

Beta-adrenergically stimulated fat oxidation is diminished in middle-aged compared to young subjects.

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β -Adrenergically Stimulated Fat Oxidation Is Diminished in Middle-Aged Compared to Young Subjects*

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ABSTRACT

The effect of aging on β -adrenergically mediated substrate utilization was investigated in nine young (25.2 ± 1.7 yr old) and eight older males (52.9 ± 2.1 yr old), matched for body weight and body composition. In a first experiment, the nonselective β -agonist isoprenaline (ISO) was infused in increasing standardized doses, and during each infusion period energy expenditure and substrate utilization were determined by indirect calorimetry. In a second experiment, forearm skeletal muscle metabolism was studied during a standardized infusion dose of ISO (19 ng/kg fat-free mass·min). During β -adrenergic stimulation there was an increased carbohydrate oxidation (at an ISO infusion dose of 24 ng/kg fat-free mass·min, 31% vs. 21% of total energy expenditure; $P < 0.05$) and a decreased fat oxidation (51 vs. 62 of total energy expenditure; $P < 0.05$) in older

compared to young subjects. Skeletal muscle lactate release significantly increased in the older subjects (from -175 ± 32 to -366 ± 66 nmol/100 mL forearm tissue·min), whereas there was no change in young subjects (from -32 ± 21 to 23 ± 57 nmol/100 mL forearm tissue·min; interaction group \times ISO, $P < 0.01$). Additionally, there was a tendency toward a blunted ISO-induced increase in nonesterified fatty acid uptake in the older subjects (interaction group \times ISO, $P = 0.062$). Thus, middle-aged subjects have a blunted ability to oxidize fat during β -adrenergic stimulation compared to young subjects. This diminished fat oxidation may be an important etiological factor in the age-related increase in body fatness and obesity by favoring fat storage above oxidation. (*J Clin Endocrinol Metab* 84: 3764–3769, 1999)

AGING IS associated with increased prevalence of chronic diseases such as cardiovascular disease and type 2 diabetes. A central phenomenon in the age-associated increased prevalence of chronic diseases is the change in body composition, including increased body fat mass, in particular abdominal fat (1). Factors involved in the age-related increase in obesity may be a decrease in physical activity (1) and a decline in energy expenditure (2–4).

The decline in energy expenditure as a result of aging has been hypothesized to be related to a decreased activity of the sympathetic nervous system (5). Indeed, numerous studies reported that aging is associated with blunted sympathetically mediated metabolic responses (6–9).

To date, little is known about the effect of aging on substrate utilization. It has recently been shown that fat oxidation is decreased whereas carbohydrate oxidation is increased during moderate intensity exercise in elderly men and women (10). Previous studies in young lean males showed that β -adrenergic stimulation resulted in increased skeletal muscle fatty acid uptake and utilization, whereas in obese subjects skeletal muscle nonesterified fatty acid (NEFA) uptake was diminished (11, 12). If aging is associated with similar changes in sympathetically mediated fat utilization, this may result in a positive fat balance contributing thereby to the age-related increase in adiposity. The present

study investigated, firstly, whole body carbohydrate and fat oxidation during iv stepwise infusion of the nonselective β -agonist isoprenaline (ISO) and, secondly, skeletal muscle substrate exchange during a standardized dose of ISO in healthy young and older males matched for body weight and body composition.

Subjects and Methods

A selected group of nine young and eight older subjects participated in this study. Subject characteristics are indicated in Table 1. The older group was, on the average, 25 yr older than the young group, and both groups had comparable weight and body composition. Data on whole body thermogenesis in the older subjects (6) and data on muscle metabolism in the young subjects (11) have been previously published. All subjects were normotensive and were generally in good health. Cardiovascular and/or respiratory diseases were excluded by a medical questionnaire and physical examination. All subjects engaged in sports activities no more than 3 h a week, and none had a physically demanding job. The study protocol was approved by the medical ethical review committee of Maastricht University, and all subjects gave written informed consent. The experiments were performed after an overnight fast, and room temperature was kept between 20–23 C. The study protocol consisted of two experiments. In the first experiment, ISO was iv infused in increasing standardized doses, and during each infusion period whole body energy expenditure, carbohydrate and fat oxidation, and plasma ISO concentrations were determined (ISO infusion test). In the second experiment, forearm skeletal muscle metabolism was studied during rest and during an iv standardized infusion of ISO (forearm muscle experiment).

