus Instruments, Columbus, OH). The experimenter grasped the rat by the tail and suspended it above a grip ring. After about 3 seconds, the animal was gently lowered toward the grip ring and allowed to grab the ring with its forepaws. The experimenter then quickly lowered the remainder of the animal’s body into a horizontal position and tugged the animal’s tail until its grasp of the ring was broken. The mean force in grams was determined with a computerized electronic pull strain gauge that is fitted directly to the grasping ring, and was divided by body weight. Average measurements from 3 successful trials were taken as the final outcome. Successful trials were defined as those in which the animal grasped the ring with both forepaws and pulled the ring without jerking.

Statistics

Descriptive data are expressed as means ± standard deviations (SD). The log-rank test was used to compare the survival distributions between the 3 groups. The primary analyses included weight, latency (normalized by weight and expressed as s/g), and grip strength (normalized by weight and expressed as g of force/kg). To achieve normality of residuals, we used the square-root transformation of normalized latency; other variables were not transformed. The primary analysis was a mixed-model analysis of variance with the rat as a random effect. Covariates included age in months as a categorical variable (rats were measured monthly), the value of the response at baseline, and treatment (3 levels). In some models, we also examined for an age-in-month by treatment interaction. Adjusted means were calculated and are reported with their associated standard errors (SE). Tukey’s or Student-Newman-Keuls adjustment for multiple comparisons was used when making post hoc pair-wise comparisons. Analyses of
the ANGII to ANGI ratio, mean arterial pressure, heart rate, activity, soleus muscle weight, cell number, and activity were analyzed using one-way or repeated measures analysis of variance with no covariates.

**RESULTS**

Table 1 summarizes baseline characteristics of the 40 mg/kg, 80 mg/kg, and saline groups. There were no significant differences between groups in total \( p = .19 \), fat \( p = .31 \), or lean mass \( p = .37 \), food consumption \( p = .66 \), or physical performance (grip strength: \( p = .61 \); inclined plane: \( p = .27 \)).

The ratio of ANGII/ANGI pg/day was calculated in a subset of animals at 30 months of age (Figure 1). There was a significant treatment effect \( p = .034 \) with rats on saline estimated to have a level of 10.66 pg/day, those on 40 mg/kg had a level of 5.06 pg/day, and those on 80 mg/kg had a level of 4.34 pg/day. Using a Student-Newman-Keuls adjustment for multiple comparisons, the saline group was different from both the 40 mg/kg \( p = .032 \) and 80 mg/kg groups \( p = .0358 \), which did not differ from each other \( p = .74 \). This is reflective of the ability of the enalapril treatment to effectively block the conversion of ANGII to ANGI resulting in higher levels of ANGI in the treatment groups (80 mg/kg: 1193 ± 348.95; 40 mg/kg: 1460 ± 882; saline: 275.2 ± 63 pg/day).

Table 2 summarizes changes scores between baseline and 6 months of follow-up on a variety of physiological measures and survival of the experimental groups. Mean arterial pressure, heart rate, and activity were sampled at 10-second intervals every 5 minutes over a 24-hour period at 24 months and 25 months of age. These data were averaged in 12-hour bins to measure possible differences in diurnal functioning. Food consumption was also measured at these same time points. There were no main effects or interactions among groups in diurnal measures, so data were combined into one daily value. There was a main effect of treatment condition in both the heart rate \( p < .0001 \) and mean arterial pressure \( p = .0132 \) measurements. All 3 treatment groups were significantly different from each other for heart rate (maximum \( p = .0060 \)), with saline showing the greatest reduction (−39.3 bpm), 40 mg/kg showing a moderate reduction (−17.6 bpm), and 80 mg/kg showing virtually no reduction (0.0 bpm). For mean arterial pressure, rats on 80 mg/kg enalapril/day had an average reduction of 10.8 mmHg, 40 mg/kg rats had an average reduction of 11.6 mmHg, and saline rats had an average reduction of 1.4 mmHg. The 40 mg/kg and 80 mg/kg groups were not significantly different \( p = .95 \) but there were significant differences between saline and 40 mg/kg \( p = .0177 \) and between saline and 80 mg/kg \( p = .0249 \). There were no differences in physical activity \( p = .58 \) or food consumption \( p = .80 \) (Table 2).

