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Effect of aging on β -adrenergically mediated thermogenesis in men

DANIËLLE A. J. M. KERCKHOFFS, ELLEN E. BLAAK,
MARLEEN A. VAN BAAK, AND WIM H. M. SARIS

Department of Human Biology, Maastricht University, 6200 MD Maastricht, The Netherlands

Kerckhoffs, Daniëlle A. J. M., Ellen E. Blaak, Marleen A. van Baak, and Wim H. M. Saris. Effect of aging on β -adrenergically mediated thermogenesis in men. *Am. J. Physiol.* 274 (*Endocrinol. Metab.* 37): E1075–E1079, 1998.—The age-dependent alterations in β -adrenergically mediated thermogenesis were investigated in 11 young (mean \pm SE age: 21.9 ± 0.5 yr) and 9 older (52.9 ± 2.1 yr) men during intravenous infusion of the nonselective β -agonist isoprenaline (Iso). The older men had higher basal plasma norepinephrine (327.7 ± 35.8 vs. 159.0 ± 18.2 pg/ml, $P < 0.001$) and epinephrine (75.1 ± 18.1 vs. 29.1 ± 5.3 pg/ml, $P < 0.05$) concentrations than the young. The β -adrenergically mediated thermogenesis was diminished in the older men, as reflected by the significantly higher plasma Iso concentration needed to increase resting energy expenditure by 15% (236.1 ± 51.0 vs. 107.6 ± 11.4 pg/ml, $P < 0.05$). Additionally, both dose (39.4 ± 6.6 vs. 19.1 ± 1.5 ng \cdot kg fat-free mass $^{-1} \cdot$ min $^{-1}$, $P < 0.01$) and plasma concentration (332.2 ± 59.1 vs. 119.3 ± 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 β -adrenergic sensitivity is a generalized defect not related to a specific tissue or response. In conclusion, aging is associated with a diminished β -adrenergically mediated thermogenesis. This blunted thermogenic response may contribute to a positive energy balance and thus promote increased fat storage and obesity.

energy expenditure; chronotropic response; age; sympathetic nervous system; isoprenaline

AGING is associated with an increased risk for several chronic diseases such as type 2 diabetes and cardiovascular disease. A factor involved in the increased prevalence of these diseases may be the age-related change in body composition that includes an increase in (abdominal) fat mass and obesity (6), since both body fat mass and abdominal fat distribution are risk factors in the development of type 2 diabetes and cardiovascular disease (11). To come to a more effective prevention or treatment of the age-related increase in body fat storage, more information is necessary on the responsible mechanisms.

Aging may be associated with altered patterns of energy expenditure (21). Several studies have demonstrated that resting metabolic rate declines with advancing age (8, 16–19, 25). In most cases, the decrease in age-related decline in fat-free mass seems to be the best available predictor of the decrease in resting metabolic rate. Furthermore, diet-induced thermogenesis (DIT) may decline with aging. It is possible that this decline plays a role in the increased adiposity found with advancing age by promoting a positive energy balance. Schwartz et al. (21) hypothesized that the reduction in DIT is related to diminished activity of the sympathetic

nervous system. This is in accordance with numerous studies that reported that aging is associated with alterations in sympathetic activity. Despite the increased basal sympathetic activity (4, 9, 17, 20, 21), as reflected by a rise in circulating norepinephrine, there appear to be blunted sympathetically mediated metabolic responses with aging. Especially, a decline in β -adrenergically mediated heart rate response in older persons is well established (3, 7, 9, 26). At present, it is, however, not known whether the sympathetically mediated thermogenesis also declines with aging. If so, this results in an increased efficiency of energy expenditure, contributing thereby to the age-related increase in body fat stores. Previous studies have shown that the β -adrenoceptors are mainly involved in the sympathetically mediated thermogenesis (1). Thus, to obtain more information on the mechanisms behind the age-related increase in obesity, the present study was intended to investigate whether the β -adrenergically mediated thermogenesis is altered with aging.

