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Endurance exercise training blunts the deleterious effect of high-fat feeding on whole body efficiency

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Endurance exercise training blunts the deleterious effect of high-fat feeding on whole body efficiency. Am J Physiol Regul Integr Comp Physiol 301: R320–R326, 2011. First published June 1, 2011; doi:10.1152/ajpregu.00850.2010.—We recently showed that a week-long, high-fat diet reduced whole body exercise efficiency in sedentary men by >10% (Edwards LM, Murray AJ, Holloway CJ, Carter EE, Kemp GJ, Codreanu I, Brooker H, Tyler DJ, Robbins PA, Clarke K. FASEB J 25: 1088–1096, 2011). To test if a similar dietary regime would blunt whole body efficiency in endurance-trained men and, as a consequence, hinder aerobic exercise performance, 16 endurance-trained men were given a short-term, high-fat (70% kcal from fat) and a moderate carbohydrate (50% kcal from carbohydrate) diet, in random order. Efficiency was assessed during a standardized exercise task on a cycle ergometer, with aerobic performance assessed during a 1-h time trial and mitochondrial function later measured using 31P-magnetic resonance spectroscopy. The subjects then underwent a 2-wk wash-out period, before the study was repeated with the diets crossed over. Muscle biopsies, for mitochondrial protein analysis, were taken at the start of the study and on the 5th day of each diet. Plasma fatty acids were 60% higher on the high-fat diet compared with the moderate carbohydrate diet. Endurance exercise performance was significantly reduced (P < 0.01), most probably due to glycogen depletion. Neither diet led to changes in citrate synthase, ATP synthase, or mitochondrial uncoupling protein 3. We conclude that prior exercise training blunts the deleterious effect of short-term, high-fat feeding on whole body efficiency.

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(or percentage) of energy liberated during chemical catabolism of metabolic substrates that is transduced to external work. The remainder is lost as heat. There are several key transduction steps that connect the oxidation of substrates to the performance of external work, any or all of which will influence overall efficiency. These are biomechanical efficiency (or effectiveness), contractile efficiency (in other words, the energy produced by the contractile proteins per mole ATP), mitochondrial efficiency (the ATP-to-O2 ratio), and the energy equivalence of oxygen [which is a property of the metabolic substrate(s)]. Excluding biomechanical efficiency, this can be written as:

Efficiency (%) = 100% × contractile efficiency

\[
\text{(J/mol ATP)} \times \text{mitochondrial efficiency (ATP/O2)} \times \text{energy equivalence of oxygen (J/mol O2)}
\]

Thus an increase in mitochondrial ATP/O2 increases ATP supply to the contractile proteins for a given O2, so that more contractile work can be performed.

Given its role in determining whole body efficiency, reduced muscle mitochondrial efficiency has several important physiological and clinical implications. In human subjects whose oxygen transport or delivery is compromised (for example, patients with anemia or lung disease), the efficiency with which the muscle mitochondria can utilize a scarce resource (oxygen) may be a key determinant of quality of life. Yet another application of changed muscle mitochondrial efficiency is in the realm of athletic performance, where whole body efficiency is a key determinant of aerobic performance (8). Our laboratory has recently shown that short-term, high-fat feeding impaired physical performance in rats, alongside increased skeletal muscle mitochondrial uncoupling and UCP3 content (26) and subsequently showed that 1 wk of high-fat feeding blunted whole body efficiency in sedentary men by >10% (12). There are obvious and important metabolic differences, however, between exercise-trained individuals and those who are sedentary. For example, endurance-trained subjects have higher mitochondrial density and lower expression of UCPs compared with sedentary controls (22), and this correlated with improved cycling efficiency. We, therefore, examined the effect of short-term, high-fat feeding on whole body efficiency, mitochondrial function, and aerobic performance in a cohort of endurance-trained men. We hypothesized that such a diet would raise plasma FFA and, as a result, decrease mitochondrial efficiency and aerobic exercise performance.

SUBJECTS AND METHODS

Subjects. We recruited 16 endurance-trained men from the Oxford University rowing crews. This study was approved by the Central Oxfordshire Research Ethics Committee and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Fully informed written consent was obtained from all subjects before the intervention. Twelve subjects consented to a muscle biopsy, although two subsequently withdrew their consent.

