Effect of aging on \( \beta \)-adrenergically mediated thermogenesis in men

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The age-dependent alterations in \( \beta \)-adrenergically mediated thermogenesis were investigated in 11 young (mean \( \pm \) SE age: 21.9 \( \pm \) 0.5 yr) and 9 older (52.9 \( \pm \) 2.1 yr) men during intravenous infusion of the nonselective \( \beta \)-agonist isoprenaline (Iso). The older men had higher basal plasma norepinephrine (327.7 \( \pm \) 35.8 vs. 159.0 \( \pm \) 18.2 pg/ml, \( P < 0.001 \)) and epinephrine (75.1 \( \pm \) 18.1 vs. 29.1 \( \pm \) 5.3 pg/ml, \( P < 0.05 \)) concentrations than the young. The \( \beta \)-adrenergically mediated thermogenesis was diminished in the older men, as reflected by the significantly higher plasma Iso concentration (39.4 \( \pm \) 6.6 vs. 19.1 \( \pm \) 1.5 ng·kg fat-free mass\(^{-1} \cdot \text{min}^{-1} \), \( P < 0.01 \)) and plasma concentration (332.2 \( \pm \) 59.1 vs. 119.3 \( \pm \) 14.0 pg/ml, \( P < 0.01 \)) of Iso needed to increase resting heart rate by 25 beats/min were higher in older than in younger subjects, suggesting that the age-related decline in \( \beta \)-adrenergic sensitivity is a generalized defect not related to a specific tissue or response. In conclusion, aging is associated with a diminished \( \beta \)-adrenergically mediated thermogenesis. This blunted thermogenic response may contribute to a positive energy balance and thus promote increased fat storage and obesity.

METHODS

Subjects. Eleven young (21.9 \( \pm \) 0.5 yr) and 9 older (52.9 \( \pm \) 2.1 yr) men participated in this study after their written informed consent was obtained (Table 1). The study protocol was approved by the Ethics Committee of Maastricht University. The results of the young subjects have been previously published (2). All subjects were normotensive and generally in good health. Cardiovascular and/or respiratory diseases were excluded by a medical questionnaire and physical examination. Subjects participated no more than 3 h/wk in sports activities, and none of the subjects had a physically demanding job.

Body composition. Body density was measured by hydrostatic weighing, with a correction for residual lung volume as determined by helium dilution (Volugraph 2000, Mijnhardt, The Netherlands). Body composition was calculated according to the formula of Siri (22).

Isoprenaline infusion test. To determine \( \beta \)-adrenergically mediated thermogenic and heart rate (HR) responses, subjects fasted overnight and came to the laboratory by car or bus. The experiments were done in the morning in a quiet room with a temperature between 23 and 25°C. The subjects remained in a supine position throughout the study. Intravenous catheters were inserted into both arms, one for infusion of the nonselective \( \beta \)-agonist isoprenaline (Iso) and the other for blood sampling.

After a 30-min rest period, Iso was infused in stepwise increasing doses of 6, 12, and 24 ng·kg fat-free mass\(^{-1} \cdot \text{min}^{-1} \) for 30 min at each dose level. The dose was related to Iso sulfate, 69% of which corresponds to Iso free base. After the baseline measurement and at the end of each infusion period, blood was sampled with a heparinized syringe for plasma concentrations of Iso, norepinephrine (NE), and epinephrine (Epi). The sample was collected into a chilled tube containing glutathione and immediately centrifuged at 3,000 rpm at 4°C. The
Table 1. Physical characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>Young (n=11)</th>
<th>Older (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>21.9 ± 0.5</td>
<td>52.9 ± 2.1†</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.9 ± 3.5</td>
<td>72.2 ± 2.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>181.5 ± 2.1</td>
<td>173.7 ± 2.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.3 ± 0.8 (17.2-26.6)</td>
<td>23.9 ± 0.6 (21.6-27.5)</td>
</tr>
<tr>
<td>%Body fat</td>
<td>11.9 ± 1.1 (5.8-18.0)</td>
<td>16.9 ± 1.9* (8.9-24.5)</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>9.1 ± 1.2 (3.8-15.8)</td>
<td>12.2 ± 1.5 (6.3-19.9)</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>64.8 ± 2.6 (43.5-76.8)</td>
<td>60.0 ± 2.6 (44.8-71.8)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>64±2 (58-72)</td>
<td>88±1 (80-95)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>120±4 (98-136)</td>
<td>139±2 (130-150)</td>
</tr>
</tbody>
</table>

Values are means ± SE; ranges are in parentheses; n = no. of subjects. BP, blood pressure. *P < 0.05, †P < 0.001 vs. young.

RESULTS

Physical characteristics of the subjects are given in Table 1. There is >30 yr of difference between the mean ages of the young (n = 11 subjects) and the older (n = 9 subjects) groups. Although weight and body mass index were similar in both groups, the older subjects had significantly higher percent body fat compared with the young (P < 0.05).

