β-Adrenergically Mediated Thermogenic and Heart Rate Responses: Effect of Obesity and Weight Loss

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β-Adrenergically mediated thermogenic and heart rate (HR) responses, as assessed by stepwise intravenous infusion of the β-agonist isoprenaline (ISO), were evaluated by partial regression analysis in a group of men with a wide range of body fat (n = 30) and in a subgroup of 16 obese men after weight loss. β-Adrenergically mediated thermogenesis (open-circuit ventilated-hood system) was blunted in obese subjects, as reflected by a significant positive correlation between percent body fat (hydrostatic weighing) and the plasma ISO concentration needed to increase resting energy expenditure (EE) by 15% ($P < .001$). The magnitude of the β-adrenergically mediated HR response was (negatively) associated with the basal plasma norepinephrine (NE) concentration ($P < .001$). Weight reduction resulted in a significant increase in thermogenic and HR responses in obese subjects. Furthermore, the increase in thermogenic response as a result of weight loss was negatively related to the magnitude of thermogenic response ($P < .01$) and positively related to the initial percent body fat ($P < .05$). The increase in HR response as a result of weight loss was positively related to the decrease in basal NE ($P < .01$) and the change in percent body fat ($P < .05$). In conclusion, the degree of adiposity was shown to be negatively related to the magnitude of β-adrenergically mediated thermogenesis, whereas the HR response was merely related to basal NE. Since weight loss resulted in a significant increase in the thermogenic response, the blunted β-adrenergically mediated thermogenesis does not seem to be a primary factor contributing to the development of obesity.

OBESITY HAS PREVIOUSLY been reported to be associated with a blunted sympathetically mediated thermogenesis,[1,2] which may be a factor contributing to a decreased energy cost of weight maintenance and may thereby be of importance in the development and maintenance of excess body weight. However, data on an impaired sympathetically mediated thermogenesis in obesity are not consistent. Several recent studies suggest a similar thermogenic response in lean and obese subjects after infusion of catecholamines[3] or a β-agonist.[4] The possibility exists that there are small differences in sympathetically mediated thermogenesis between lean and obese subjects that are hard to detect but may be of physiologic significance over longer periods of time.

Weight reduction, as well as the hypocaloric state per se, has been shown to decrease various indexes of basal sympathetic activity in obese subjects, such as norepinephrine (NE) appearance rate[5] and circulating plasma NE.[6] A diminished basal sympathetic activity is expected to be associated with the development of supersensitivity to agonist stimulation and an upregulation of adrenoceptor numbers.[7] However, both diminished[8] and increased[6] sympathetically mediated physiologic responses have been reported in obese subjects as a result of weight loss. It remains to be clarified by what factors the (change in) β-adrenergically mediated thermogenesis after weight loss is determined and how this relates to the initial thermogenic response in obese subjects.

The present study investigated β-adrenergically mediated thermogenesis and heart rate (HR) responses in a relatively large group of subjects with a wide range of adiposity to increase the probability of detecting small differences between lean and obese subjects. Several other factors that may have an impact on β-adrenergic sensitivity, such as age and basal sympathetic activity (as reflected by the basal plasma NE concentration[9]), were also taken into account. In addition, the effect of weight reduction on β-adrenergically mediated thermogenesis and HR responses was evaluated.

SUBJECTS AND METHODS

In this study, body composition and β-adrenergically mediated HR and thermogenic responses were determined in a group of men with a wide range of adiposity (n = 30; % body fat, 5.8 to 42.2). A subgroup of obese men (n = 16; % body fat > 25) was also studied after a period of weight reduction. Physical characteristics of the subjects are listed in Table 1. Eight obese subjects were already involved in a previous study.[4] All subjects were normotensive and in good health as assessed by a medical history and physical examination. Furthermore, subjects participated no more than 3 hours per week in sports, and none had a physically demanding job. The study protocol was reviewed and approved by the Ethics Committee of the University of Limburg, and all subjects provided written consent.

