Thermic effect of food and β-adrenergic thermogenic responsiveness in habitually exercising and sedentary healthy adult humans

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Stob NR, Bell C, van Baak MA, Seals DR. Thermic effect of food and β-adrenergic thermogenic responsiveness in habitually exercising and sedentary healthy adult humans. J Appl Physiol 103: 616–622, 2007. First published April 26, 2007; doi:10.1152/japplphysiol.01434.2006.—The thermic effect of food (TEF) is an important physiological determinant of total daily energy expenditure (EE) and energy balance. TEF is believed to be mediated in part by sympathetic nervous system activation and consequent β-adrenergic receptor (β-AR) stimulation of metabolism. TEF is greater in habitually exercising than in sedentary adults, despite similar postprandial sympathetic nervous system activation. We determined whether augmented TEF in habitually exercising adults is associated with enhanced peripheral thermogenic responsiveness to β-AR stimulation. In separate experiments in 22 sedentary and 29 habitually exercising adults, we measured the increase in EE (indirect calorimetry, ventilated hood) during β-AR stimulation (intravenous isoproterenol; 6, 12, and 24 ng·kg−1·fat-free mass−1·min−1) and EE before and after a liquid meal (40% of resting EE; 53% carbohydrate, 32% fat, 15% protein). The increase in EE during incremental isoproterenol administration was greater (P = 0.01) in habitual exercisers (0.34 ± 0.03, 0.54 ± 0.04, 0.81 ± 0.05 kJ/min; means ± SE) than in sedentary adults (0.26 ± 0.03, 0.40 ± 0.03, 0.64 ± 0.04 kJ/min). The area under the TEF response curve was also greater (P = 0.04) in habitual exercisers (160 ± 9 kJ) than in sedentary adults (130 ± 11 kJ) and was positively related to β-AR thermogenic responsiveness (r = 0.32, P = 0.02). We conclude that TEF is related to β-AR thermogenic responsiveness and that the greater TEF in habitual exercisers is attributable in part to their augmented β-AR thermogenic responsiveness. Our results also suggest that peripheral thermogenic responsiveness to β-AR stimulation is a physiological determinant of TEF and hence energy balance in healthy adult humans.

sympathetic nervous system; energy expenditure; isoproterenol

TOTAL DAILY ENERGY EXPENDITURE (EE) is composed of resting energy expenditure (REE), physical activity EE, and the thermic effect of food (TEF) (14). TEF is the increase in EE in response to acute energy intake and accounts for ~10% of total daily EE (28, 29). Thus it is an important physiological determinant of EE and energy balance and, over time, may contribute to changes in body weight (10, 15, 20, 26, 27).

Two components of TEF have been identified: obligatory and facultative. The obligatory component is the energy necessary for nutrient digestion, absorption, transport, and storage (2) and is modulated by factors such as parasympathetic nervous system activity (13, 22) and glucose tolerance (20, 25, 33). The facultative component is thought to occur in several tissues, including skeletal muscle (39), and may be mediated in part by energy intake-evoked sympathetic nervous system (SNS) activation and resulting β-adrenergic receptor (β-AR) stimulation of cellular energy metabolism (1, 2, 30); the latter is believed to account for up to 40% of TEF (40). This SNS-β-AR element of TEF should be a function of the magnitude of the postprandial increase in SNS activity to the peripheral tissues (30, 31) and the responsiveness of the peripheral β-AR system to that SNS activation (18).

We and others have established that TEF is greater in healthy adult humans who habitually exercise than in their sedentary peers (11, 18, 37), despite similar postprandial SNS activation (18). Recently, in a separate set of experiments, we (4) observed greater thermogenic responsiveness to nonspecific β-AR stimulation (isoproterenol) in a group of habitually exercising adults than in sedentary controls. Collectively, these observations suggest that differences in TEF between habitually exercising and sedentary humans may be related in part to differences in peripheral β-AR responsiveness.