Figure 1 shows the changes in plasma Iso, NE, and Epi with infusion of stepwise increasing doses of Iso in young and older men. There were dose-dependent increases in plasma Iso in both groups (for young and older subjects: one-factor ANOVA for repeated measurements, P < 0.001), but the mean plasma concentrations with the increasing standardized doses were higher in the older than in the young subjects (two-factor ANOVA for repeated measurements, P < 0.05; Fig. 1A). Basal values of plasma NE and Epi were significantly different between young and older subjects (unpaired t-test: NE, 159.0 ± 18.2 vs. 327.7 ± 35.8 pg/ml, P < 0.001; Epi, 29.1 ± 5.3 vs. 75.1 ± 18.1 pg/ml, P < 0.05, respectively; Fig. 1, B and C). During Iso infusion, there was an increase in plasma NE (for young and older subjects, P < 0.001) and no significant change in plasma Epi in both groups as illustrated in Fig. 1, B and C. Moreover, the older men had higher mean plasma NE (P < 0.001) and Epi (P < 0.05) concentrations with increasing doses of Iso compared with the young subjects (Fig. 1, B and C).

REE was not significantly different between young and older subjects (Table 2). Figure 2 shows the changes in EE (as %change above baseline), RER, and HR (as %change) with infusion of stepwise increasing doses of Iso in young and older men. The young and the older subjects showed Iso-induced increases in EE (for both groups, P < 0.001). There were no significant differences in the increases in EE with increasing doses of Iso between the young and older groups, irrespective of whether increases were expressed as percent increase above baseline (Fig. 2A, P = 0.30) or absolute increase (young vs. older men: change in EE, 6 ng, 0.44 ± 0.06 vs. 0.27 ± 0.10 kJ/min; 12 ng, 0.70 ± 0.08 vs. 0.51 ± 0.06 kJ/min; 24 ng, 1.10 ± 0.11 vs. 0.82 ± 0.12 kJ/min, respectively), although the absolute increases in EE tended to be lower in the older men (P = 0.08). In addition, dose EE = 15% was not significantly different between groups, as indicated in Table 2. However, when responses were related to plasma concentrations of Iso, concn EE = 15% was lower in the young than the older men (Table 2), indicating a blunted β-adrenergically mediated thermogenic response in the older men.

Resting values of the RER were similar in young and older subjects (0.81 ± 0.01 vs. 0.82 ± 0.01, respectively). The RER decreased with higher doses of Iso in the young (P < 0.001), whereas there was no significant change in the older subjects. However, there were no
significant differences in the RER with Iso between young and older subjects (Fig. 2B).

The Iso-induced increases in HR of the young and older subjects (for both groups, P < 0.001) were lower in the older men than in the young (P < 0.01) when related to the dose of Iso, either expressed as absolute increase above baseline (CD25, Table 2) or as percent change in HR (Fig. 2C). Basal HR levels were lower in the young than in the older men (Table 2). HR responses to Iso expressed as CD25 and CC25 values are shown in Table 2. Both CD25 and CC25 values were lower in the young than in the older men. Thus the older men also seem to have blunted β-adrenergically mediated HR responses. Furthermore, there was a significant correlation between Iso-induced thermogenic and HR response in both young (R = 0.80, P < 0.01) and older subjects (R = 0.69, P < 0.05).

A multiple regression analysis with age and percent body fat as independent variables and concn_{EE}15% and CC25 as dependent variables showed that age was the only factor significantly contributing to the variation in concn_{EE}15% (multiple R = 0.55, P < 0.05) and CC25 (multiple R = 0.66, P < 0.01). This is confirmed in the observation that exclusion of the lowest values of percent body fat in the young and the highest values in the older men resulted in two groups with comparable percent body fat [young men (n = 9) 13.2 ± 0.9 vs. older men (n = 6) 13.6 ± 1.4%] and a still lowered thermogenic in the older men (concn_{EE}15%: young men 111.9 ± 12.0 vs. older men 201.7 ± 45.9 pg/ml; P = 0.052).

DISCUSSION

The present study was undertaken to obtain more information on the underlying mechanisms for the age-related increase in body fat mass by investigating whether the β-adrenergically mediated thermogenesis was altered with aging. The main finding of the present study was that the β-adrenergically mediated thermogenic response was diminished in the older men, as reflected by the significantly higher concn_{EE}15%. This blunted thermogenic response in the older men was not statistically significant when the thermogenic response was related to the administered standardized dose of Iso per fat-free mass. In accordance with several studies (2, 10, 13), the above findings indicate that using individual venous plasma Iso concentration-response curves instead of dose-response curves increases the precision of the Iso-infusion test, as interindividual variations of plasma Iso pharmacokinetics between individuals are taken into account. This is of special importance in the comparison of groups with differences in age, since aging is associated with a reduced

| Table 2. RREE, basal HR, and β-adrenergic sensitivity in young and older men |
|---------------------------------|--------|--------|
|                                | Young (n = 11) | Older (n = 9) |
| RREE, kJ/min                   | 5.6 ± 0.2     | 5.1 ± 0.3     |
| Basal HR, beats/min            | 54.5 ± 1.4    | 64.4 ± 4.0*   |
| Dose_{EE}15%, ng·kg FFM⁻¹·min⁻¹ | 18.9 ± 1.9    | 28.2 ± 5.7    |
| Concn_{EE}15%, pg/ml           | 107.6 ± 11.4  | 236.1 ± 51.0* |
| CC25, ng·kg FFM⁻¹·min⁻¹         | 19.1 ± 1.5    | 39.4 ± 6.6†   |
| CC25, pg/ml                    | 119.3 ± 14.0  | 332.2 ± 59.1† |