Body Composition

Body composition was determined by hydrostatic weighing with simultaneous lung volume measurement (Volugraph 2000, Mijnhardt, The Netherlands). Body composition was calculated according to the formula reported by Siri.[10]

Isoprenaline Infusion Test

For measurement of β-adrenergic sensitivity, subjects fasted from 8 PM the evening before and were allowed to drink water freely. The experiments started at 8 AM, and subjects came to the laboratory by car or bus. Room temperature was kept between 23° and 25°C. After a 30-minute baseline measurement, the β-agonist isoprenaline (ISO) was infused in increasing doses of 6, 12, 23, and 46 ng/kg fat-free mass · min, with each dose administered for 30 minutes. The dose is related to ISO sulfate, 69% of which

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Table 1. Physical Characteristics of the Subjects

	Mean ± SE	Range
Age (yr)	29 ± 1	20-39
Weight (kg)	94.9 ± 3.8	48.0-143.1
Body mass index (kg/m²)	29.1 ± 1.1	17.2-40.1
% body fat	24.7 ± 1.9	5.8-42.2
Fat mass (kg)	24.6 ± 2.5	3.8-48.3
Fat-free mass (kg)	70.3 ± 1.9	42.2-87.4

corresponds to ISO free base. Whole-body energy expenditure (EE) was determined by an open-circuit ventilated-hood system (Oxycon Beta, Mijnhardt, The Netherlands). EE was calculated according to the abbreviated formula reported by Weir.[11] After 15 minutes in each infusion period, a blood sample was taken with a heparinized syringe and placed into a glutathione-containing tube in ice. The sample was immediately centrifuged at 3,000 rpm at 4°C, and the plasma was stored at −50°C. In plasma samples, concentrations of ISO and NE were determined by high-performance liquid chromatography.[12] The coefficient of variation for repeated measurements of ISO or NE is 8.4%. During the experiments, HR was recorded continuously. When HR had increased by 30 beats per minute, the infusion was stopped.

Diet

During a period of 4 weeks, 16 obese men ate a very–low-calorie diet of 2,000 kJ/d, which provided 52 g protein, 50 g carbohydrate, 7 g fat, and 1.3 g sodium per day. Furthermore, the micronutrient content of this diet meets the Dutch recommended daily allowances. At the end of the 4-week diet period, subjects returned to their habitual eating pattern. Measurements of body composition and β-adrenergic sensitivity were repeated in the sixth week. Sodium concentrations in 24-hour urine samples, collected before and after the diet under conditions near energy balance, were determined by flame photometry.

Calculations and Statistics

Data are presented as the mean ± SE. After 10 minutes of ISO infusion, thermogenic and HR responses reached a steady state, ie, 5-minute values for these variables kept stable until the end of the infusion period. Therefore, mean values for the last 20 minutes were considered representative of the administered dose. The RER reached a steady state after 20 minutes of infusion after a rapid initial increase at the start of the infusion, as described previously.[13] The steady-state value for RER was therefore taken as the mean of the last 10 minutes of infusion.

β-Adrenergic sensitivity was defined as the dose or plasma concentration of ISO to increase resting energy expenditure (REE) by 15% for thermogenic responses (Dose ΔEE = 15% and Conc ΔEE = 15%, respectively). In addition, the decrease in RER was determined at ΔEE = 15% [defined as ΔRER(ΔEE = 15%)]. Sensitivity for HR responses was defined as the dose or plasma ISO concentration to increase resting HR by 25 beats per minute (CD25 and CC25, respectively). These values were determined by linear regression of response versus dose or plasma concentration. The relationship between thermogenic and HR responses and body composition, age, and basal NE concentration was evaluated by partial regression analysis.