ISO infusion experiment

In this experiment, ISO was infused in increasing doses of 6, 12, and 24 ng/kg fat-free mass (FFM)·min. The dose is related to ISO sulfate; 69% corresponds to ISO free base. Body density was determined by hydrostatic weighing with simultaneous lung volume measurement (Volu-graph 2000, Mijnhardt, Breda, The Netherlands). Body composition was calculated according to the equation proposed by Siri (13). Whole body

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TABLE 1. Physical characteristics of the subjects

	Young (n = 9)	Older (n = 8)
Age (yr)	25.2 ± 1.7	52.9 ± 2.1
Wt (kg)	76.5 ± 1.9	72.2 ± 2.9
BMI (kg/m ²)	23.0 ± 1.5	23.9 ± 0.6
Body fat (%)	17.0 ± 2.2	16.9 ± 1.9
Fat mass	13.0 ± 1.7	12.2 ± 1.5
Fat-free mass	63.5 ± 2.8	60.0 ± 2.8

Values are the mean ± SE.

carbon dioxide and oxygen exchange was measured by an open circuit ventilated hood system (Oxygen Beta, Mijnhardt). The abbreviated equation of Weir was used for calculating energy expenditure (14), and the equations described by Frayn (15) were used for calculating carbohydrate and fat oxidation. At the end of each infusion period, a venous blood sample was taken with a heparinized syringe and was put into a glutathione-containing tube on ice. The sample was immediately centrifuged at 3000 rpm at 4°C, and the plasma was stored at -80°C. In the plasma samples, concentrations of ISO were determined by high performance liquid chromatography (16). During the experiments heart rate was registered continuously. When heart rate had risen 30 beats/min, the infusion was stopped.

Forearm muscle experiment

Design. Forearm skeletal muscle metabolism was investigated under baseline conditions and during iv infusion of the nonselective β -agonist ISO (in a dose of 19 ng/kg FFM·min). Before the start of the experiment, three cannulas were inserted. For the sampling of arterialized (young subjects) or arterial blood (older subjects), a cannula was inserted in a superficial dorsal hand vein or under local anesthesia in the radial artery of the forearm, respectively. In the same arm, a second cannula was inserted in a forearm vein for the infusion of ISO and the stable isotope tracer. In the contralateral arm, a third catheter was inserted in retrograde direction in an antecubital vein for the sampling of deep venous blood, draining forearm muscle. To obtain arterialized blood, the hand was heated for 30 min before the first baseline sample was taken. After 30 min of rest and after 30 min of ISO infusion, blood flow through different forearm compartments (see below) and arterio-venous concentration differences across forearm muscle of various metabolites were determined.

Blood flow. Total forearm blood flow (TBF) was measured by venous occlusion plethysmography with a mercury strain gauge (Periflow 0699, Janssen Pharmaceuticals, Beerse, Belgium) (11, 17).

To obtain an indication of whether TBF was representative of forearm skeletal muscle blood flow, forearm skin blood flow, forearm sc adipose tissue blood flow, and forearm composition were also determined, as described previously (17). Subcutaneous adipose tissue blood flow (ATBF) was measured after a sc deposition of xenon 133 (5.5 megabecquerels; 150 μ Ci) on the dorsal side of the forearm about 10 cm proximal to the wrist joint (for details, see Ref. 17). Skin blood flow (SBF) was determined by the laser Doppler technique (Periflux PF3, Perimed, Stockholm, Sweden) placed on the ventral side of the forearm near the wrist joint. The amounts of forearm sc adipose tissue and bone and muscle of the forearm were determined by a cross-sectional analysis at the site of the greatest circumference of the forearm with magnetic resonance imaging (Gyrosan T5, Philips Medical Systems, Eindhoven, The Netherlands) (17).