There was a highly significant interaction between month and treatment for total body weight \( p < .0001 \). As can be

**Table 1. Baseline Measurements of Body Composition and Physical Performance**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Saline</th>
<th>40 mg/kg</th>
<th>80 mg/kg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>346.6 ± 1.4</td>
<td>331.0 ± 4.7</td>
<td>323.7 ± 2.9</td>
<td>.12</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>105.3 ± 3.2</td>
<td>109.5 ± 9.6</td>
<td>102.4 ± 1.5</td>
<td>.30</td>
</tr>
<tr>
<td>Physical activity (movement/s)</td>
<td>1.6 ± 0.1</td>
<td>2.3 ± 0.7</td>
<td>1.6 ± 0.7</td>
<td>.51</td>
</tr>
<tr>
<td>Food consumption (g)</td>
<td>17.1 ± 1.4</td>
<td>16.7 ± 1.2</td>
<td>19.1 ± 2.4</td>
<td>.66</td>
</tr>
<tr>
<td>Body mass (g)</td>
<td>586.8 ± 7.2</td>
<td>588.6 ± 7.2</td>
<td>607.7 ± 8.3</td>
<td>.19</td>
</tr>
<tr>
<td>Lean mass (g)</td>
<td>426.7 ± 5.2</td>
<td>408.8 ± 5.2</td>
<td>418.4 ± 4.1</td>
<td>.37</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>160.0 ± 3.8</td>
<td>162.2 ± 3.8</td>
<td>171.4 ± 4.5</td>
<td>.31</td>
</tr>
<tr>
<td>Grip strength (g/kg)</td>
<td>2.0 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>.61</td>
</tr>
<tr>
<td>Inclined plane (s/g)</td>
<td>0.2 ± 0.03</td>
<td>0.1 ± 0.02</td>
<td>0.1 ± 0.03</td>
<td>.27</td>
</tr>
</tbody>
</table>

**Table 2. Physiological Characteristics of Animals After Receiving Saline or 40 mg/kg or 80 mg/kg Enalapril Daily From 24 to 30 Months of Age**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Saline</th>
<th>40 mg/kg</th>
<th>80 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Heart rate (bpm)</td>
<td>−39.3 ± 0.3</td>
<td>−17.6 ± 0.7⁰</td>
<td>0.0 ± 0.3⁰</td>
</tr>
<tr>
<td>Δ Mean arterial pressure (mmHg)</td>
<td>−1.4 ± 3.3</td>
<td>−11.6 ± 1.5⁰</td>
<td>−10.8 ± 1.5⁰</td>
</tr>
<tr>
<td>Δ Physical activity</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.7</td>
<td>−0.3 ± 0.8</td>
</tr>
<tr>
<td>Δ Food consumption (g/day)</td>
<td>1.9 ± 1.7</td>
<td>0.7 ± 2.1</td>
<td>0.0 ± 2.4</td>
</tr>
</tbody>
</table>

**Notes:** Change scores (Δ) indicate differences between 24 and 30 months of age.

⁰Significant difference from saline control.

ⁱSignificant difference between 40 and 80 mg/kg (all \( p < .05 \)).
seen in Figure 2, this was mainly attributable to a loss of fat mass (p < .001). Both the 40 mg/kg and 80 mg/kg groups lost significant amounts of total fat mass between 27 and 30 months of age relative to the saline group (both p < .001). This represented a change from baseline to 30 months of age of −12.3% and −22.4%, respectively, in the 40 mg/kg and 80 mg/kg groups and an increase of 4.8% in the saline group. There were equivalent losses of lean mass in all groups that occurred between 24 and 27 months of age (p < .001) that remained stable thereafter. This represented a 5.7%, 5.4%, and 6.3% reduction in lean mass in the 40 mg/kg, 80 mg/kg, and saline groups, respectively.

Figure 3 shows the adjusted means of inclined plane latency and grip strength over the 6-month period of the study. There was no evidence of an interaction between month and treatment either for inclined plane (p = .22) or for grip strength (p = .41). Consequently, we examined models without this interaction. There was no effect of treatment on latency (p = .17) with adjusted means of 0.32 for saline, 0.36 for 40 mg/kg, and 0.35 for 80 mg/kg (note: all are on the square-root scale). Similarly, there was no evidence of a treatment effect for grip strength (p = .17) with adjusted means of 0.0019 g/kg for saline, 0.0020 g/kg for 40 mg/kg, and 0.0019 g/kg for 80 mg/kg.

Because we initially suspected that changes in physical performance might not be evident until the end of testing, when aged animals tend to show the largest declines (11), the change in normalized scores between baseline (24 months) and the end of testing (30 months) were calculated. These supplementary analyses were performed using only those animals that survived to the end of testing on grip strength and inclined plane performance; because there were no differences between the two enalapril groups on any measure of physical performance, their data were combined and compared to saline controls (enalapril, n = 47; saline, n = 23). These data are presented in Figure 4 and summarize 6-month changes in these measures. Compared with the enalapril group, the saline group experienced a greater...
6-month decline in the inclined plane ($p = .0106$) and a marginally significant greater decline in grip strength ($p = .07$).

