Steroid sulfatase gene variation and DHEA responsiveness to resistance exercise in MERET

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Riechman, Steven E., Tanya J. Fabian, Patricia D. Kroboth, and Robert E. Ferrell. Steroid sulfatase gene variation and DHEA responsiveness to resistance exercise in MERET. Physiol Genomics 17: 300–306, 2004.—Genetic influences and endurance exercise have been shown to alter circulating concentrations of dehydroepiandrosterone (DHEA) and its sulfated conjugate, DHEAS. We hypothesized that acute resistance exercise (RE) and training (RET) would increase DHEA steroids, and the magnitude of the increase would be influenced by a steroid sulfatase (STS) gene variation. Fasting blood samples were collected before and after the first (S1) and last (S30) session of a 10-wk RET program in 62 men and 58 women [age: 21.0 yr (2.4)]. Acute RE increased both DHEA [+2.8 (0.4), S1; +1.6 ng/ml (0.4), S30; P < 0.001] and DHEAS [+154 (24), S1; +166 ng/ml (15), S30; P < 0.001] and decreased DHEAS:DHEA [−27 (8), S1; −15 (7), S30; P < 0.01]. RET reduced resting DHEAS (−122 ng/ml, P < 0.01) and decreased DHEA response to RE (−50%, P < 0.05). Subjects with an STS “G” allele (n = 36) had greater acute changes in DHEA [+4.4 (0.7) vs. +2.0 ng/ml (0.5), S1; +3.2 (0.6) vs. +1.0 ng/ml (0.4), S30; P < 0.01] and DHEAS:DHEA [−37 (11) vs. 5 (7), S30, P < 0.05] than those subjects with only an “A” allele (n = 84). The observed increase in DHEA and DHEAS and decrease in DHEAS:DHEA suggest RE-induced STS activation which is influenced by the STS polymorphism.

X-linked; steroids; sex; polymorphism; sulfated dehydroepiandrosterone

THE ENDOGENOUS ADRENAL STEROID dehydroepiandrosterone (DHEA) has been titled the “mother steroid” for its role as a precursor to many other steroids including androstenedione, estradiol, testosterone, and dihydrotestosterone (reviewed in Ref. 23). Its sulfated conjugate DHEAS is the most abundant adrenal steroid in circulation (12, 23). Concentrations of DHEA and DHEAS peak in the third decade of life and decline with age (12, 23, 37), which has led researchers to examine the potential role of these hormones in health and aging. Several investigators have reported an association between decreased concentrations of DHEAS and the female sex (23, 37), lower physical activity (32), and elevated blood lipids (9, 23), reduced insulin sensitivity (6, 13), and unfavorable body composition including reduced lean body mass (1, 23), increased body fat (13), and central fat distribution (11). Not surprisingly, lower concentrations of DHEA and DHEAS have also been associated with epidemiological and clinical studies of cardiovascular disease (23, 36, 5, 28) and diabetes (36, 40, 42), although these studies have been done predominantly in men. Therefore, identification of genetic and environmental factors that increase endogenous concentrations of DHEA and/or DHEAS may be useful in mitigating these negative health outcomes.

While there are several reports of increased concentrations of DHEA and DHEAS in response to acute endurance exercise (14, 22, 23, 39), the effect of chronic endurance training is less clear. In a cross-sectional study of active and sedentary elderly men, physical activity was positively associated with DHEAS (32). In two prospective studies, DHEAS was unchanged after 12 or 14 wk of moderate-intensity endurance exercise in middle-aged men (19) or subjects with coronary artery disease (23). However, 8 wk of similar training in middle-aged weight-stable type II diabetic men resulted in a 36% increase in resting DHEA (8).

Despite the positive association between preservation of lean mass and both resistance exercise training (RET) (15) and plasma DHEA steroids (1, 23), studies have failed to demonstrate a change in resting concentrations of DHEA and DHEAS following RET (15, 18). These studies used middle-aged and older individuals performing moderate intensity training. To our knowledge, no study has addressed the effects of either acute resistance exercise (RE) or chronic high-intensity RET on circulating concentrations of DHEA and DHEAS in younger men and women.