METHODS

Subjects. Eleven young (21.9 ± 0.5 yr) and 9 older (52.9 ± 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 β -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 β -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 \cdot kg fat-free mass $^{-1} \cdot$ min $^{-1}$ for 30 min at each dose level. The dose is 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*

	Young ($n=11$)	Older ($n=9$)
Age, yr	21.9 \pm 0.5 (20–25)	52.9 \pm 2.1 \dagger (45–62)
Weight, kg	73.9 \pm 3.5 (48.0–90.0)	72.2 \pm 2.9 (57.6–85.9)
Height, cm	181.5 \pm 2.1 (167.0–192.0)	173.7 \pm 2.8* (160.7–187.5)
Body mass index, kg/m ²	22.3 \pm 0.8 (17.2–26.6)	23.9 \pm 0.6 (21.6–27.5)
%Body fat	11.9 \pm 1.1 (5.8–18.0)	16.9 \pm 1.9* (8.9–24.5)
Fat mass, kg	9.1 \pm 1.2 (3.8–15.8)	12.2 \pm 1.5 (6.3–19.9)
Fat-free mass, kg	64.8 \pm 2.6 (43.5–76.8)	60.0 \pm 2.6 (44.8–71.8)
Diastolic BP, mmHg	64 \pm 2 (58–72)	88 \pm 1 \dagger (80–95)
Systolic BP, mmHg	120 \pm 4 (98–136)	139 \pm 2 \dagger (130–150)

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

plasma samples were stored at -80°C until concentrations of Iso, NE, and Epi were determined by HPLC with electrochemical detection (23).

During the experiment, whole body energy expenditure (EE) was determined by an open-circuit ventilated hood system (Oxycon Beta, Mijnhardt, The Netherlands). A clear Plexiglas "hood" was placed over the subject's head and sealed off by plastic straps around the neck. Air is sucked through the hood with a pump and blown into a mixing chamber where a sample is taken for analysis. The oxygen consumption and the carbon dioxide production were estimated from the total airflow and the oxygen and carbon dioxide concentrations of the air flowing in and out. Total EE was calculated according to the formula of Weir (27).

During the experiment, HR was monitored by continuous electrocardiogram recording. When HR had increased by 30 beats/min, the Iso infusion was stopped.

β -Adrenergically mediated thermogenic and HR responses. EE and HR responses of the young and older men reached a steady state after 10 min of Iso infusion, i.e., 5-min values were stable until the end of the infusion period. Therefore, mean values over the last 20 min were considered as representative for the administered doses. The respiratory exchange ratio (RER) in both groups reached a steady state after 20 min of infusion after a rapid increase within the first 5 min of the Iso infusion that was most probably caused by a change in ventilation (1). Therefore, RER values over the last 10 min of infusion were averaged.

To summarize the response of the subject to Iso infusion in a single value (2), the β -adrenergically mediated thermogenesis was expressed as the dose or plasma concentration of Iso required to increase resting EE (REE) by 15% (dose $_{\Delta\text{EE}=15\%}$ and concn $_{\Delta\text{EE}=15\%}$, respectively). To evaluate the β -adrenergically mediated HR responses, both the chronotropic dose (CD25) and the chronotropic concentration (CC25) were calculated from the dose and plasma concentration, respectively, of Iso required to increase resting HR by 25 beats/min (13). These values were determined by individual linear regression of response vs. dose or plasma concentration of Iso.

Statistical analysis. Values are presented as means \pm SE. Differences between the young and older groups were analyzed by use of Student's unpaired t -test. The effects of Iso infusion on various parameters within each group and between both groups were analyzed by use, respectively, of one-factor and two-factor ANOVA for repeated measure-

ments. Simple and multiple regression analyses were used to determine which variables contributed to variations in response between subjects. A value of $P < 0.05$ was considered significant.

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 \pm 18.2 vs. 327.7 \pm 35.8 pg/ml, $P < 0.001$; Epi, 29.1 \pm 5.3 vs. 75.1 \pm 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 \pm 0.06 vs. 0.27 \pm 0.10 kJ/min; 12 ng, 0.70 \pm 0.08 vs. 0.51 \pm 0.06 kJ/min; 24 ng, 1.10 \pm 0.11 vs. 0.82 \pm 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 $_{\Delta\text{EE}=15\%}$ was not significantly different between groups, as indicated in Table 2. However, when responses were related to plasma concentrations of Iso, concn $_{\Delta\text{EE}=15\%}$ 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 \pm 0.01 vs. 0.82 \pm 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