Biochemical methods. Plasma NEFA, glucose, glycerol, and lactate were measured using standard enzymatic techniques automated on the Cobas Fara centrifugal analyzer at 340 nm (for FFA: FFA-C test kit, Wako Chemicals, Neuss, Germany; for glucose: Unikit III, Hoffman-La Roche, Basel, Switzerland; for glycerol and lactate: Boehringer Mannheim, Mannheim, Germany). Plasma insulin was measured using a specific double antibody RIA for human insulin (Kabi Pharmacia, Uppsala, Sweden). Also, the hematocrit was determined in heparinized blood using a microcapillary system.

Calculations and statistics

The exchange of metabolites across forearm muscle (nanomoles per 100 mL forearm tissue/min) was calculated by multiplying the arterio-venous difference of metabolites (micromoles per L) by total forearm plasma blood flow [=total blood flow \times (1 - hematocrit/100)]; units: milliliters per 100 mL forearm tissue/min]. Skeletal muscle blood flow (SMBF) was calculated according to the following equation (17): TBF = amount of muscle \times SMBF + amount of skin \times SBF + amount of fat \times ATBF, where amount of tissue = % of total forearm area/100, blood flow is expressed as milliliters per 100 mL tissue/min, SBF is the forearm skin blood flow, and ATBF is forearm sc adipose tissue blood flow.

The number of subjects in the present study was based on previous studies in our laboratory in which eight subjects per group were sufficient to show significant differences in muscle substrate metabolism (NEFA flux) in lean and obese subjects (11) and as result of weight reduction (12).

Data are represented as the mean ± SE. To compare baseline and ISO-induced responses between groups, a two-factor repeated measures ANOVA was performed.

Results

ISO infusion test

Both young and older subjects showed dose-related increases in plasma ISO ($P < 0.001$). The increase tended to be more pronounced in older subjects (basally and at 6, 12, and 24 ng, 0, 72 ± 55, 118 ± 19, and 212 ± 11 pg/mL) compared to the young (basally and at 6, 12, and 24 ng, 0, 62 ± 5, 102 ± 8, and 189 ± 10 pg/mL), but differences did not reach statistical significance. Plasma norepinephrine and epinephrine concentrations were significantly higher in the older subjects compared to the young subjects (both $P < 0.001$; norepinephrine basally and 6, 12, and 24 ng: young, 176 ± 16, 217 ± 28, 226 ± 29, and 265 ± 28 pg/mL; older, 318 ± 34, 358 ± 35, 415 ± 43, and 440 ± 116 pg/mL; epinephrine basally and 6, 12, and 24 ng: young, 24 ± 5, 15 ± 4, 16 ± 5, and 16 ± 4 pg/mL; older, 71 ± 16, 57 ± 14, 59 ± 13, and 56 ± 12 pg/mL). Figure 1 shows whole body energy expenditure and carbohydrate and fat oxidation during infusion of increasing doses of ISO. Resting energy expenditure was not significantly different between the groups. Energy expenditure significantly increased during ISO infusion in both groups ($P < 0.001$). There were no significant differences in the ISO-stimulated energy expenditure between the groups, although values were slightly lower in the older group. Basal carbohydrate oxidation was comparable in both groups. Carbohydrate oxidation tended to decrease during ISO in the young, whereas there was no change in the older group (Interaction group \times ISO; $P = 0.084$). Basal fat oxidation was similar in both groups. The ISO-induced increase in fat oxidation ($P < 0.001$) was blunted in the older group compared to that in the young subjects ($P < 0.05$). Figure 2 shows the percent contribution of carbohydrate and fat oxidation to total energy expenditure during baseline conditions and during ISO infusion at dose of 24 ng/kg FFM·min. Under baseline conditions the contributions of fat and carbohydrate oxidation to total energy expenditure are comparable in both groups. During ISO stimulation the percent contribution of carbohydrate oxidation to total energy expenditure is increased in the older subjects compared to that in the young ($P < 0.05$), whereas there is a blunted increase in the percent contribution of fat ($P < 0.05$).