The effect of weight reduction on β-adrenergically mediated HR and thermogenic responses was evaluated in 16 obese subjects. Furthermore, we related the change in thermogenic and HR responses to the magnitude of these variables. However, since the initial magnitude of a variable may automatically be related to the magnitude of change in this variable as a result of an intervention, an artificial correlation may be obtained. For this reason, the magnitude of thermogenic or HR responses was defined as the average of the thermogenic or HR response before and after diet, as described elsewhere.[14] Body composition and parameters of β-adrenergic sensitivity before and after diet intervention were compared with Student's paired t test. P less than .05 was considered statistically significant.

Table 2. REE, RER, Basal Plasma NE, Basal HR, and β-Adrenergic Sensitivity in Men

	Mean ± SE	Range
EE (kJ/min)	6.22 ± 0.16	4.43-7.51
RER	0.82 ± 0.01	0.75-0.86
Basal NE (pg/mL)	146 ± 9	80-275
Basal HR (beats per min)	61 ± 2	49-81
Dose ΔEE = 15% (ng/kg FFM · min)	21.4 ± 1.4	10.5-44.9
Conc ΔEE = 15% (pg/mL)	156 ± 11	60-287
ΔRER(ΔEE = 15%)	−0.02 ± 0.01	−0.07-0.02
CD25 (ng/kg FFM · min)	22.9 ± 1.9	11.5-66.0
CC25 (pg/mL)	177 ± 17	55-335

NOTE. Statistical analysis was performed by partial regression analysis, which is presented in Table 3.

Abbreviation: FFM, fat-free mass.

RESULTS

As a result of ISO infusion, there were dose- and plasma ISO concentration–related increases in HR and EE in all subjects, as reported previously.[13]

Table 2 lists subject data on EE, RER, basal values for NE and HR, and β-adrenergically mediated thermogenic and HR responses.

Table 3 lists partial correlations between thermogenic and HR responses and percent body fat, basal NE, and age, each with adjustment for the other two. Percent body fat (adjusted for basal NE and age) was (negatively) correlated with the β-adrenergically mediated thermogenic response, as reflected by a significant positive correlation between percent body fat and Conc ΔEE = 15%. Notably, this correlation was not seen when the thermogenic response was related to the administered dose of ISO. Furthermore, expressing the thermogenic response as the absolute increase per kilogram fat-free mass does not change its negative relationship with percent body fat (partial correlation between % body fat, adjusted for age and basal NE, and the plasma concentration to increase EE by 0.015 kJ/kg fat-free mass · min is .58, $P < .001$). Unadjusted correlations between percent body fat and Conc ΔEE = 15% or

Table 3. Partial Correlation Coefficients Between β-Adrenergically Mediated Thermogenic and HR Responses and Percent Body Fat, Basal NE, and Age, Each Adjusted for the Other Two

	Dose ΔEE = 15% (ng/kg FFM · min)	Conc ΔEE = 15% (pg/mL)	ΔRER (ΔEE = 15%)	CD25 (ng/kg FFM · min)	CC25 (pg/mL)
% body fat	.15	.57*	.27	.15	.27
Basal NE (pg/mL)	.31	.31	.27	.62*	.72*
Age (yr)	.09	.02	.00	.26	.25

Abbreviation: FFM, fat-free mass.

*$P < .001$.

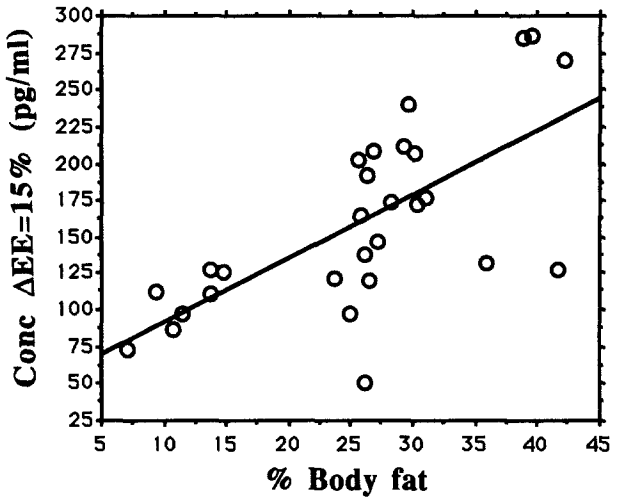

Fig 1. Simple (unadjusted) correlation between % body fat and Conc ΔEE = 15% (n = 30, r = .68, P = .001; standard error of estimate, 47 pg/mL).

the percent change in EE at a fixed plasma ISO concentration (165 pg/mL) are shown in Figs 1 and 2, respectively.