To determine whether TEF and thermogenic responsiveness to β-AR stimulation are related, for the first time in the present study we measured both TEF and thermogenic responsiveness to β-AR stimulation in the same subjects. Our hypotheses were that TEF is related to thermogenic responsiveness to β-AR stimulation and that the greater TEF in healthy adult humans who habitually exercise than in their sedentary peers is attributable in part to their augmented β-AR thermogenic responsiveness. We also wished to extend previous observations of greater TEF in habitual exercisers based on the selective experimental stimulus of glucose intake (11, 18) by establishing a greater TEF in response to a meal of mixed macronutrient composition, a stimulus more representative of a normal meal and, therefore, a state that can be generalized to a free-living situation.

MATERIALS AND METHODS

Subjects. We studied 55 healthy adult men and women (18–74 yr): 24 sedentary and 31 habitual exercisers. Sedentary subjects did not perform any type of regular exercise during the previous 2 yr and, compared with population norms in the United States, were in the lower 50th percentile for maximal oxygen uptake (VO2 max), a measure of maximal aerobic exercise capacity, based on their age (16). Habitually exercising subjects performed a minimum of 40 min of vigorous aerobic-type exercise ≥4 days/wk during the previous 2 yr and were in the upper 10th percentile for age-adjusted VO2 max. All

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subjects were healthy, as assessed by medical history and fasting glucose, insulin, and lipid profiles (Table 1). In addition, subjects ≥35 yr old underwent a physical examination with resting ECG as well as ECG and blood pressure assessments during graded treadmill exercise to volitional exhaustion. Subjects were nonsmokers and were not regularly taking any medications or vitamin or antioxidant supplements. The nature, purpose, and risks of the study were explained to each subject before written, informed consent was obtained. The experimental protocol conformed to the standards set by the Declaration of Helsinki and was approved by the Human Research Committee at the University of Colorado at Boulder.

Table 1. Selected subject characteristics

<table>
<thead>
<tr>
<th>Sex, males/females</th>
<th>Sedentary Adults</th>
<th>Habitual Exercisers</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/12</td>
<td>17/12</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>44±2</td>
<td>43±4</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.72±0.02</td>
<td>1.73±0.02</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>72.6±2.9</td>
<td>68.7±2.1</td>
</tr>
<tr>
<td>Body mass-index, kg/m²</td>
<td>24.5±0.7</td>
<td>22.8±0.5*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>81±3</td>
<td>77±2</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>31.0±1.9</td>
<td>21.9±1.3*</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>22.4±1.6</td>
<td>14.8±0.9*</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>50.3±2.6</td>
<td>53.9±2.2</td>
</tr>
<tr>
<td>VO₂max, ml·kg⁻¹·min⁻¹</td>
<td>32.1±1.8</td>
<td>43.0±1.6*</td>
</tr>
<tr>
<td>REE + FM, kJ/day</td>
<td>5531±253</td>
<td>5831±198</td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>60±2</td>
<td>53±1*</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>117/68±2/1</td>
<td>111/64±1/1*</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>48.6±6.9</td>
<td>40.3±4.2</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.9±0.1</td>
<td>4.9±0.1</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>5.0±0.2</td>
<td>5.0±0.1</td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>1.5±0.1</td>
<td>1.6±0.1</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>1.1±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>3.0±0.2</td>
<td>2.9±0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. VO₂max, maximal oxygen uptake; REE + FM, resting energy expenditure (adjusted for fat-free mass); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. *Different from sedentary (P < 0.05).