Genetic variability may also influence circulating concentrations of DHEA steroids. Data from twin and family studies estimate that inherited factors account for between 39% and 65% of the variability in DHEAS concentrations (4, 20, 21, 25, 34). A within-twin-pair similarity was reported for increases in concentrations of DHEAS following endurance-training-induced weight loss (31). In addition, sex differences in the familiality of this trait have been documented (3, 33). Moreover, an investigation within the HERITAGE Family Study estimated the heritability for the effect of chronic endurance exercise training on resting DHEAS at about 30%. This suggests a moderate effect of genes influencing the variability of endogenous concentrations of DHEAS. An et al. (2) demonstrated significant linkage in five genomic regions for DHEA fatty acid ester and suggestive linkage in three regions for DHEAS in Caucasians of the HERITAGE Family Study. Although several biologically plausible candidate genes are contained in these regions, no specific genetic variation has been identified to account for the variability in DHEA steroids. As an alternative to the linkage approach to candidate selection, we chose a gene known to be X-linked and involved in DHEA metabolism. Variability in this gene, steroid sulfatase (STS), might contribute to the interindividual variability in DHEA steroids through its role in DHEA metabolism as well.
as to the variability between men and women through the effects of being X-linked (16).

Thus we designed a prospective RET study of young men and women to assess body composition changes and acute and chronic changes in circulating DHEA steroids. Based on the reports of heritable, sex, and exercise contributions to variability in circulating concentrations of DHEAS and the concomitant association of DHEA, DHEAS, and RE with preservation of lean mass, we hypothesized that sequence variation in the STS gene would be significantly associated with variation in changes in plasma concentrations of DHEA, DHEAS, and DHEAS:DHEA in response to acute RE and RET in young men and women.

**METHODS**

**Subjects.** This study was approved by the University of Pittsburgh Institutional Review Board. After all procedures were explained, subjects gave written informed consent prior to participation in the study. This study is part of and includes subjects from the MERET study (“Molecular Epidemiology of Resistance Exercise Training”). Recruitment of subjects was accomplished through presentations given by the investigators to students at the University of Pittsburgh. Recruitment efforts attempted to reflect the gender, racial, and ethnic characteristics of the University of Pittsburgh. Subjects were eligible for this study if they were between 18 and 31 yr of age. Excluded were individuals with a positive medical history for disorders involving the cardiovascular, endocrine, or skeletal muscle systems. Also excluded were those individuals who engaged in 3 h or more of RE per week and/or who reported taking putative performance-enhancing substances. Participants were instructed not to perform RET outside of the RET program. Subjects were given an information packet on proper nutrition and/or who reported taking putative performance-enhancing substances. Participants were instructed not to perform RET outside of the RET program and were encouraged to consume at least 0.5 g of protein per pound of body weight per day equivalent to 1.1 g/kg body wt (37.5% greater than RDA).

**Resistance exercise training.** Three familiarization–exercise sessions were conducted prior to the initiation of the RET program using the minimum weight to induce resistance (24). After these three sessions, one repetition maximum (1 RM), defined as the highest resistance at which one repetition can be successfully completed, were determined following a 3-min warm-up on an aerobic exercise machine and stretching. One RM was obtained on all exercise equipment used for the RET program. Baseline and posttraining body composition assessments were conducted for the following: height (wall-mounted stadiometer), weight (Detecto clinical scale), and body composition by hydrostatic weighing (35). Hydrostatic weighing was conducted in minimal attire within 2–4 days from starting or completing the RET. Subjects removed all jewelry and accessories and wore the same clothes for the post-RET assessments. Five to 10 hydrostatic weighing trials were conducted to ensure maximal performance. Subjects were verbally instructed and encouraged to achieve maximal performance on each trial. Residual volume was estimated according to the expectations of Hardy-Weinberg equilibrium (26).