Experimental design. Subjects attended the Oxford Centre for Clinical Magnetic Resonance Research for an initial assessment. Subjects were screened to exclude impaired glucose tolerance, diabetes, hypercholesterolemia, thyroid dysfunction, abnormal hepatic and renal function, and standard magnetic resonance contraindications. A physical examination was performed to exclude major cardiac, respiratory, or abdominal pathology and ensure baseline heart rate, blood pressure, and electrocardiograms were normal. At this initial visit, subjects’ peak aerobic capacity was measured, as described previously (12). The percentage of maximum O2 uptake (VO2peak) at which the ventilatory threshold occurred was calculated according to the V-slope method (4).

After 1 wk, subjects were started on the main protocol, commencing with 3 days of a standardized, normal human diet, on day 2 of which a biopsy was taken from most subjects’ left or right vastus lateralis. Biopsies were taken under local anesthetic using a modified Bergstrom technique that has been described elsewhere (15), immediately frozen in liquid nitrogen, and stored at −80°C. On the morning of day 3, fasted subjects were transported to Oxford Centre for Clinical Magnetic Resonance Research, where a venous blood sample was collected, after which subjects were transferred to the exercise physiology laboratory, where they performed a structured warm-up followed by a 1-h time trial on the bicycle ergometers. The subjects were then randomly assigned to either a high-fat (identical in macronutrient composition to the one we used earlier) or moderate-carbohydrate diet (MCD) (Table 1) for 5 days, and the blood collection, warm-up, and exercise testing were repeated as described above for the 4 remaining days. Diet adherence and composition were assessed post hoc using nutritional assessment software (DietPlan 6, Forestfield Software, West Sussex, UK). On day 5 of the diet intervention, another biopsy was taken. There was then a “wash-out” period of 2 wk, after which the protocol was repeated, with the diets crossed over.

Measurement of whole body efficiency. The protocol used to measure gross and delta efficiency was similar to that described previously (11, 12). Testing was performed on a CycleOps ergometer (CycleOps Pro 300PT, Saris Cycling Group, Madison, WI). Subjects performed a structured warm-up that consisted of three 5-min work periods at 50, 100, and 150 W, without break, in ascending order, (9, 22, 24). Cadence was fixed at 90 rpm for all testing. Expired gases were collected breath by breath using a Metamax portable gas analyzer (Cortex Biophysik). In all cases, data used were the mean averages taken over the last minute at each workload. Metabolic cost was calculated using the equation in Ref. 24.

\[
\text{Metabolic cost} = (3.869 \cdot \text{VO}_2 + 1.195 \cdot \text{VO}_2 \times (4,186/60) \times 100, \text{and } 150 \text{ W, without break, in ascending order, (9, 22, 24).}
\]

Power output was measured directly and continuously at the ergometer’s back wheel using a PowerTap hub (14, 30). Gross efficiency was calculated at each work rate as follows: gross efficiency (%) = 100% × (work done/metabolic cost). Delta efficiency was calculated as the slope of the linear regression of the relationship between metabolic cost and external work done (24).

Aerobic exercise performance testing. Aerobic exercise performance was assessed during a 1-h time trial on the bicycle ergometer. After the structured warm-up described above, each subject was given a starting power output for the time trial. On day 1, this target was set as 60% of each subject’s peak 1-min power from the maximal test. On subsequent days, it was 10 W less than the mean power achieved during the time trial on the day before. For the first 8 min of the test, power was fixed to these targets. After this initial period, subjects were free to vary work rate as necessary. Power output and gas analysis data were recorded at 1-s intervals on the ergometer computer and downloaded later for analysis. Capillary blood was collected from the ear lobe on day 5 of the diet intervention using the Bergstrom technique that has been described elsewhere (15), immediately frozen in liquid nitrogen, and stored at −80°C.