The thermogenic response to β-AR stimulation was determined by the increase in EE above REE in response to intraintravenous administration of the nonselective β-AR agonist isoproterenol [6, 12, and 24 ng·kg⁻¹·min⁻¹ as previously described by us (4, 5) and others (19, 41)]. Briefly, subjects were instrumented for measurement of heart rate (ECG) and blood pressure, and a catheter was placed in an antecubital vein and kept patent with heparin. After a 30-min rest period and instrumentation, REE was measured. The first 15 min were considered a habituation period after which oxygen consumption (VO₂) and carbon dioxide production were averaged each minute for 30 min using a ventilated hood indirect calorimetry system (DeltaTrac II Metabolic Monitor; SensorMedics, Yorba Linda, CA) calibrated daily with precision-mixed gases and biannually with an alcohol burn procedure. In our laboratory, this technique has a coefficient of variation (CV) of 4.9% and a test-retest r² of 0.92. This measurement was then repeated over three consecutive 30-min periods during incremental infusion of isoproterenol. EE was calculated from the average of the final 25 min of each 30-min collection using the Weir formula (43). We have previously established that steady-state conditions are attained during each of these 25-min periods by comparing VO₂ and carbon dioxide production during the first and last minute (4, 5) and that dosing of isoproterenol relative to FFM results in similar plasma isoproterenol concentrations in subjects with different body mass and composition (7).

TEF was determined by a modification of previously described procedures (18). After measurement of REE, subjects consumed a liquid meal (Ensure Plus, Ross Laboratories, Abbott Park, IL; 53% carbohydrate, 32% fat, 15% protein). To standardize the stimulus for each individual, the administered caloric load was equivalent to 40% of REE, resulting in meal sizes ranging between 340 and 765 kcal. The 40% caloric load was chosen because it represents ~30% of total daily caloric requirements, assuming that REE accounts for ~75% of total daily EE (26) and is reflective of a normal meal. Subjects consumed the liquid meal within 15 min. The TEF (i.e., the increase in EE above preprandial baseline levels during the postprandial period) was then measured for 4 h. Indirect calorimetric measurements were made for 15 min for each 30-min period, allowing the subjects relief from the ventilated hood for half of each 0.5 h, at which time the postprandial blood samples (10 ml) were drawn with K₂·EDTA plus 5 ml preserved with EGTA-glutathione) were collected in chilled tubes for measurement of concentrations of plasma glucose, insulin, and norepinephrine. Plasma norepinephrine was determined to confirm the absence of group differences in the SNS response to acute feeding; this was necessary to isolate the influence of β-AR responsiveness per se. Measurements of plasma glucose were needed to determine whether our mixed meal stimulus caused different glucose response in the two groups, which, in turn, could influence TEF. We measured insulin concentration to determine a possible relation between group differences in insulin sensitivity and TEF. That is, a lower insulin response in the habitual exercisers may be indicative of greater insulin sensitivity. TEF was calculated for each individual as the change (increase) from baseline across each time point and as the area under the response curve (trapezoidal rule).

Fat mass and FFM were measured with dual-energy x-ray absorptiometry (DXA-IQ; Lunar Radiation, Madison, WI, software version 4.1). VO₂max was determined with a metabolic cart (CardiO2/CP; MedGraphics, St. Paul, MN) during incremental treadmill exercise as previously described (3). Briefly, subjects walked and/or ran on a treadmill at an increasing grade until three of the following criteria were satisfied: volitional exhaustion (defined as an inability to continue), a heart rate within 10 beats/min of their age-related maximum (38), a plateau in the VO₂-work rate relation, and a rating of perceived exertion >19 (8).

All postprandial blood samples were immediately placed on ice and centrifuged within 60 min of collection to isolate plasma. Plasma samples were stored at −80°C until analysis. Plasma norepinephrine concentration was analyzed in duplicate by HPLC (CV: 4.5%; Dionex, Sunnyvale, CA). Insulin concentration was measured in duplicate by radioenzymatic assay (CV: 5.2%; Diagnostic Systems Laboratories, Webster, TX). Glucose concentration was determined in duplicate by enzymatic assay (CV: 0.67%; Roche Diagnostic Systems, Boulder, CO). Baseline (health screening) plasma was analyzed for cholesterol and lipids by enzymatic assays (CVs: 0.5–0.85%; Olympus America, Center Valley, PA).