**Hormone measurement and genetic analysis.** Fasting (≥8 h) blood samples were collected in 10-ml EDTA anticoagulant vials (Vacutainer) immediately before and after both the first session (S1) and 30th session (S30) of the RET program. All blood samples were collected between the hours of 8 AM and 3 PM (76% before 11 AM). Samples were immediately placed on ice and were subsequently centrifuged at 1,200 g for 25 min. Plasma was collected and stored at –70°C in 1-ml aliquots. Genomic DNA was extracted from the buffy coat from these samples using standard methods (26).

Human genomic DNA (100 ng) from study subjects was amplified for the G/A marker 3922 bp 3′ of the STS gene (SNP accession no. rs_13648, GenBank accession no. AH002991) with the following primers: forward, 5′-tag caa gag cta cc ac-3′; reverse, 5′-agt gga tgg aag att-3′. The 50-μl reaction mixtures contained 10 mM Tris-HCl (pH 8.0), 1.5 mM MgCl₂, 0.2 mM dNTP, 1 U of each primer, and 0.8 U Taq DNA polymerase (Invitrogen, Gaithersburg, MD). The reaction mixture was held at 95°C for 5 min followed by 35 cycles of 95°C for 30 s, 50°C for 30 s, 72°C for 30 s, and 72°C for 5 min.

The following procedures for fluorescence polarization (FP) for SNP detection are based on Chen et al. (10). At the end of the PCR reaction, 10 μl of an enzymatic cocktail containing shrimp alkaline phosphatase (2 U) and Escherichia coli exonuclease I (1 U) in shrimp alkaline phosphatase buffer [20 mM Tris-HCl (pH 8.0), 10 mM MgCl₂] was added to the 10-μl PCR product. The mixture was incubated at 37°C for 120 min before the enzymes were heat inactivated at 95°C for 15 min. The samples were then added to 10 μl of TDI reaction mixture containing the TDI buffer [50 mM Tris-HCl (pH 9.0), 50 mM KCl, 5 mM MgCl₂, 8% glycerol, 0.1% Triton X-100], 1.25 μM TDI primer (acc taa cag gat tca tgc tga agg), 25 nM of each allele-specific dye-labeled dideoxy-NTP, 100 nM unlabeled other two dideoxy-NTPs, and Taq DNA polymerase (1 U). The reaction mixtures were incubated at 94°C for 1 min, followed by 30 cycles of 94°C for 10 s and 55°C for 30 s. After the primer extension reaction, 100 μl of TDI buffer and 50 μl of methanol were added to each tube before FP measurement on a LJI Analyst HT fluorescence reader (LJI Biosystems, Sunnyvale, CA) controlled by LJI Criterion software. The average FP value was compared with the negative control samples using AlleleCaller software (LJI Biosystems). If the net change was more than seven times the standard deviation of the controls (>40 mP), then the test sample was scored as positive for the allele (10).

Plasma samples were assayed for concentrations of DHEA and DHEAS using an 125I-radioimmunoassay method (Diagnostic Systems Lab, Webster, TX). The detection ranges for DHEA and DHEAS are 0.2–30 ng/ml and 25–8,000 ng/ml, respectively. The inter- and intra-assay coefficients of variation for each assay were <10% throughout the assays.

**Statistical analysis.** SPSS software (ver. 10.0.7; SPSS, Chicago, IL) was used to determine whether acute or chronic RE alters plasma concentrations of DHEA and/or DHEAS and whether a marker in the STS gene predicts this response and the related changes in body composition. We used t-tests to compare baseline characteristics between genotype groups to define any limitations common in small sample populations. Tests of fit to the expectations of Hardy-Weinberg equilibrium (χ²) were conducted to determine normal distribution of the study sample STS allele frequencies. Independent samples t-test analyses were then used to test for differences in baseline character-
Percent Caucasian 90.3 91.4
Post, posttraining.

DHEA and DHEAS concentrations. Therefore, these variables were included when appropriate. Data from men and women were analyzed separately as well as in pooled analyses.

RESULTS

Subjects. Table 1 presents the characteristics of 62 men and 58 women who completed the study (total n = 154), were genotyped for the STS polymorphism, and had all blood samples available for DHEA and DHEAS analysis. Age was similar in men and women, but otherwise characteristics were significantly different. Significant increases in strength, weight, lean mass, and body mass index (BMI) were observed for both men and women (P < 0.01), whereas fat percent was significantly decreased. No change in waist-to-hip ratio (WHR) occurred with RET. Nine percent of this study group was not Caucasian.