<table>
<thead>
<tr>
<th>Table 1. Subjects’ descriptive data</th>
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<tr>
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<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
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<tr>
<td><strong>Absolute VO2peak, l/min</strong></td>
</tr>
<tr>
<td><strong>Relative VO2peak, ml·min⁻¹·kg⁻¹</strong></td>
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</table>

Values are means ± SE; n, no. of subjects. VO2peak, peak aerobic capacity.
an earlobe at 25 and 50 min. The sample was immediately used to determine the subjects’ blood lactate concentrations using a small handheld device [Lactate Pro, Arkay (31)].

Magnetic resonance spectroscopy exercise/recovery protocol. The magnetic resonance protocol was similar to one described previously (13). Subjects performed a series of plantar flexion exercises while in the bore of a 3-T Siemens Trio clinical magnetic resonance system. Subjects lay supine in the magnet with their foot secured to a custom-built plantar flexion ergometer. A dual-tuned $^3$P and $^1$H surface coil was placed under the widest part of the right gastrocnemius in a specially designed wooden housing. The subject was immobilized with the leg straight and strapped across the shins, knees, hips, and shoulders. The exercise protocol consisted of 5 min of rest, followed by three bouts of exercise, each 5 min long, interspersed with 7-min recovery periods. The work rates, which were established during pilot studies, were 4, 5, and 6 W at a pedal rate of 1 Hz. The subjects were continuously monitored; no subject had any difficulty keeping time, although one subject was unable to complete the exercise bouts. The first exercise bout was treated as a warm-up and familiarization effort; reported values are the means of the bouts at 5 and 6 W.

Magnetic resonance acquisition protocol and calculations. Spectra were acquired as described previously (13). All spectra were processed using jMRUI version 2.2 (28) and quantified using a nonlinear example, aerobic performance), differences were tested for significance using a 5 × 2 repeated-measures ANOVA. Day-by-day differences were subsequently tested using paired t-tests. When day 1 (pre) and day 6 (post) data only were available for example, $^3$P-NMR measurements), differences were assessed using a two-way repeated-measures ANOVA. For unpaired data that failed the tests of normality, a Mann-Whitney U-test was used. Statistical analyses were conducted using PASW 18.0 (SPSS, Chicago, IL). All data are reported as means ± SE with $\alpha = 0.05$.

RESULTS

Descriptive measures, diet adherence, and fasting plasma FFA. Subjects were aged 22 ± 1 yr, weighed 82 ± 2 kg, and had a mean peak VO$_2$ of 4.7 ± 0.2 l/min, confirming their trained status (Table 1). There was no significant difference between the total caloric content of the two diets. Calories derived from fats in the high-fat diet (HFD) comprised 74% of total intake (the target was 70%), whereas calories from carbohydrates comprised ~50% of total intake (the target was 50%) on the MCD (Table 2). As a result of the HFD, plasma FFA were 60% higher compared with the MCD ($P < 0.01$) (Fig. 1). There was no significant effect of either diet on body mass (data not shown).

Aerobic exercise performance and whole body efficiency. The HFD significantly reduced exercising respiratory quotient (RQ) when measured at the three standardized work rates of 50 W (0.75 ± 0.01 vs. 0.86 ± 0.01), 100 W (0.78 ± 0.01 vs. 0.90 ± 0.02), and 150 W (0.81 ± 0.01 vs. 0.92 ± 0.02, all $P < 0.001$) (Fig. 2A). As would be expected, this tended to increase VO$_2$ at all three work rates, becoming significant at 150 W (2.6 ± 0.1 vs. 2.5 ± 0.1 l/min, $P < 0.05$). We then calculated the VO$_2$ that would be required at each work rate based solely on the new, lower RQ. There was no disparity between the predicted and actual VO$_2$ (Fig. 2C), so that the increased VO$_2$ we observed could be entirely explained by the altered RQ. Consequently, there was no significant effect of diet on whole body efficiency at any work rate [50 W: 11 ± 0.6 (HFD) vs. 11 ± 0.3% (MCD); 100 W: 15 ± 0.4 vs. 16 ± 0.2%; 150 W: 18 ± 0.4 vs. 18 ± 0.3%; all $P > 0.05$] (Fig. 2B). Likewise, delta efficiency was not systematically different between diets [26 ± 1 (HFD) vs. 27 ± 1% (MCD), $P = 0.19$]. Performance in the 1-h time trials was significantly poorer from day 2 on the HFD [day 5: 215 ± 13 (HFD) vs. 243 ± 11 W (MCD), $P < 0.001$], with a correspondingly lower blood lactate concentration during exercise diet [day 5: 1.6 ± 0.1 (HFD) vs. 2.9 ± 0.4 mM (MCD), $P < 0.01$], which was highly significant when tested across the