Statistical analyses. Four of the original 55 subjects (2 sedentary and 2 habitual exercisers) were excluded from the final analyses because of technical issues that arose during data collection. REE was positively related to FFM (r = 0.86, P < 0.001); hence, REE was adjusted for differences in FFM using analysis of covariance. Two-way ANOVA (dose of isoproterenol × habitual activity status) with repeated measures (isoproterenol dose) was used to examine differences in the thermogenic response to β-AR stimulation between sedentary and habitually exercising adults. Differences in TEF between sedentary and habitually exercising adults were examined with one-way ANOVA (area under the response curve). Multiple comparisons of factor means were performed with the Neuman-Keuls test. A
weighted mean (6) was calculated to provide a single expression of peripheral β-AR thermogenic responsiveness:

\[
\text{Weighted mean} = [(\text{Iso}_1 \times 6) + (\text{Iso}_2 \times 12) + (\text{Iso}_3 \times 24)]/(6 + 12 + 24) \quad (1)
\]

where \(\text{Iso}_1\), \(\text{Iso}_2\), and \(\text{Iso}_3\) represent increases in EE above REE during administration of each isoproterenol dose (6, 12, and 24 ng·kg\(^{-1}\)·FMM\(^{-1}\)·min\(^{-1}\)), respectively.

Simple correlation analysis was used to examine the relation between β-AR thermogenic responsiveness and TEF. The level of statistical significance was set at \(P < 0.05\). Data are expressed as means ± SE.

RESULTS

There were no significant differences between the habitual exercisers and sedentary subjects for age, height, body mass, FFM, waist circumference, REE (adjusted for FFM), diastolic blood pressure, and plasma insulin, glucose, cholesterol, or lipids (Table 1). Habitual exercisers had a lower body mass index, %body fat, total fat mass, resting heart rate, and systolic blood pressure and a greater VO\(_2\) than the sedentary subjects (\(P < 0.05\); Table 1).

Responsiveness to β-AR stimulation. The increase in EE during β-AR stimulation was greater in habitual exercisers than in sedentary adults [Fig. 1; main effect of activity status \(P = 0.01\) and interaction (dose × activity status) \(P = 0.25\)]. Similarly, the weighted mean change in EE response during β-AR stimulation was also greater (\(P = 0.01\)) in habitual exercisers (0.66 ± 0.04 vs. 0.52 ± 0.04 kJ/min). Respiratory exchange ratio, a crude marker of substrate utilization, was similar between groups at rest but lower in the habitual exercisers during the highest dose of isoproterenol [interaction (dose × activity) \(P = 0.01\); Table 2], suggesting greater fat oxidation in the exercisers. Before and during each of the three doses of isoproterenol, heart rate and diastolic blood pressure were lower in the habitual exercisers [main effect of activity \(P < 0.05\) and interaction (dose × activity status) \(P > 0.05\); Table 2], whereas systolic blood pressure did not differ between groups [main effect of activity status \(P = 0.11\) and interaction (dose × activity) \(P = 0.35\); Table 2].

TEF response. Absolute EE in the pre- and postprandial conditions is shown in Fig. 2A. The increase in EE above REE after consumption of the liquid meal was greater in the habitual exercisers than in the sedentary adults (Fig. 2B; main effect of activity status \(P = 0.04\)). In line with this observation, the area under the TEF response curve was 23% greater in the habitual exercisers (Fig. 2C; \(P = 0.04\)). Furthermore, the area under the TEF response curve was positively related to VO\(_{2}\)\(_{\text{max}}\) [absolute VO\(_{2}\)\(_{\text{max}}\) (l/min): \(r = 0.42, P = 0.002\); relative VO\(_{2}\)\(_{\text{max}}\) (ml·kg\(^{-1}\)·min\(^{-1}\)): \(r = 0.35, P = 0.012\)]. The plasma norepinephrine responses to the meal were similar between the habitual exercisers and sedentary subjects regardless of whether expressed as absolute values (Fig. 3A; main effect of activity status \(P = 0.40\) and activity status-time interaction \(P = 0.75\)) or area under the curve (Fig. 3B; \(P = 0.41\)), suggesting that differences in TEF between groups were not related to differences in SNS activation. Similarly, plasma glucose concentrations did not differ between the habitual exercisers and sedentary subjects (Fig. 4A; main effect of activity status \(P = 0.18\) and activity status-time interaction \(P = 0.61\); Fig. 4B: area under the curve \(P = 0.21\)). However, plasma insulin concentrations were greater in the sedentary adults than in the habitual exercisers (Fig. 5A; main effect of activity status \(P = 0.01\) and activity status-time interaction \(P = 0.20\); Fig. 5B: area under the curve \(P = 0.03\), consistent with the idea of greater insulin sensitivity in the habitual exercisers.