**DHEA and DHEAS** response. Table 2 presents arithmetic means (with SD) DHEA and DHEAS concentrations of peripheral blood plasma, taken immediately before and immediately after RE for S1 and S30. Acute RE resulted in significant increases in DHEA and DHEAS concentrations for both S1 and S30 in both men and women. The acute change in the ratio DHEAS:DHEA was significantly reduced at S1 in men and at S1 and S30 in the total cohort, indicating a greater relative increase in DHEA than DHEAS. The values for DHEA, DHEAS, and DHEAS:DHEA were significantly greater in men than women at all time points. Men also had a significantly greater DHEAS:DHEA response to acute RE (S1) than women (39% vs. 24%, and −13% vs. −1%, respectively). The acute DHEA response with RET at S30 was reduced compared with the acute response at S1. This reduction was similar between women (−52%) and men but was only significant in men (−49%) and in the total cohort (−50%). Resting concentrations of DHEAS were significantly lower after the RET program (S1 minus S30) in men and in the total cohort (Table 2). Body composition, age, activity history, time of day, and birth control use variables did not alter these conclusions.

**Association of DHEA and DHEAS to body composition.** WHR was significantly correlated to resting concentrations of DHEAS:DHEA at S1 in men and DHEA at S30 in women (Table 3) whereas DHEAS was significantly correlated to WHR in the combined sample at S1 (r = 0.468, P < 0.001) and S30 (r = 0.397, P < 0.001). Body fat percent was inversely correlated to resting DHEA at S1 in men (Table 3) and resting DHEAS at S1 (r = −0.239, P = 0.007) and S30 (r = −0.296, P = 0.001) in the combined sample.
WHR was significantly correlated \((P < 0.05)\) to acute change in DHEA and DHEAS at \(S1\) in women (Table 4), inversely correlated \((P < 0.05)\) to DHEAS:DHEA at \(S1\) in men, and significantly correlated to change in DHEA \((r = 0.317, P < 0.001)\), DHEAS \((r = 0.229, P = 0.009)\), and DHEAS:DHEA \((r = -0.278, P = 0.001)\) in the combined sample. Acute change in DHEA was significantly correlated to body fat percent at \(S1\) in women but inversely correlated to acute change in DHEA and DHEAS at \(S30\) in men. Percent fat was significantly correlated to acute change in DHEA \((r = -0.206, P = 0.019)\) and DHEAS \((r = -0.190, P = 0.033)\) in the combined sample.

The increase in lean mass and decrease in body fat percent over 10 wk of RET was significantly correlated with the increase in DHEA at \(S30\) in the combined sample, although no correlations were significant with sex stratification. Stratification by genotype resulted in a significant correlation of change in lean mass to change in DHEA at \(S30\) in those with only A allele \((r = 0.220, P = 0.044)\) but not in those with any G allele \((r = 0.078, P = 0.653)\). Conversely, change in fat mass with RET was significantly correlated to change in DHEA at \(S30\) in those with any G allele \((r = -0.340, P = 0.043)\) but not in those with any A allele \((r = -0.095, P = 0.389)\).

**STS genotype and RET responses.** The frequency of the common A allele in men \((77.4\%)\) was not significantly different from the frequency in women \((78.4\%)\), and the frequencies in men and women were in Hardy-Weinberg equilibrium \((P > 0.05)\). The increases in DHEA and DHEAS with acute RET were greater in both men and women who possessed the STS G allele (Table 5). The DHEA increases were statistically significant except for men at \(S1\). The DHEAS:DHEA decreases were statistically significant in men and the total cohort for \(S30\).

Moreover, the DHEA response to acute RE was significantly reduced after training in men and in the total cohort possessing only an A allele. Resting DHEAS concentrations were also significantly reduced following the 10-wk RET program in those individuals with an A allele (data not shown).