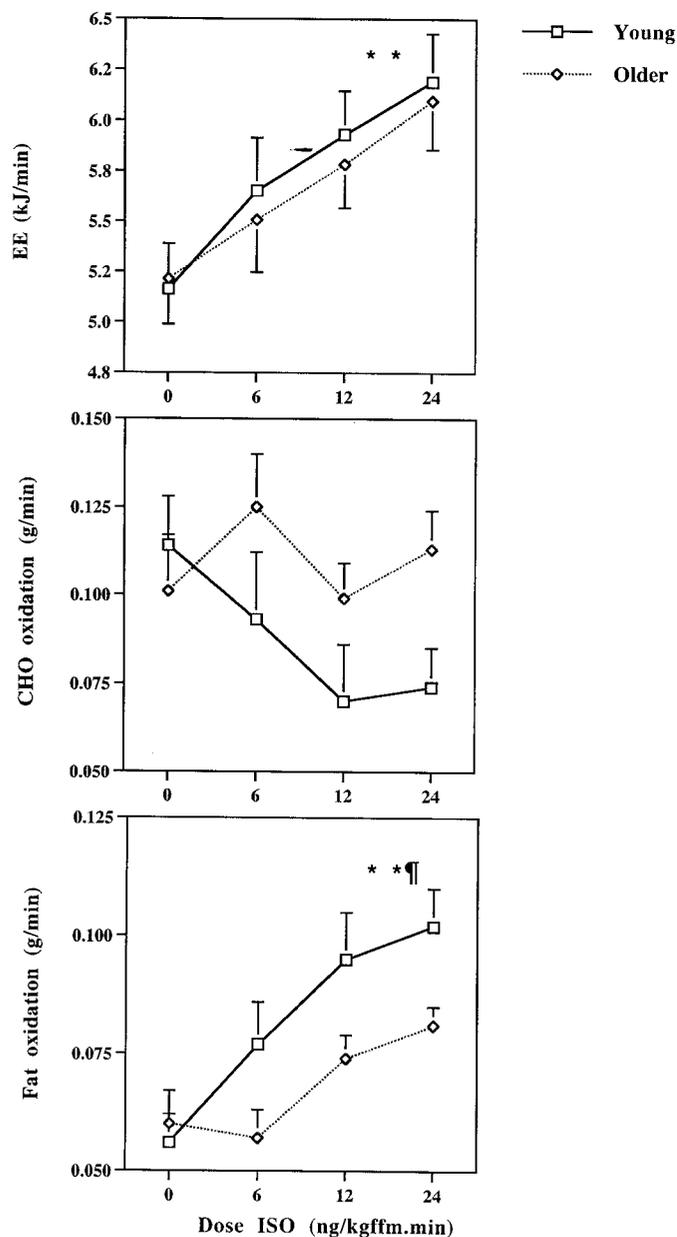


FIG. 1. Energy expenditure (EE) and carbohydrate and fat oxidation during stepwise infusion of increasing doses of the nonselective β -agonist ISO in young and older subjects. By repeated measures ANOVA, ISO effect: **, $P < 0.001$; ISO, $P = 0.001$; interaction group \times ISO, $P < 0.05$.

Forearm muscle experiment

Heart rate responses. Basal heart rate values were not different between groups (young, 57.0 ± 2 ; older, 57.1 ± 3.2 beats/min), whereas the increase in heart rate during ISO infusion tended to be less pronounced in older subjects (young, 75.8 ± 3 ; older, 71.1 ± 4 beats/min; interaction group \times ISO, $P = 0.074$).