Relation between TEF and β-AR responsiveness among individual subjects. The area under the TEF response curve was positively related to thermogenic responsiveness to β-AR stimulation (weighted mean) among individual subjects (Fig. 6; \(r = 0.32, P = 0.02\)).

Lack of influence of sex on primary outcome variables. All statistical comparisons were repeated with sex as an additional independent variable. None of the observations with respect to any of the primary outcome variables (thermogenic response to β-AR stimulation and TEF) was influenced by sex (all \(P > 0.10\)).

DISCUSSION

The presented study is the first to determine both TEF and thermogenic responsiveness to peripheral β-AR stimulation in the same group of humans. The key findings were, first, that exercising adults demonstrate enhanced TEF and augmented β-AR thermogenic responsiveness compared with their healthy sedentary peers. Thus increased thermogenic responsiveness to postprandial β-AR activation could play a role in the greater TEF metabolic phenotype of habitually exercising adult humans. Second, TEF and β-AR thermogenic responsiveness are related among individual healthy adults. In a broader context, our results also suggest that peripheral thermogenic responsiveness to β-AR stimulation is a physiological determinant of TEF and, hence, total daily EE in healthy adult humans.

Several lines of evidence support the view that SNS-β-AR activation of cellular energy metabolism contributes significantly to TEF in humans. The most compelling support comes from findings that inhibition of SNS activation or blockade of peripheral β-ARs results in a reduction in TEF (1, 30, 40), although this has not been observed in all studies (21, 32). This SNS-β-AR component of TEF should be determined by a combination of the extent of postprandial SNS activation (30, 31) and the responsiveness of the peripheral β-AR system to that stimulus (18).
Recently, we established that adult humans who regularly perform aerobic endurance exercise demonstrate greater TEF than their sedentary peers in the absence of differences in postprandial SNS activation (18). The results of the present study confirm the greater TEF of exercising adults and, based on the lack of difference in plasma norepinephrine responses, suggest that the enhanced TEF was not mediated by increased SNS activation. It also is noteworthy that, in our previous study, the composition of the liquid meal was 100% glucose, whereas in the present study the composition was mixed and thus more representative of the stimulus provided by a conventional meal. This finding indicates that the greater TEF observed in habitual exercisers is not specific to meal composition, a factor thought to influence differences in TEF between other populations (12, 28).

The present findings extend our previous observations (18) by showing that the greater TEF of habitually exercising adults occurs in a physiological setting of increased thermogenic

### Table 2. Metabolic and cardiovascular functions before and during β-adrenergic receptor stimulation

<table>
<thead>
<tr>
<th>Isoproterenol Dose</th>
<th>Sedentary Adults</th>
<th>Habitual Exercisers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>RER</td>
<td>0.81 ± 0.01</td>
<td>0.83 ± 0.02</td>
</tr>
<tr>
<td>HR</td>
<td>59 ± 2</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>SBP</td>
<td>117 ± 2</td>
<td>117 ± 2</td>
</tr>
<tr>
<td>DBP</td>
<td>68 ± 1</td>
<td>64 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Isoproterenol dose is in ng·kg FFM⁻¹·min⁻¹. RER, respiratory exchange ratio; HR, heart rate (beats/min); SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg). *Different from sedentary (P < 0.05).
responsiveness to β-AR stimulation, the latter being consistent with recent findings from our laboratory (4). This suggests that enhanced peripheral β-AR responsiveness could be a contributing mechanism to the greater TEF of healthy adults who regularly exercise than that shown in sedentary adults. However, we wish to emphasize that these associations do not provide direct cause and effect support for a physiological connection between these events. Rather, the present results provide a necessary initial experimental basis for proposing more complex and invasive experiments in the future to determine whether enhanced β-AR thermogenic responsiveness actually contributes to the enhanced TEF of exercising adults. These experiments likely will require manipulation of β-AR responsiveness to determine a predictable effect on TEF.