Table 2. Details of the actual macronutritional composition of the diets

<table>
<thead>
<tr>
<th></th>
<th>Carbohydrate (%total)</th>
<th>Fat (%total)</th>
<th>Protein (%total)</th>
<th>Total kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-carbohydrate diet</td>
<td>47.7 ± 0.3</td>
<td>26.3 ± 0.4</td>
<td>26.6 ± 0.4</td>
<td>4,210 ± 214</td>
</tr>
<tr>
<td>High-fat diet</td>
<td>3.4 ± 0.1</td>
<td>74.4 ± 0.5</td>
<td>25.4 ± 3.3</td>
<td>4,321 ± 261</td>
</tr>
</tbody>
</table>

Values are means ± SE.
4 days of the dietary intervention using a repeated-measures ANOVA ($P = 0.001$), as well as on separate days.

Skeletal muscle phosphorus metabolism and pH. The HFD had no significant effect on phosphorus metabolism, although resting PCr concentration was raised marginally after both diets (for example, pre-HFD: 29.1 ± 0.5 vs. post-HFD: 29.6 ± 0.4 mM, $P < 0.05$). Likewise, resting pH decreased fractionally by 0.3% after both diets ($P < 0.05$). Many previous studies have shown $31^P$-magnetic resonance spectroscopy measurements to be stable and reproducible in healthy subjects in the absence of interventions, and so these small changes presumably represent minor metabolic adjustments, resulting from the repeated exercise testing. The only significant difference between diets was an increase in exercising pH from 6.98 ± 0.24 to 7.03 ± 0.13 on the HFD ($P < 0.05$). There was no difference in contractile efficiency between the diets (HFD: 67 ± 5 vs. MCD: 70 ± 4 μM ATP/J). There were no effects on muscle PCr recovery half time, which was 20 s throughout. An example of typical PCr recovery kinetics on both diets in a single subject is shown in Fig. 3.

**Skeletal muscle protein content.** UCP3, citrate synthase (CS), and ATP-synthase protein contents in whole muscle remained unchanged as a result of high-fat feeding.

**DISCUSSION**

Whole body efficiency is a key determinant of endurance exercise performance (8) with a substantial part of the variation in the physical performance of runners with similar aerobic capacities explained by their running economy (closely related to their whole body efficiency) (23). Furthermore, in conditions in which oxygen supply may be limited (for example, at high altitude or in hypoxic disease states), a reduction in the oxygen cost of doing work may be expected to produce improvements in performance (21). In patients suffering from diseases, such as cyanotic congenital heart disease, chronic obstructive pulmonary disease, or anemia, therapeutic interventions to im-

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![Graph](image_url) - Fig. 1. The effect of a high-fat vs. moderate-carbohydrate diet on plasma free fatty acids in endurance-trained men. Values are means ± SE ($n = 16$). *Significant at $P < 0.05$. **Significant at $P < 0.01$.

![Graph](image_url) - Fig. 2. The effect of a high-fat vs. moderate-carbohydrate (control) diet on exercising respiratory quotient (RQ; A), exercising oxygen uptake ($\dot{V}O_2$; B), and exercise efficiency (D). C: predicted vs. actual $\dot{V}O_2$. Predicted values are based on data from the moderate-carbohydrate diet, adjusted for reductions in RQ with unchanged efficiency. $\dot{V}CO_2$, CO$_2$ consumption; GE50, GE100, GE150: gross efficiency at 50, 100, 150 W, respectively; DE, delta efficiency. Values are means ± SE ($n = 16$). *Significant at $P < 0.05$. **Significant at $P < 0.01$. 

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AJP-Regul Integr Comp Physiol • VOL 301 • AUGUST 2011 • www.ajpregu.org
prove whole body efficiency may subsequently improve morbidity and mortality.