RET resulted in significant gains in lean mass. Individuals with only an A genotype (AA in women or A in men) had mean lean mass gains of 1.6 kg compared with gains of 1.1 kg in individuals with any G (GG, GA in women, or G in men). This difference was not statistically significant \((P = 0.148)\). RET also resulted in a more modest but significant loss in fat mass in men and women. While individuals with the A (men) or AA (women) genotype had little mean change in fat mass \((<0.3\,\text{kg})\), individuals with any G averaged a 0.9 kg loss. This difference was not statistically significant \((P = 0.089)\).

**DISCUSSION**

The MERET study was designed to examine how genetic variation influences responses to RET. In this report, we examined the effect of common genetic variation on a potential intermediate end point of RET responses, endogenous steroid hormone concentrations, in particular DHEA and DHEAS, which may be affected by RET. The results of this study show

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**Table 4. Pearson correlation coefficients of waist-to-hip ratio, body fat percent, change in lean mass, and change in fat mass to acute change in DHEA and DHEAS at sessions 1 and 30**

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<th>Variable</th>
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<td><strong>WHR</strong></td>
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<td><strong>ΔDHEA</strong></td>
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<td>S1</td>
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<td>0.190</td>
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<td>S30</td>
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<td>-0.294</td>
<td>0.017</td>
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<td><strong>ΔDHEAS</strong></td>
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<td>S30</td>
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<td><strong>ΔDHEAS:DHEA</strong></td>
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<td>S1</td>
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<td>-0.247</td>
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<td>0.052</td>
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<td>S30</td>
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<td>-0.002</td>
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<td><strong>ΔLean</strong></td>
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<td>-0.106</td>
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<td>S30</td>
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<td></td>
<td>-0.073</td>
<td>0.569</td>
<td>-0.132</td>
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<td><strong>ΔFat</strong></td>
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<td>S1</td>
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<td>-0.006</td>
<td>0.965</td>
<td>0.020</td>
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<td>S30</td>
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<tr>
<td></td>
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ΔLean, change in lean mass; ΔFat, change in fat mass.

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that acute RE results in increased plasma DHEA and DHEAS concentrations in men and women, an effect that is greater in men and in subjects with the G allele of an STS gene polymorphism. The acute changes in DHEA and DHEAS in response to RE decreased following 10 wk of RET particularly in subjects with only an A allele. Acute DHEA responsiveness to RE at the end of training was significantly correlated with more favorable body composition changes (Table 4), whereas these data suggest that individuals with the more DHEA-responsive G allele (Table 5) may have had less lean mass gain but greater fat loss than individuals with an STS A allele only (Fig. 1).

Two studies conducted in small samples of middle-aged and older subjects reported no changes in resting DHEA or DHEAS with 6 mo of RET (15, 18). We studied DHEA and DHEAS to examine whether this observation was an age-dependent effect but report here that resting DHEAS decreased modestly and DHEA was relatively stable with RET. However, the effect of training on basal concentrations may require greater training duration than has been studied to date. Several investigations have demonstrated that physically active individuals have higher DHEAS concentration than their sedentary counterparts (7, 32, 38). Maximal oxygen consumption, a measure of physical fitness, has also been associated to circulating DHEAS (1, 7), suggesting differences exist in the context of long-term exercise.

The acute change in DHEAS and DHEA with RET is consistent with acute changes reported for endurance exercise (14, 22, 23, 39). In contrast to those who have emphasized the possible importance of changing resting concentrations, the acute change in these steroid hormones may be sufficient to alter gene expression (primary role of steroids) and metabolism as part of the adaptive response to acute exercise and exercise training without necessarily altering resting concentrations. Since the precise physiological roles of DHEA and DHEAS are not well known in this context, alternate explanations should be sought for the differences observed between active and sedentary individuals and the lack of changes in resting concentration with chronic training.