In the present study, TEF and β-AR thermogenic responsiveness were only moderately related within the pooled group of subjects. There are a number of probable explanations as to why the observed correlation was not stronger. First, β-AR stimulation of cellular energy metabolism appears to account for <50% of TEF (40). As such, other factors, including insulin resistance and factors involved in mediating the obligatory component of TEF, contribute to total TEF and could weaken a relation between TEF and β-AR thermogenic responsiveness (12, 25). Indeed, although the plasma glucose response did not differ between sedentary adults and habitual exercisers in the present study, the postprandial increase in plasma insulin was greater in the sedentary adults. This may be a reflection of a relative, subclinical insulin resistance compared with the exercising adults. Second, there is some error associated with experimental measurements of all physiological functions, including TEF and β-AR thermogenic responsiveness in the present study. The respective errors would act to reduce the correlation coefficient between the two events, thus underestimating their true physiological relation. Third, the in vivo SNS response to a mixed meal and the consequent activation of peripheral β-ARs may be different from the β-AR stimulation produced by systemic infusion of isoproterenol. This also would act to reduce the relation between TEF and β-AR thermogenic responsiveness. Fourth, it is possible that variations in the level of fitness within the sedentary and habitually active groups might account for some of the remaining unexplained variance as $V_O^2_{max}$ (both absolute and relative) was related to the area under the TEF response curve in the pooled sample and in the habitual exercisers (absolute: $r = 0.38$, $P = 0.04$; relative: $r = 0.41$, $P = 0.03$) but not in the sedentary group. Fifth, with such a wide range of age in our
subject pool, the inclusion of both men and women, and the varying levels of body fat, it is possible that several other factors may have contributed to variance that could act to weaken the correlation. However, we found no significant relations between either of our primary outcome variables (TEF and the thermogenic response to β-AR stimulation) with age, sex status, fat mass, or waist circumference (all \( P > 0.05 \)).

The absence of a relation between age and the thermogenic response to β-AR stimulation in the present study differs from the results of an earlier investigation in humans (19). Our inclusion of habitually exercising adults may be a factor in this difference, although we did not see a relation within our sedentary subjects, perhaps because of the limited group size. Finally, our data collection spanned a 12-mo period, and the season of testing was not standardized. Seasonal changes have been reported to influence basal and total daily EE and metabolic responses to temperature challenges (23, 24, 42); however, in the present study, both sedentary and habitual exercisers were tested throughout the entire calendar year. Thus group differences cannot be explained by seasonal variation, although we cannot rule out its potential influence on the unexplained variance. In any case, what can be reasonably concluded from our results is that TEF and the thermogenic responsiveness to β-AR stimulation are positively associated among healthy adults.