The basal NE concentration (adjusted for % body fat and age) was the only variable with a significant (negative) partial correlation with the β-adrenergically mediated HR response, as indicated by the positive partial correlation between basal NE and CC25 or CD25. Partial correlations between the decrease in RER(ΔEE = 15%) and percent body fat, basal NE, and age did not reach statistical significance.

Table 4 lists the changes in body composition, EE, and indices of basal sympathetic activity and β-adrenergic sensitivity as a result of weight loss. EE decreased by 10% as a result of weight loss. There was an average weight loss of 10 kg, which can be explained by a 70% loss of fat mass and a 30% loss of fat-free mass. Basal NE concentration tended to be decreased after weight reduction (P = .11). Basal HR decreased as a result of weight loss, whereas

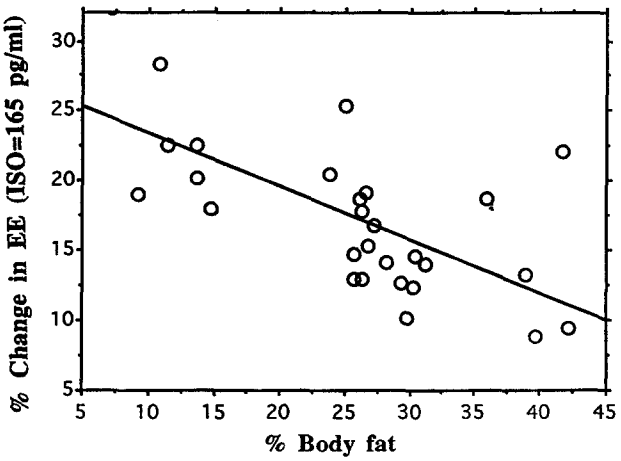

Fig 2. Simple (unadjusted) correlation between % body fat and the increase in EE at a plasma ISO concentration of 165 pg/mL (n = 30, r = .67, P = .001; standard error of estimate, 4.2%).

Table 4. Body Composition, EE, Basal Plasma NE, Basal HR, and β-Adrenergic Sensitivity Before and After Weight Loss in Obese Men

	Before	After
Weight (kg)	104.8 ± 4.4	94.3 ± 4.5‡
% body fat	29.7 ± 1.2	25.7 ± 1.3‡
Fat mass (kg)	31.1 ± 2.6	23.7 ± 2.7‡
Fat-free mass (kg)	72.5 ± 2.3	69.4 ± 2.4‡
EE (kJ/min)	6.48 ± 0.23	5.81 ± 0.17‡
Basal NE (pg/mL)	149 ± 14	117 ± 9
Basal HR (beats per min)	64.6 ± 2.6	55.5 ± 1.6‡
Conc ΔEE = 15% (pg/mL)	165 ± 17	104 ± 7†
ΔRER(ΔEE = 15%)	−0.01 ± 0.01	−0.02 ± 0.01
CC25 (pg/mL)	217 ± 31	165 ± 21*

NOTE. Results are the mean ± SE; n = 16.
*P < .05.
†P < .01.
‡P < .001.

β-adrenergically mediated thermogenesis and HR responses were significantly greater after weight reduction as compared with before. There was no significant difference in the change in RER at EE = 15% before as compared with after diet. Sodium excretion in 24-hour urine was comparable before and after weight reduction and amounted to 157 ± 12 versus 166 ± 18 mmol/24 h (NS), respectively.