Intermediary metabolites. Changes in arterial concentrations of metabolites are indicated in Table 2. Insulin concentrations were not significantly different between groups in both conditions. ISO infusion resulted in a significant increase in

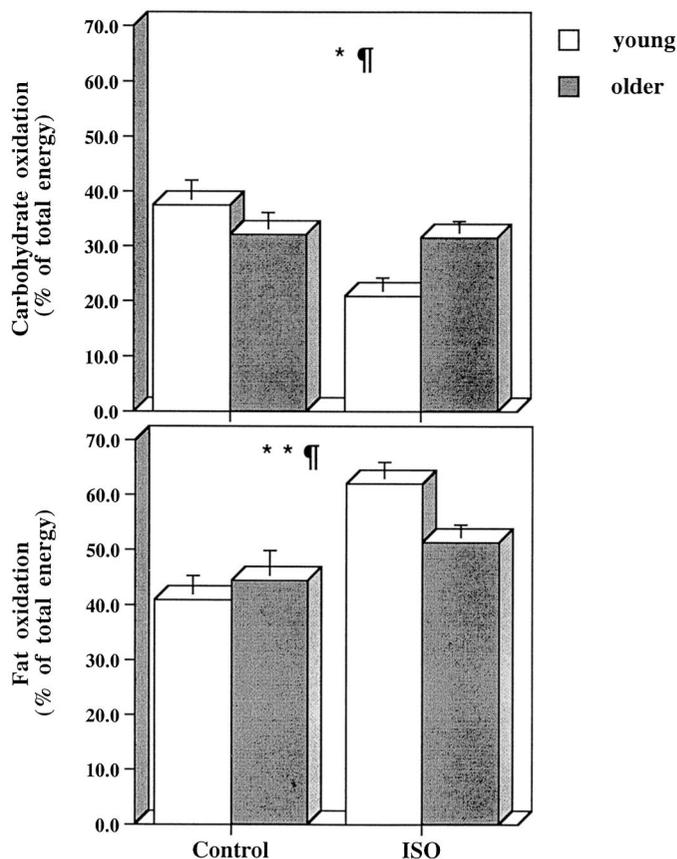


FIG. 2. Carbohydrate and fat oxidation, expressed as a percentage of total energy expenditure, during the highest dose (24 ng/kg FFM·min) of a stepwise infusion of increasing doses of the nonselective β -agonist isoprenaline (ISO) in young and older subjects. By repeated measures ANOVA: carbohydrate oxidation, ISO effect, * $P < 0.05$, ** $P < 0.001$; interaction group \times ISO, $P < 0.05$.

insulin concentrations. Glucose concentrations were not different between groups in the control group as well as during ISO infusion. Lactate concentrations were similar in both groups, whereas there was a significant increase in plasma lactate during ISO infusion. Basal NEFA concentrations as well as the ISO-induced increase in NEFA concentrations were similar in both groups. Basal glycerol concentrations, the ISO-induced increase in glycerol concentrations, and glycerol concentrations during ISO infusion were significantly lower in older compared to young subjects.

Forearm muscle blood flow and forearm composition. As indicated in Table 3, the ISO-induced increase in total forearm blood flow tended to be blunted in older compared to young subjects. Forearm sc adipose tissue blood was not different between groups under both conditions. Relative values for skin blood flow were comparable in both, and values for skin blood flow did not change as a result of ISO infusion. Total forearm area was comparable in both groups (young vs. older, 5576 ± 144 vs. 5839 ± 133 mm²), and the percentage of sc adipose tissue ($13.9 \pm 1.0\%$ vs. $13.0 \pm 1.0\%$), muscle ($62.4 \pm 1.1\%$ vs. $64.5 \pm 1.0\%$), and skin ($9.3 \pm 0.13\%$ vs. $9.1 \pm 0.1\%$) were similar in both groups. As for TBF, the changes in SMBF tended to be blunted in the elderly ($P = 0.09$). Changes in TBF reflected mainly changes in SMBF. For this