**DISCUSSION**

The purpose of this study was to assess the effects of an ACE inhibitor (ACEi), enalapril, on body composition and physical performance in aged rats. We have demonstrated that long-term ACEi in aged male rats moderately attenuates declining physical performance, and was most likely explained by a significant reduction in total fat mass, as no differences in skeletal muscle mass, fiber loss, or area were observed between either enalapril groups or the saline group. Unfortunately, no other measures of metabolic functioning of adipose or skeletal muscle were assessed in the current study, so there still remains the possibility that the quality of the muscle in the enalapril groups was different from that of controls. These findings are pertinent because of the growing body of evidence linking differences in fat mass and fat distribution to physical decline ([7–10] and see below].

Clinically, the association between fat mass and declining performance has been documented by several studies in humans. A recent cross-sectional analysis of a cohort of men and women aged 70–79 participating in the Health ABC study showed that lower strength with age was accounted for mostly by loss of muscle mass, but that age and body fat also had a significant association with strength and muscle quality (8). A cross-sectional and prospective trial in men and women aged 55 years and older showed that physical performance and self-reported functional limitation was negatively impacted by higher fat mass and higher fat-to-lean ratio (10). Finally, a cross-sectional examination of men and women aged 65–100 years in the Cardiovascular Health Study who reported disability at baseline showed a positive association between fat mass and disability but no relationship with lean mass. Of those not reporting disability at baseline, fat mass but not low fat-free mass was predictive of disability 3 years later (7). These studies show that fat mass itself is a predictor of impaired physical function and disability.

There is evidence that motor performance is improved with other manipulations that alter body mass, especially fat mass, in rodents. Rodents placed on a caloric restrictive diet across the life span show improved survival and a sparing of function in various motor performance tests including increased locomotor activity (12,13). Furthermore, physiological, molecular, and genetic measures of declines in muscle function and visceral adipose tissue accumulation that are observed in the ad libitum-fed animals are delayed by caloric restriction (14,15). Removal of visceral fat in both aged (20 months) and obese Zucker rats results in improvements in metabolic functioning of adipose tissue suggesting that prevention of the age-dependent accumulation of visceral fat could also help prevent insulin resistance seen with aging and perhaps the onset of diabetes itself (16).

One current hypothesis suggests that age-related “insulin resistance” contributes to the disregulation of metabolic functioning of both adipose and skeletal muscle tissue and may contribute to declining performance. There are many studies in humans showing that the onset of diabetes begins with the development of insulin resistance in adipocytes and ultimately results in skeletal muscle insulin resistance (17). There is relatively little data concerning the metabolic effects of ACE in normotensive aged rodents, although these animals demonstrate age-related pathophysiological changes (e.g., insulin insensitivity and obesity-related metabolic impairments) similar to those seen in hypertensive rodents. Studies in hypertensive and obese humans and rat models of these conditions show that ACE inhibition results in weight loss and that weight loss itself is associated with lower levels of both ACE in humans (18,19) and rodents (20,21).

However, it is unclear how ACE may contribute to declining performance or whether the effects seen with ACEi are mediated by the angiotensin receptor or other mechanisms. ACEi has two well-established effects: 1) prevent the conversion of ANGI to ANGII, and 2) block the proteolytic degradation of bradykinin (BK). Long-term
clinical trials in hypertensive persons using either angiotensin receptor blockers (ARBs), which only block the action of ANGII by antagonizing the AT1 receptor, or ACEi have shown that both treatments reduce the risk for the development of metabolic abnormalities in fat associated with type II diabetes. However, there is still some debate as to which intervention is more efficacious (22). Clearly, alterations in either pathway have profound hemodynamic effects but they have powerful metabolic consequences as well, most notably in conditions of hypertension, obesity, and insulin resistance.

There is ample evidence to show that BK is modulator of insulin action in muscle and adipose tissue through its action at the B2 receptor (23–25). BK potentiates the downstream signaling of insulin-dependent or independent GLUT-4 translocation in skeletal muscle through a cascade involving IRS-1 and PI3K, which ultimately results in translocation of GLUT-4 to the membrane. Old Wistar rats (20 months) demonstrate improved insulin sensitivity following both acute ACEi and BK administration versus the ARB losartan. This was accompanied by an increase in insulin-induced insulin receptor expression and IRS-1 phosphorylation as well as in IRS-1/PI 3-kinase association in the liver and muscle. Within skeletal muscle, acute or chronic ACEi improves insulin-dependent glucose transport in Zucker rats (26,27). In spontaneously hypertensive rats (SHR), chronic administration of trandolapril enhances insulin sensitivity of muscle glycogen synthesis (28), and application of BK leads to increased insulin stimulated glucose metabolism in soleus muscle. Compared with losartan, ACEi improves whole-body and tissue-specific insulin sensitivity (adipose or skeletal muscle). These effects are reversed with the B2 receptor blocker L-NAME (nitro-L-arginine methyl ester) and the nitric oxide (NO) synthase blocker Hoe140. In a murine model of type II diabetes, those mice treated with a low dose of temocapril had a decrease in plasma glucose and insulin, and enhanced 2-DG uptake in skeletal muscle but not in white adipose tissue, an effect that is attenuated with either Hoe140 or L-NAME (29).