To properly interpret our results, we have considered several alternative explanations. FFM was slightly smaller in the sedentary group; consequently, the absolute dose of isoproterenol received by the habitual exercisers was slightly larger and may, in part, account for the greater thermogenic response. We believe that this alternative explanation is unlikely, based on several lines of evidence. First, van Baak and colleagues (7) previously demonstrated that dosing isoproterenol relative to FFM results in similar plasma isoproterenol concentrations in subjects with different body mass and composition. Second, the thermogenic response during β-AR stimulation is greater in habitual exercisers than in sedentary adults who do not differ in FFM (4). Furthermore, in subgroups of the sedentary adults (\( n = 12 \)) and habitual exercisers (\( n = 9 \)) matched for FFM (41.8 ± 0.5 vs. 41.5 ± 0.7 kg; \( P = 0.63 \)) (and thus total isoproterenol administration) in the present study, the thermogenic response to isoproterenol remained greater in the exercisers (5.6 ± 0.8, 9.1 ± 0.6, 14.6 ± 1.5% vs. 8.4 ± 0.7, 11.9 ± 1.0, 17.6 ± 1.0%; \( P = 0.02 \)). Finally, augmented vasodilator responses to isoproterenol administration have been reported in habitual exercisers compared with that shown in sedentary adults even when the plasma isoproterenol concentrations were smaller in the habitual exercisers (36).

A second alternative explanation of our findings pertains to the slightly greater, albeit nonsignificant (\( P = 0.64 \)), mean REE values in the habitual exercisers. As a consequence, the habitual exercisers have received a slightly higher caloric intake (stimulus) during the TEF measurement. Given that TEF is determined in part by the caloric value of a meal (28), the greater TEF in the habitual exercisers could have been mediated in part by their larger meal. However, in subgroups of sedentary adults (\( n = 9 \)) and habitual exercisers (\( n = 11 \)) matched for REE (sedentary: 5,028 ± 87 vs. habitual exercisers: 4,953 ± 126 kJ/day; \( P = 0.64 \)) TEF remained elevated in the exercisers (area under the TEF response curve: 121 ± 8.7 vs. 148 ± 9.9 kJ; \( P = 0.03 \)).

In the present study, TEF was measured for 4 h after energy intake, although EE can remain elevated above baseline for \( >5 \) h (28, 34, 35, 45). It is possible that, had we measured TEF over a longer duration, the difference between sedentary and habitually active adults may have become nonsignificant; however, inspection of the data in Fig. 2, A and B, suggests that this is unlikely. Indeed, it has been argued that measuring 70% of the TEF response is sufficient for purposes of comparing groups of subjects (17, 34). Moreover, the initial 4-h postprandial period is the period that appears to be most modulated by sympathetic β-adrenergic signaling (18). At the very least, our data suggest that TEF over 4 h is greater in habitual exercisers and that this response is related to the thermogenic response to β-AR stimulation.

Our protocol for determination of the thermogenic response to β-AR stimulation involved consecutive and incremental intravenous administration of isoproterenol. With this approach, there is a possible risk of gradual B-AR downregulation (tachyphylaxis), an effect that would be particularly evident during the higher doses. However, the data displayed in Fig. 1 do not support this idea. Another potential limitation associated with our β-AR response protocol relates to possible “drift” in the metabolic measurements between isoproterenol doses. This unaccounted variability may have weakened the relation between TEF and the thermogenic response to β-AR stimulation.

In contrast to thermogenic responsiveness, in the present study as well as in our previous investigation (4), the changes in heart rate and blood pressure during β-AR stimulation were similar in the sedentary adults and habitual exercisers. This should not be interpreted, however, as indicating a selective influence of habitual exercise status on thermogenic responsiveness to β-AR activation. Cardiovascular responsiveness to β-AR stimulation cannot be assessed under the conditions of the present study because the hemodynamic effects of systemic isoproterenol administration activate baroreflexes that, in turn, actively buffer heart rate via cardiac autonomic adjustments (9). This effect can conceal group differences in cardiovascular responsiveness to isoproterenol that are apparent during con-
ditions of attenuated baroreflex signaling with ganglionic blockade (44).

In conclusion, the results of the present study show that habitually exercising adults demonstrate both enhanced TEF and increased peripheral β-AR thermogenic responsiveness and that these metabolic functions are related. Thus our findings provide initial evidence that increased β-AR thermogenic responsiveness could contribute to greater TEF in the habitually exercising state. Our results also indicate that β-AR thermogenic responsiveness is a physiological determinant of TEF and therefore EE and energy balance in healthy adults.

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