TABLE 2. Arterial(ized) circulating concentrations of metabolites in young and older subjects during rest and during iv infusion of the nonselective β -agonist isoprenaline (ISO)

	Control	ISO	ANOVA		
			Group	ISO	Interaction
Insulin (U/L)					
Young	7.2 \pm 0.6	13.2 \pm 1.5		0.05	
Older	5.9 \pm 1.0	9.3 \pm 1.4			
Glucose (mmol/L)					
Young	4.9 \pm 0.1	5.0 \pm 1.1			
Older	5.3 \pm 0.2	5.3 \pm 1.6			
Lactate (μ mol/L)					
Young	496 \pm 35	547 \pm 54		0.02	
Older	477 \pm 39	540 \pm 31			
NEFA (μ mol/L)					
Young	412 \pm 45	1249 \pm 118		0.0001	
Older	588 \pm 56	1311 \pm 86			
Glycerol (μ mol/L)					
Young	69 \pm 40	124 \pm 7	0.001	0.001	0.02
Older	49 \pm 5 ^a	83 \pm 7 ^a			

Values are the mean \pm SE. *P* values of two-factor repeated measures ANOVA are indicated in the *right*.

^a *P* < 0.05, older vs. young (by *post-hoc* testing).

TABLE 3. Blood flow through the different compartments of the forearm, forearm composition, and estimated forearm skeletal muscle blood flow during rest and during iv infusion of the nonselective β -agonist isoprenaline (ISO)

	Control	ISO	ANOVA		
			Group	ISO	Interaction
TBF					
Young	1.56 \pm 0.36	4.27 \pm 1.1		0.01	0.09
Older	1.82 \pm 0.10	2.65 \pm 0.45			
ATBF					
Young	2.13 \pm 0.39	2.50 \pm 0.59			
Older	2.35 \pm 0.59	2.72 \pm 0.66			
SBF					
Young	5.9 \pm 0.6	5.6 \pm 0.6			
Older	5.2 \pm 0.6	5.1 \pm 0.3			
Estimated SMBF					
Young	1.2 \pm 0.6	5.6 \pm 1.8		0.01	0.09
Older	1.5 \pm 0.2	2.9 \pm 0.6			

Values are the mean \pm SE. *P* values of ANOVA are indicated on the right. TBF, Total forearm blood flow; ATBF, forearm adipose tissue blood flow; SBF, forearm skin blood flow; SMBF, forearm skeletal muscle blood flow.

reason, TBF was used for calculating skeletal muscle substrate exchange.

Forearm muscle substrate fluxes. Figure 3 shows skeletal muscle substrate fluxes with ISO. In the basal state, forearm muscle glucose uptake tended to be higher in older subjects compared to young, whereas lactate release was significantly increased in the older subjects (*P* < 0.01). During ISO infusion, there were no changes in glucose uptake in either group, whereas lactate release did not change in young subjects and increased in older subjects (*P* < 0.01). Muscle NEFA uptake increased during ISO infusion (*P* < 0.05). The ISO-induced increase in NEFA uptake tended to be blunted in the older subjects (*P* = 0.062). There were no differences in glycerol flux between the groups.