Adipocytes also express BK B2 receptors. BK boosts tyrosine phosphorylation of the insulin receptor in insulin-treated adipocytes, and potentiates signaling of downstream effects such as phosphorylation of IRS-1 and activation of PI3-kinase and membrane translocation of the GLUT4 receptor—all insulin-dependent processes (25). Long-term enalapril treatment of SHR rats corrects insulin resistance of the adipocytes, is blocked by Hoe140, but is unaffected with losartan treatment. Taken together, increased BK activity on adipocytes and skeletal muscle may further help to ward off muscle insulin resistance and potentially diabetes (17).

The data concerning the effects of ARBs on insulin sensitivity are more ambiguous regarding tissue-specific analyses. Chronic oral administration of ARBs induces an enhancement of whole-body insulin action in Zucker (30), SHR (31), and fructose-fed rats (32), as well as humans with essential hypertension. Some evidence suggests that ARBs do not influence local insulin action at the cellular level (33,34); however, other studies demonstrate effects in soleus (35), a muscle group that is more responsive to insulin action.

As in skeletal muscle, all components of the RAS are found in adipose tissue. In rodent models (36), upregulation of both angiotensinogen (AGT) and ANGII levels produced locally in adipose tissue leads to further adipose tissue development associated with adipocyte hypertrophy and an increase in lipogenesis and triglyceride accumulation. These findings are consistent with studies showing that age-related white adipose tissue hypertrophy is also prevented with long-term losartan administration (37). In contrast, there are studies demonstrating that infusion of ANG II results in weight loss and reduction of white adipose tissue mass (38–40). A more detailed examination would lead to a better understanding of the mechanisms by which ARBs modulate tissue-specific insulin sensitivity and adipose tissue accumulation.

In the current study, the effects on physical performance were modest even in light of a significant decrease in total body fat mass. A possible interpretation is that perhaps the intervention was started too late or did not last long enough. However, as described above, there are several studies of acute and chronic treatment with enalapril in aged, hypertensive, and obese rats that resulted in improvements in many metabolic aspects of skeletal muscle and adipose tissue functioning. In addition, these studies were not conducted within the same age range (24 to 30 months) as animals used in this study and they did not assess physical performance. Another caveat is that even though performance was better maintained in the enalapril-treated groups, functional outcomes of activity level and survival were unchanged. Therefore, earlier intervention may be indicated in order for the physiological effects to have a more profound impact on physical function and possibly longevity. Because these data are correlational in nature, and because all doses of enalapril used in the current study result in both lower blood pressure and possibly to improvements in various aspects of cardiac function, future experiments are necessary to determine whether the observed effects with enalapril occur through its hemodynamic or metabolic-regulating properties. In fact, because this F1 strain of rat demonstrates fewer age-related pathologies relative to other strains (41), perhaps also including decreased incidence of cardiovascular abnormalities, it is quite possible that ACEi treatment would have less effect on cardiac function and hence performance. Finally and importantly, future studies should also include female rats as subjects given the increased susceptibility of this population, in humans, to disability and frailty (42).

**Conclusion**

Our findings suggest that ACEi in aged rats (24 to 30 months of age) attenuates age-related declines in physical performance and is associated with a reduction in total body fat mass. These rodent data are consistent with observational evidence in humans suggesting that ACEi may both preserve physical function and reduce visceral adiposity in older individuals. The data are also consistent with a large experimental literature in rodents. These findings raise the possibility that pharmacological manipulation of ACE in elderly people could be used as an intervention to prevent or slow the progression of muscle loss and/or increases in
adiposity that may contribute to age-related declines in physical performance. Therefore, the next step is to provide a more detailed description of these effects in rodents. There is relatively little data concerning the metabolic effects of ACEIs or ARBs in normotensive aged rodents, although these animals demonstrate age-related pathophysiological changes (e.g., insulin insensitivity and obesity-related metabolic impairments) similar to those seen in hypertensive rodents. The rodent model of age-related physical decline we have developed may accelerate the pace of research in this area by providing a paradigm in which to test interventions that would investigate how selectively altering these pathways would affect biological outcomes and the trajectory of physical performance decline.

ACKNOWLEDGMENTS

The study was supported by National Institutes of Health/National Institute on Aging grant P30 AG10484.

The authors would like to thank Dr. Drake Morgan for reading earlier versions of this manuscript and providing insightful commentary.

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Received December 2, 2003
Accepted February 27, 2004
Decision Editor: Edward J. Masoro, PhD

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