Values are means ± SE; n = no. of subjects. RREE, resting energy expenditure; HR, heart rate; dose_{EE}15%, and concn_{EE}15%, dose and plasma concentration, respectively, of isoprenaline (Iso) needed to increase resting energy expenditure by 15%; CD25 and CC25, dose and concentration, respectively, of Iso needed to increase resting HR by 25 beats/min. *P < 0.05, †P < 0.01 vs. young.
clearance of drugs within the body, as also reflected by
the higher Iso concentrations in older men in the
present study during infusion of doses standardized for
fat-free mass. The diminished clearance has been re-
ported to be caused by decreases in hepatic metabolism
and renal elimination capacity (15).

Our data of a blunted thermogenic response with
advancing age seem to correspond with a previous
study of Schwartz et al. (21), who showed a reduced DIT
in older men. Our study is, however, the first to
demonstrate that a diminished \( \beta \)-adrenergic sensitivity
may be responsible for this blunted response. Because
of the fact that in the present study, percent body fat in
the older group was already slightly higher than in the
younger subjects, we cannot make a definite statement
on whether the impaired thermogenesis is a cause or a
consequence of the increased percent body fat. How-
ever, multiple regression analysis with age and percent
body fat as independent variables indicated that only
age significantly contributed to the variations in ther-
monic response, strongly indicating that in these
nonobese older men, the blunted thermogenesis is a
consequence of aging per se. This seems to correspond
to previous data showing that the Iso-induced thermo-
genesis is only blunted in obese subjects with a percent
body fat > 30 (2). The age-related decrease in thermogen-
esis may contribute to the elevated percent body fat in
the older men and may thereby play an important role
in the increased risk for chronic diseases such as type 2
diabetes and coronary heart disease.

The exact mechanism for the decline in \( \beta \)-adrenergic
sensitivity remains to be determined. Basal plasma NE
concentrations were significantly higher in the older
subjects, reflecting an increase in basal sympathetic
activity, as previously reported (4, 9, 17, 20, 21). It is
possible that this increased basal plasma NE concentra-
tion in the older men may lead to a downregulation (24)
and decreased agonist binding of adrenoceptors (14,
24). Additionally, alterations in adrenoceptor density
(7, 9, 24) and postreceptor defects, such as changes in G
protein-mediated signal transduction (4, 5, 24) or in
activity of hormone-sensitive lipase (12), may probably
contribute to the blunted responses in the older men. It
is noteworthy that besides the decreased \( \beta \)-adrener-
gically mediated thermogenesis with aging, HR response
was also significantly blunted in the older men, as
reported before (3, 7, 9, 26). Moreover, there was a
significant positive relationship between \( \beta \)-adrener-
gically mediated thermogenic and HR responses in both
groups. These data suggest that the age-related de-
crease in \( \beta \)-adrenergic sensitivity is a generalized de-
fect not related to a specific organ or response. It
remains, however, to be elucidated whether the de-
crease in \( \beta \)-adrenergic sensitivity is caused by a de-
crease in sensitivity of all \( \beta \)-adrenoceptor subtypes or is
caused by a \( \beta \)-adrenoceptor subtype-specific decrease in
sensitivity.

During \( \beta \)-adrenergic stimulation, there was a signifi-
cant decrease in the RER in young but not in older men,
which may indicate a higher increase in fat oxidation
during \( \beta \)-adrenergic stimulation in the young subjects.
However, differences in the changes in RER with Iso
infusion between the two groups did not reach statisti-
cal significance.

In conclusion, \( \beta \)-adrenergically mediated thermo-
genic and HR responses are blunted in older persons
(45–62 yr) compared with a younger control group
(20–25 yr). The exact mechanism for this decrease in
sensitivity remains to be determined. The reduction in
the Iso-induced thermogenic response with age may
contribute to the increased percent body fat in the older
men and the related risk for chronic diseases such as
type 2 diabetes and cardiovascular disease. Further

![Fig. 2. Changes in energy expenditure (EE, as %change; A), respira-
tory exchange ratio (RER; B) and heart rate (HR, as %change; C)
with infusion of stepwise increasing doses of nonselective \( \beta \)-agonist
Iso in young (○) and older (●) men. Values are means ± SE. One-factor
ANOVA for repeated measurements: %change in EE and
HR, \( P < 0.001 \) for young and older subjects; RER, young men,
\( P < 0.001 \). Two-factor ANOVA for repeated measurements: young
vs. older subjects, %change in HR, \( P < 0.01 \).](image-url)
studies are necessary to elucidate the responsible mechanisms for the age-related blunting of the thermogenic response.

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