Discussion

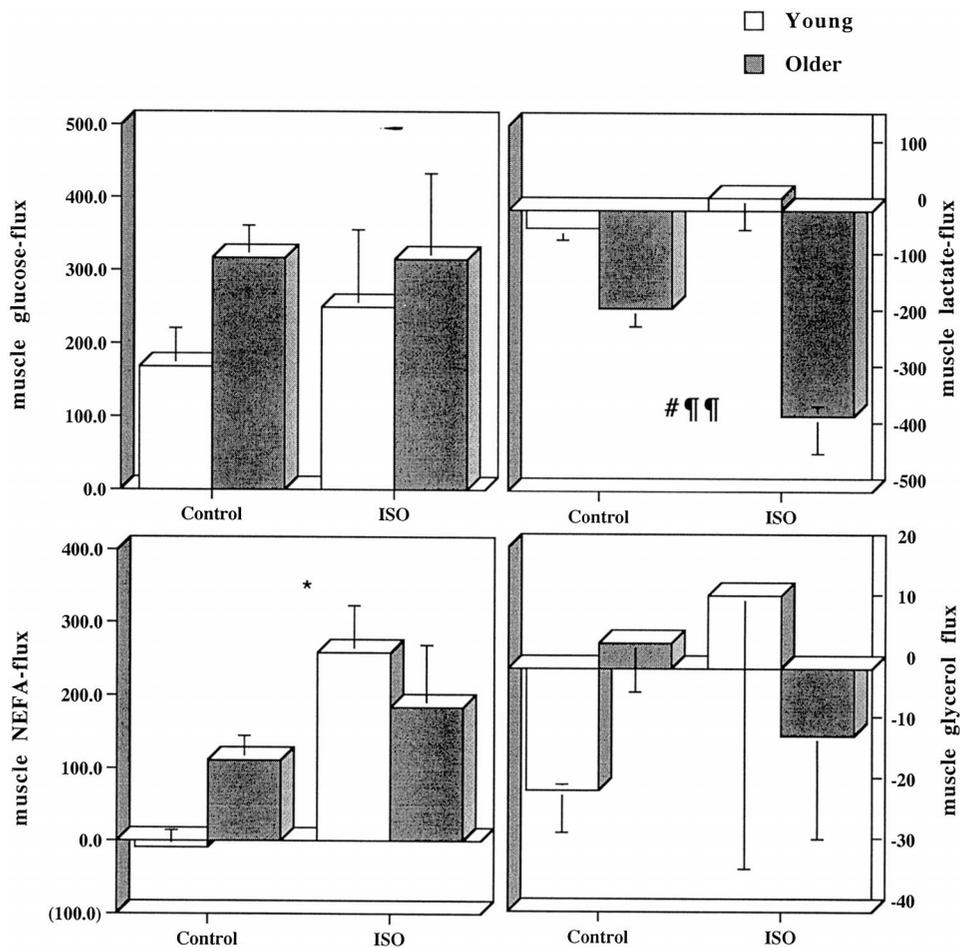
The present study intended to investigate whole body and skeletal muscle substrate utilization during β -adrenergic stimulation in young and older subjects with comparable body weight and percent body fat. The present study shows that there is increased carbohydrate oxidation and decreased

fat oxidation during iv infusion of the nonselective β -agonist ISO in the older subjects. Furthermore, the pronouncedly increased muscle lactate release during ISO infusion in the older subjects indicates an increased glycolytic activity. In combination with the diminished ISO-induced increase in NEFA uptake suggests that skeletal muscle plays an important part in this shift in substrate utilization.

Methodological considerations

An estimation of skeletal muscle blood flow was made by determining total sc adipose tissue and skin blood flow and by measuring forearm composition (17). The results of the present study show that changes in TBF are similar to changes in skeletal muscle blood flow in both groups, indicating that it is valid to use total forearm blood flow (or forearm plasma flow) for calculating forearm skeletal muscle substrate fluxes. Secondly, the young subjects were studied by using arterialized blood, whereas in the older subjects direct arterial sampling took place. The warm air box method has been adequately validated for the determination of most metabolites (18), but has been criticized when applied by

FIG. 3. Forearm skeletal muscle glucose, lactate, NEFA, and glycerol flux (in nanomoles per 100 mL forearm tissue) during infusion of a standardized dose of the nonselective β -agonist ISO (19 ng/kg FFM \cdot min). By repeated measures ANOVA: lactate, group effect: # $P < 0.001$; interaction group \times ISO, ¶¶ $P < 0.001$; NEFA, ISO effect, * $P < 0.05$; interaction group \times ISO, $P = 0.062$.



means of warming blankets because it may affect blood flow to the contralateral arm (19). However, in a previous study we showed that hand heating by a warm air box had no or a very slight effect on body and skin temperature, deep venous oxygen saturation, TBF, and glucose-induced oxygen consumption of the contralateral forearm (20). On the basis of these findings, we can exclude that the use of the warm air box method in young subjects has interfered with the differences in muscle metabolism in older and young subjects.