Table 5 lists partial correlations between changes in β-adrenergically mediated thermogenic and HR responses and changes in body composition and basal NE, each adjusted for the other variables. The initial percent body fat and the magnitude of Conc ΔEE = 15% appeared to be positively correlated with the change in the ISO-induced thermogenic response. Furthermore, changes in percent body fat and in basal NE appeared to be positively correlated with the change in CC25.

DISCUSSION

The issue of whether a possible decreased energy cost for weight maintenance in obesity is associated with a diminished thermogenic response as a result of infusion of sympathomimetics is still a matter of debate.[2,3] This may be partly due to differences in expression of the thermogenic response across groups that have a different EE. The thermogenic response in the present study was expressed as a percentage increase from baseline. However, expressing

Table 5. Partial Correlation Coefficients Between Changes in β-Adrenergically Mediated Thermogenesis and HR Responses and Changes in Body Composition and Basal NE as a Result of Weight Loss, Each Adjusted for the Other Variables

	ΔConc ΔEE = 15% (before minus after)	ΔCC25 (before minus after)
% body fat before	.55*	.09
Mean level (Conc ΔEE = 15% or CC25)‡	.70†	.34
Basal NE before (pg/mL)	.11	−.05
Δ% body fat (before minus after)	.12	.64*
Δbasal NE (before minus after)	.13	.76†

*P < .05.
†P < .01.
‡Mean of values Conc ΔEE = 15% or CC25 before and after diet.

the thermogenic response as the absolute increase per kilogram fat-free mass would not alter the conclusions of this study. The results of the present study indicate a diminished β-adrenergically mediated thermogenic response in obesity, as reflected by the significant positive correlation between percent body fat (adjusted for basal NE and age) and Conc ΔEE = 15%. In a previous study,[4] we found no difference in β-adrenergically mediated thermogenesis between lean and obese subjects (mean % body fat for lean *v* obese, 17 *v* 32), which is consistent with the results of another study that used epinephrine infusion.[3] This apparent discrepancy may be due to the fact that the relatively small differences in thermogenesis are only detectable when including very obese and very lean subjects into the analyses, as we did in the present study (range % body fat, 5.8 to 42.2). Moreover, this negative partial correlation between the thermogenic response and degree of adiposity was not detected when relating the thermogenic response to the administered standardized dose of ISO. This indicates that using individual plasma ISO concentration-response curves instead of dose-response curves improves accuracy of the determination of β-adrenergic sensitivity, as reported previously.[15]

In a previous study reported by Spraul et al,[16] a positive correlation between percent body fat and basal muscle sympathetic activity has been found. These findings may imply that the present finding of blunted β-adrenergically mediated thermogenesis in obese subjects is associated with an increased basal sympathetic activity, resulting in a diminished sensitivity to agonist stimulation or a downregulation of adrenoceptors. However, we could not detect a relationship between basal NE concentration and the thermogenic response, whereas the magnitude of the β-adrenergically mediated HR response (adjusted for % body fat and age) was negatively associated with the basal NE concentration. These findings indicate that the level of basal sympathetic activity is a determinant of the magnitude of β-adrenergically induced tachycardia, whereas the negative association between the β-adrenergically mediated thermogenic response and percent body fat is probably determined by factors other than the magnitude of basal sympathetic activity.