Our laboratory previously found that 1 wk of high-fat feeding reduced whole body efficiency by ~13% in sedentary men (12), and this has both clinical and human performance implications. Clinical implications aside, however, generalizing findings in a cohort of sedentary subjects to a trained population is often unwise, given the well-documented changes in physiology and metabolism that result from training. Therefore, we sought to test the hypothesis that a short-term HFD identical in macronutrient composition to the one we used previously (~75% calories from fats with minimal (<2%) carbohydrate) would have the same detrimental effect on whole body efficiency in endurance-trained as in sedentary men, and that this loss of efficiency would blunt aerobic exercise performance. We, therefore, measured performance during a 1-h time trial to investigate possible changes in endurance performance (18).

In the present study, 1 wk of high-fat feeding raised plasma FFA by ~60% compared with a MCD. The diet was, therefore, even more effective at raising plasma FFA in this group than in our earlier sedentary cohort (in our earlier sedentary cohort, a similar absolute increase from a higher baseline value represented an ~40% rise (12)). As might be expected, the increase in plasma FFA was reflected in a significantly reduced RQ when exercising at all three work rates (50, 100, and 150 W), demonstrating a shift in whole body substrate preference, away from glucose and toward fatty acids. Yet despite a significant increase in plasma FFA and a reduction in RQ at all work rates, we were unable to detect a decline in whole body efficiency in the endurance-trained subjects consuming a HFD. To exclude the possibility that we were committing a type II error, we calculated the mean differences and 95% confidence intervals for two measures that were directly comparable between this and the earlier study: gross efficiency at 100 W and delta efficiency (Table 3). First, it was apparent from this analysis that, despite the smaller number of subjects being studied, the confidence intervals under comparable conditions were smaller in the present study, possibly due to the more homogeneous cohort. Second, it was clear that the magnitude of the effect observed earlier was considerably greater (approximately double). Therefore, some factor had significantly blunted the effect of high-fat feeding on whole body efficiency in the present study, compared with our earlier work.

We previously suggested that the effect we observed in sedentary men might have been due to the acute action of fatty acids on UCPs (including UCP3). Given that there is a relationship between physical fitness and muscle UCP3 content (6, 34, 35), we directly compared the content of UCP3 and CS in the biopsies taken from our endurance-trained subjects with those from our earlier study (Table 4). Although UCP3 and CS were not systematically different, the ratio of UCP3 to CS (which reflects the quantity of UCP per mitochondrion) was significantly lower in our endurance-trained subjects compared with our sedentary subjects. We suggest, therefore, that the blunted effect of high-fat feeding on whole body efficiency in endurance-trained subjects may be due to their low muscle UCP3 content. There was no consistent effect of diet on UCP3 content in whole skeletal muscle in our endurance-trained cohort, a finding that is consistent with earlier work showing that UCP3 is not increased in response to high-fat feeding in endurance-trained subjects (7). That CS did not differ significantly between the trained and untrained cohorts was somewhat surprising. However, the discrepancy was most likely due to the acute variability of CS, particularly in response to training (36).

As in our earlier study, high-fat feeding had no significant effect on mitochondrial function, measured in vivo using 31P-magnetic resonance spectroscopy. As before, for technical reasons, we measured mitochondrial function in the gastro-

![Fig. 3. The effect of high-fat vs. moderate-carbohydrate (control) diet on phosphocreatine (PCr) recovery kinetics in a single subject.](http://ajpregu.physiology.org/ by 10.220.33.3 on June 26, 2017)

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**Table 3. Mean difference and 95% CI for selected measures from this study and that of Edwards et al. (12)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE100W (trained cohort)</td>
<td>–0.4</td>
<td>0.9</td>
<td>16</td>
</tr>
<tr>
<td>GE100W [sedentary cohort (12)]</td>
<td>–1.1</td>
<td>1.0</td>
<td>20</td>
</tr>
<tr>
<td>DE (trained cohort)</td>
<td>–1.6</td>
<td>2.4</td>
<td>16</td>
</tr>
<tr>
<td>DE [sedentary cohort (12)]</td>
<td>–3.1</td>
<td>3.0</td>
<td>20</td>
</tr>
</tbody>
</table>

n, No. of subjects. CI, confidence interval; GE100W, gross efficiency at 100 W; DE, delta efficiency.