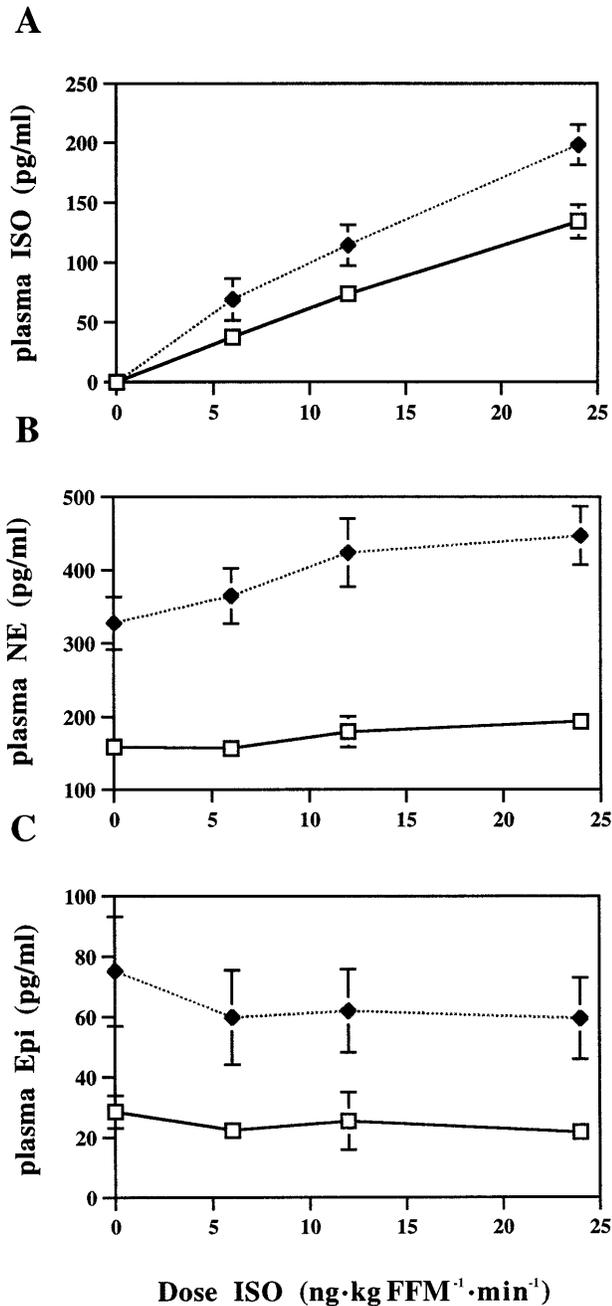


Fig. 1. Changes in plasma isoprenaline (Iso; A), norepinephrine (NE; B), and epinephrine (Epi; C) with infusion of stepwise increasing doses of nonselective β -agonist Iso in young (\square) and older (\blacklozenge) men. Values are means \pm SE. FFM, fat-free mass. One-factor ANOVA for repeated measurements: plasma Iso and NE, $P < 0.001$ for young and older subjects. Two-factor ANOVA for repeated measurements: young vs. older subjects, plasma Iso, $P < 0.05$; plasma NE, $P < 0.001$; and plasma Epi, $P < 0.05$.

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 $\text{concn}_{\Delta\text{EE}=15\%}$ and CC25 as dependent variables showed that age was the only factor significantly contributing to the variation in $\text{concn}_{\Delta\text{EE}=15\%}$ (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 ($n = 6$) $13.6 \pm 1.4\%$] and a still lowered thermogenesis in the older men ($\text{concn}_{\Delta\text{EE}=15\%}$: 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 $\text{concn}_{\Delta\text{EE}=15\%}$. 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. REE, basal HR, and β -adrenergic sensitivity in young and older men

	Young ($n = 11$)	Older ($n = 9$)
REE, kJ/min	5.6 ± 0.2	5.1 ± 0.3
Basal HR, beats/min	54.5 ± 1.4	$64.4 \pm 4.0^*$
Dose $_{\Delta\text{EE}=15\%}$, ng·kg FFM ⁻¹ ·min ⁻¹	18.9 ± 1.9	28.2 ± 5.7
Concn $_{\Delta\text{EE}=15\%}$, pg/ml	107.6 ± 11.4	$236.1 \pm 51.0^*$
CD25, ng·kg FFM ⁻¹ ·min ⁻¹	19.1 ± 1.5	$39.4 \pm 6.6^\dagger$
CC25, pg/ml	119.3 ± 14.0	$332.2 \pm 59.1^\dagger$

Values are means \pm SE; n = no. of subjects. REE, resting energy expenditure; HR, heart rate; dose $_{\Delta\text{EE}=15\%}$ and concn $_{\Delta\text{EE}=15\%}$, 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. * $P < 0.05$, $^\dagger P < 0.01$ vs. young.