Fat oxidation

A blunted fat oxidation has been reported before during exercise in elderly subjects (10). The present study shows for the first time that this may be related to a decrease in β -adrenergically mediated fat oxidation. A factor contributing to the diminished ISO-induced fat oxidation may simply be an impaired β -adrenergically mediated lipolytic response in the older subjects (9), resulting in diminished NEFA release from adipose tissue. However, ISO-mediated arterial(ized) NEFA concentrations as well as NEFA supply to skeletal muscle [blood flow \times arterial(ized) NEFA concentrations] were not significantly different between both groups, suggesting that differences in NEFA supply to skeletal muscle may not have played a role in the present study. This is consistent with studies showing that lipolytic rates and NEFA availability were not rate limiting for blunted exercise-induced fat ox-

idation in elderly subjects (10). Secondly, the shift in substrate utilization during β -adrenergic stimulation may have been caused by an age-related decline in the capacity of skeletal muscle to oxidize fatty acids (21). Thirdly, the higher ISO-induced increase in skeletal muscle lactate release in the older subjects suggests increased glycolysis that may be accompanied by increased glucose oxidation and glycogen breakdown, as reported with epinephrine infusion (22). This increased glycolytic flux may limit the rate of fat oxidation by inhibiting carnitine acyltransferase, the rate-limiting enzyme for long chain fatty acid transport into the mitochondria (23). Finally, it has been shown that the membrane transport of long chain fatty acids may be under β -adrenergic control (24), which implies that differences in the activation of this transport between young and older subjects may contribute to the lowered fat oxidation in the older subjects. However, at present evidence is lacking to support this speculation.

Although subjects in the present study were selected to participate no more than 3 h a week in sports activities, we cannot exclude the possibility that at least part of the observed differences are due to an age-related decline in physical fitness and are not related to the aging process *per se*. Indeed, training has been shown to increase mitochondrial oxidative capacity and fat oxidation in elderly subjects (25). However, from the latter results it cannot be determined

whether training compensates for or corrects a diminished oxidative capacity. Additionally, although the subjects were matched for percent body fat, we cannot exclude the possibility that differences in fat oxidation can at least partly be explained by differences in body fat distribution, as aging is associated with increased abdominal fat mass (1). Thus, age-related changes in physical fitness and body fat distribution have to be taken into account when interpreting the disturbances in fat oxidation in the middle-aged subjects.

Lipolysis

Rates of lipolysis at rest in aging men have been reported to be either similar to or slightly higher than rates in younger males (10, 26). This seems to contrast with data from the present study showing lower resting arterial(ized) glycerol concentrations in the older subjects. This apparent discrepancy may be explained by the fact that in most previous studies the amount of body fat in the older subjects was higher than that in younger subjects, and that lipolysis per unit body fat may have actually been lower (26).

Thermogenesis

In a previous study we showed a blunted ISO-induced thermogenesis in the older subjects (6). The present study shows that when the young and older subjects are matched for percent body fat, the ISO-induced thermogenesis is not significantly different between the groups. These findings suggest that the previously found blunted thermogenesis may be explained in large part by differences in percent body fat between the young and elderly groups.

Conclusion

In summary, older (middle-aged) subjects have decreased fat oxidation and increased carbohydrate oxidation during β -adrenergic stimulation compared to young subjects. This shift in substrate utilization is reflected in increased skeletal muscle lactate release and a tendency toward a diminished increase in NEFA uptake during β -adrenergic stimulation. This diminished β -adrenergically mediated fat utilization may be an important contributing factor to the increase in adiposity with advancing age.

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