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**Table 4. A comparison of selected measures from this study and that of Edwards et al. (12)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sedentary Subjects [data from Edwards et al. (12)]</th>
<th>Trained Subjects</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>36 ± 1</td>
<td>22 ± 1†</td>
<td>36 (20 + 16)</td>
</tr>
<tr>
<td>VO2max, l/min</td>
<td>3.6 ± 0.2</td>
<td>4.7 ± 0.2‡</td>
<td>35 (20 + 15)</td>
</tr>
<tr>
<td>VO2max, ml·min⁻¹·kg⁻¹</td>
<td>44 ± 2</td>
<td>58 ± 2‡</td>
<td>35 (20 + 15)</td>
</tr>
<tr>
<td>Muscle UCP3, AU</td>
<td>0.9 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>24 (12 + 12)</td>
</tr>
<tr>
<td>Muscle CS, AU</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>24 (12 + 12)</td>
</tr>
<tr>
<td>Muscle UCP3/CS, AU</td>
<td>1.2 ± 0.2</td>
<td>0.8 ± 0.2‡</td>
<td>24 (12 + 12)</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. n values show total and (sedentary n + trained n). VO2max, maximum O2 uptake; UCP3, uncoupling protein 3; AU, arbitrary units; CS, citrate synthase. *Different from sedentary at P < 0.05. †Different from sedentary at P < 0.01. ‡Mann-Whitney U-test; all other tests are unpaired t-tests.
nemius, not the quadriceps group (which is one of the principal locomotor muscles during cycling exercise and was our choice for biopsies). Thus there may have been an effect of the HFD on mitochondrial function in the quadriceps that was not apparent in the gastrocnemius. However, mitochondrial function in these two muscle groups is not systematically different (1), and both muscles would have been exposed to the same increases in FFAs, so it is unlikely that mitochondrial function would have been blunted in one and not the other.

Although high-fat feeding did not impair whole body efficiency, the diet significantly blunted exercise performance. The loss of performance was most likely due to the depletion of intramuscular glycogen stores, as the HFD would have supplied insufficient carbohydrate for the muscle cells to restock glycogen stores after exercise, and contractile efficiency was unaffected. The low levels of blood lactate during exercise, as well as the reduction in exercise-induced acidosis on the HFD, support this interpretation.

Limitations. Given the difficulty of recruiting a homogeneous cohort of endurance-trained subjects who were age-matched with our earlier study, we decided instead to maximize statistical power for the present study by recruiting as homogeneous a group as possible from the Oxford college rowing crews (a decision that is retrospectively justified by the smaller confidence intervals in Table 3). Yet this meant that the group studied here was significantly younger than the cohort in our earlier study (22 ± 1 vs. 36 ± 1 yr). Several lines of evidence led us to conclude that it was exercise training, rather than age, that explained the blunted effect of high-fat feeding we observed. First, the marked differences in physiology between the two groups (for example, in maximum V˙O2) were unquestionably the result of endurance-training rather than age. Second, there was no correlation between age and UCP3/CS across the groups. Third, the cohort in our earlier study, although significantly older, was not particularly old. Finally, the correlation between UCP3/CS and delta efficiency across both studies was not significantly affected by the inclusion of age as a control variable.

Perspectives and Significance

We previously showed that short-term, high-fat feeding blunted whole body efficiency in sedentary men. We sought here to test our hypothesis that a similar dietary regime would blunt whole body efficiency and, as a consequence, endurance exercise performance in a cohort of endurance-trained subjects. However, we found that 1-wk-long HFD had no detectable effect on whole body efficiency in this group. Therefore, exercise training appeared to partly offset the deleterious effect of high-fat feeding on whole body efficiency. We compared UCP content in muscle from our trained vs. our sedentary cohort and found that the trained subjects had significantly less UCP3 per mitochondrion. Therefore, we hypothesize that the blunted effect of high-fat feeding was due to a lower UCP content. Our findings suggest that a HFD is contraindicated for sufferers of hypoxic or ischemic diseases, but that exercise may partly offset this effect.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