DHEA-related steroids may have a governing role in nutrient partitioning in the regulation of body composition. The positive correlation of lean mass gain and fat mass loss to acute change in DHEA at the end of training supports this contention. Likewise, STS genotype appears to influence this acute responsiveness as well as differences in fat loss and lean mass gain. The trend for lower fat loss and greater lean mass in those with only the A allele compared with those with a G allele presents an apparent conflict under the assumption that one allele will be associated with all the desired physiological outcomes. The elevated metabolism associated with higher DHEA levels (G allele) may result in accelerated energy utilization but create a physiological circumstance (low energy reserves) that inhibits anabolism of muscle. However, the uncertainty of the effects on body composition in the present study are mirrored by a collection of investigations with similar objectives.

In a study by Nestler et al. (29), administration of 1,600 mg of DHEA for 28 days resulted in 31% decrease in fat with an equal increase in lean mass. In another study, 100 mg DHEA/day for 6 mo resulted in an increase in muscle mass and strength (27). In contrast, administration of DHEAS for 1 yr to 60- to 80-yr-old subjects resulted in restoration of plasma DHEAS levels to that of their youth counterparts but did not
change muscle strength or thigh cross-sectional area of muscle or fat (30). Similarly, 1,600 mg of DHEA/day for 28 days did not change energy or protein metabolism, body mass, or lean mass (41). Taken together, no firm conclusions can be drawn about the effect of DHEA on body composition; however, there was considerable within-study, between-subject variability in response in these studies, suggesting other factors such as genetic predisposition may play a role.

Since the STS enzyme converts DHEAS to the more active DHEA, the greater relative increase in DHEA than DHEAS (decreased DHEAS:DHEA) suggests that the STS enzyme activity is increased in response to RE. Alteration in other enzymatic activity may also contribute to the observed variability in DHEA steroid changes; however, the association of this response with the STS gene polymorphism suggests this enzyme is involved. The physiological significance of the shift to greater relative amounts of DHEA lies in possible direct effects of the more active DHEA or greater substrate availability for production of other steroid hormones. The decreases in DHEAS:DHEA in response to RE were greater in subjects possessing the G allele at S30. This observation may be attributed to decreased responsiveness with RET in those subjects with only an A allele and a relatively constant responsiveness in those subjects possessing a G allele. Therefore, these data suggest that RE results in activation of the STS enzyme and the STS polymorphism is associated with the RE-induced activation mechanism and adaptive response of the activation with training.

It is not currently known how this genetic variation might affect the STS enzyme activity. The distal 3′ location of this variant makes it unlikely that the effect observed is due to the base pair change. It is anticipated that this variation is in linkage disequilibrium with functional variation in coding or regulatory regions of the STS gene. Further study is required to characterize variation in the STS gene that is directly responsible for the observed effects.

Men had higher concentrations of DHEAS and DHEA than women at all measurement time points. Sučková et al. (37) reported similar differences in DHEAS but not DHEA in this age range. Higher concentrations of DHEA were observed in females between the ages of 1 mo and 100 yr of age, differences that were not significant in the 18–30 yr age range studied here. These previous results are consistent with the observation that the STS gene escapes X-inactivation, and therefore women have greater enzyme activity (16) which is demonstrated presently by lower DHEAS:DHEA in women. The difference of concentration between men and women may also be explained by the origin of DHEA and DHEAS (adrenal is the source for 95% of the steroid in women). We also report that men are more responsive to RE at S1, suggesting a sex-dependent regulation of RE-induced increase in DHEA.

Variables including time of day, menstrual phase, or previous exercise history may influence DHEA steroids. Using various techniques such as covariance or exclusion of subsets of subjects, we did not observe a change in the conclusions of this study. However, S1 and S30 were conducted in the fasting state in which the fasting by exercise interaction may result in different hormone responses than would be observed in the fed state. Menstrual phase may also contribute to the variation in hormone concentrations and their responses to RET. Menstrual phase data were not documented but would likely obscure findings (reduce power) rather than result in a false-positive effect (type I error).

This study provides evidence that acute RE results in elevated plasma concentrations of DHEA, DHEAS, and reduced DHEAS:DHEA, suggesting an activation of the STS enzyme. A polymorphism near the STS gene is associated with the acute response in DHEA and DHEAS:DHEA after training and perhaps body composition changes. Therefore, this variation or linked variation may be associated with a component of the enzyme that is responsive to a RE stimulus.

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GRANTS

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