The magnitude of β-adrenergically mediated thermogenesis is probably related to the degree of stimulation of β-adrenergically mediated energy-requiring processes, which implies that obesity is associated with a blunted activation of these processes. Energy-requiring processes that have been reported to be stimulated during adrenergic activation are Na^+-K^+ pump activity[17] and the activity of futile cycles.[18] However, there is no conclusive evidence that supports a relationship between the rate of substrate cycling or Na^+-K^+ pump activity and the decreased adrenergically mediated thermogenesis in obese subjects. Another possibility is that the magnitude of β-adrenergically mediated thermogenesis is determined by the capacity to induce changes in substrate metabolism. An indication for differences in β-adrenergically mediated substrate metabolism comes from the finding that the decrease in RER as a result of ISO infusion was greater in lean than in obese subjects, which indicates a higher fat oxidation in lean subjects. Moreover, in a previous study,[4] we found that the ability to mobilize and oxidize fat as a result of β-adrenergic stimulation may be impaired in obesity. β-Adrenergic stimulation resulted in an increased muscle fatty acid uptake and probably oxidation in lean subjects, whereas in obese subjects glucose seemed to be the preferred substrate, as reflected by an increased skeletal muscle glucose uptake and lactate release. Furthermore, a diminished thermogenic response to glucose ingestion has been reported in insulin-resistant subjects,[19,20] which suggests that insulin resistance may also be of importance in the ability to increase glucose metabolism during β-adrenergic stimulation. However, further research is required to elucidate which mechanisms are of importance in explaining the blunted β-adrenergically mediated thermogenesis in obesity.

Weight loss resulted in a significant increase in ISO-induced HR and thermogenic responses. Furthermore, the magnitude of the thermogenic response and the initial percent body fat (both adjusted for the other variables indicated in Table 5) were, respectively, negatively and positively related to the change in this response as a result of weight loss. These data suggest that the origins of obesity are unlikely to be found in a decreased β-adrenergically mediated thermogenesis. In addition, weight reduction seemed to produce a β-adrenergic supersensitivity with respect to the thermogenic response in reduced-obese subjects: the mean value for Conc ΔEE = 15% after weight loss (104 ± 7 pg/mL) was not only less than before diet intervention, but was similar to the mean value of subjects with a percent body fat less than 20 (108 ± 11 pg/mL), despite the still considerably higher percent body fat in reduced-obese subjects. This relatively increased β-adrenergically mediated thermogenesis seems to be in accordance with the previously reported increased contribution of the sympathetic nervous system to 24-hour EE in weight-stable reduced-obese subjects[21] and in post-obese subjects consuming a high-carbohydrate diet[22] in comparison to lean subjects. The present study offers no explanation for the underlying mechanism for the increased contribution of the β-adrenergic system to 24-hour EE in reduced-obese subjects.

The increase in the HR response as a result of weight loss was positively related to the decrease in basal NE concentrations, independent of the other variables indicated in Table 5. As suggested earlier, a larger decrease in basal plasma NE concentration may reflect a more pronounced decrease in basal sympathetic activity, which may be related to a larger upregulation of the number of adrenoceptors or increased sensitivity to agonist stimulation. Furthermore, the increase in the HR response was positively associated with the magnitude of decrease in percent body fat (adjusted for other variables indicated in Table 5). The exact mechanism for this is not clear. It can be speculated that the decrease in percent body fat is positively related to the change in adrenoceptor number or sensitivity and may thereby be positively related to the change in HR response.

In several studies,[15,23] a decreased HR response as a result of ISO infusion was found with increasing age within a very narrow age range (20 to 40 years). In agreement with this, Pearson's product-moment correlation coefficients between age and Conc $\Delta EE = 15\%$ and CC25 were statistically significant (both $P < .01$). However, the partial correlation coefficient between age (adjusted for % body fat and basal NE) and Conc $\Delta EE = 15\%$ or CC25 did not reach statistical significance. This may be explained by the fact that a strong correlation exists between percent body fat and age ($P < .001$), which indicates that, implicit linearity between the variables in the regression model, the previously reported association between age and sympathetically mediated physiologic responses is mainly due to differences in adiposity.

In conclusion, the degree of adiposity was shown to be negatively associated with the magnitude of the ISO-induced thermogenic response, whereas the HR response seems to be merely related to basal sympathetic activity. Since weight loss resulted in a significant increase in β-adrenergically mediated thermogenesis, the blunted thermogenic response does not seem to be a factor related to the origins of obesity. However, it is possible that a decrease in β-adrenergically mediated thermogenesis as a result of increasing fat stores may be a factor involved in the further development and maintenance of the obese state.

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