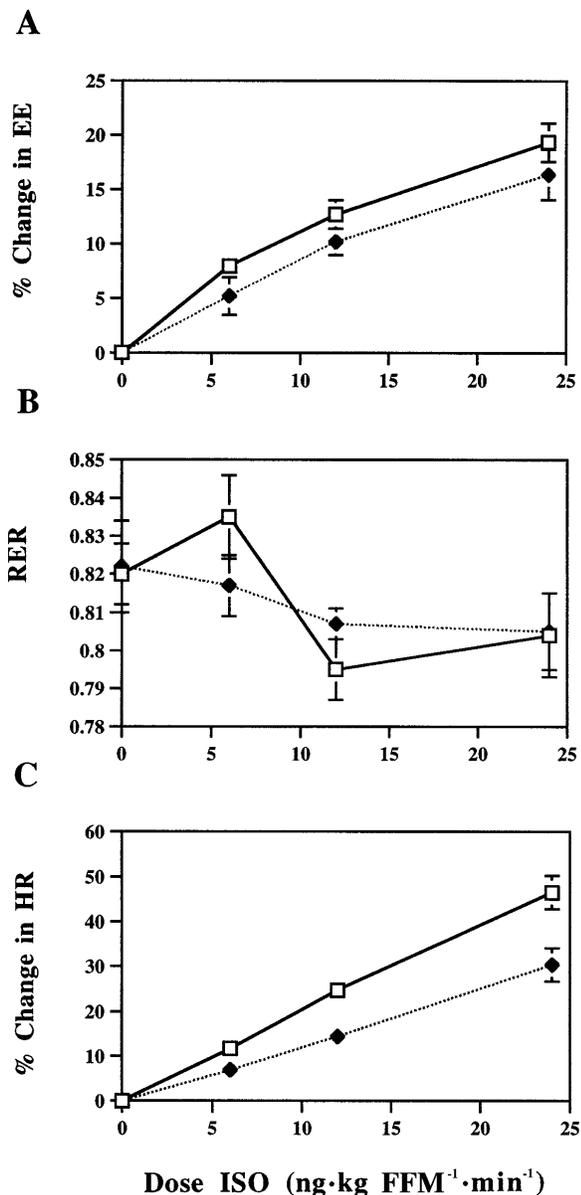


Fig. 2. Changes in energy expenditure (EE, as %change; A), respiratory exchange ratio (RER; B) and heart rate (HR, as %change; C) with infusion of stepwise increasing doses of nonselective β -agonist Iso in young (\square) and older (\blacklozenge) men. Values are means \pm SE. One-factor ANOVA for repeated 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, $P < 0.01$.

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 reported 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 β -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. However, multiple regression analysis with age and percent body fat as independent variables indicated that only age significantly contributed to the variations in thermogenic 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 thermogenesis is only blunted in obese subjects with a percent body fat >30 (2). The age-related decrease in thermogenesis 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 β -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 concentration 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 β -adrenergically 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 β -adrenergically mediated thermogenic and HR responses in both groups. These data suggest that the age-related decrease in β -adrenergic sensitivity is a generalized defect not related to a specific organ or response. It remains, however, to be elucidated whether the decrease in β -adrenergic sensitivity is caused by a decrease in sensitivity of all β -adrenoceptor subtypes or is caused by a β -adrenoceptor subtype-specific decrease in sensitivity.

During β -adrenergic stimulation, there was a significant decrease in the RER in young but not in older men, which may indicate a higher increase in fat oxidation during β -adrenergic stimulation in the young subjects. However, differences in the changes in RER with Iso infusion between the two groups did not reach statistical significance.

In conclusion, β -adrenergically mediated thermogenic 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

studies are necessary to elucidate the responsible mechanisms for the age-related blunting of the thermogenic response.

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Address for reprint requests: E. E. Blaak, Dept. of Human Biology, Faculty of Health Sciences, Maastricht Univ., PO Box 616, 6200 MD Maastricht, The Netherlands.

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