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Training-Induced Enhancement of Insulin Action in Human Skeletal Muscle: The Influence of Aging

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Age-induced reduction of whole body insulin action has been attributed to decreased insulin action in skeletal muscle. Physical training improves insulin action, but the effect has never been investigated specifically in aged human skeletal muscle. Seven young men [age: 23 ± 1 yr (mean ± SE; range, 21–24 yr); weight: 70 ± 1 kg; body fat: 8 ± 1%] and eight aged men [59 ± 1 yr (range, 58–64 yr); 83 ± 2 kg; 20 ± 2%] performed one-legged bicycle training on a modified ergometer cycle for 10 weeks, 6 days/week, at 70% of $\dot{V}O_2$ peak. Glucose clearance rates in whole body and leg were measured 16 hr after training by a hyperinsulinemic (28, 88, and 480 mU·min^{-1}·m^{-2}), isoglycemic clamp combined with leg balance technique. Peak oxygen uptake during the bicycle test was always lower ($p < .05$) in aged vs. young subjects. Furthermore, $\dot{V}O_2$ peak was higher after training in trained (T) vs. untrained (UT) ($p < .05$) legs. Whole body glucose clearance rate was lower in aged vs. young subjects ($p < .05$) when expressed per kg body weight, but similar when expressed relative to fat free mass. Leg blood flow was always lower in aged vs. young men ($p < .05$). At basal and during insulin infusion, leg blood flow in young men did not differ significantly in T vs. UT legs (maximum insulin: 81 ± 7 vs. 71 ± 5 ml·min^{-1}·kg leg^{-1}), while in aged subjects it increased ($p < .05$) with training (maximum insulin: 57 ± 5 vs. 48 ± 5 ml·min^{-1}·kg leg^{-1}). Leg glucose extraction was always higher in aged vs. young men during the two last clamp steps ($p < .05$). Furthermore, leg glucose extraction was increased by training in young ($p < .05$) but not significantly in aged subjects. Leg glucose clearance rates increased ($p < .05$) with training and was similar in aged men (T: 1 ± 1, 8 ± 1, 21 ± 2, and 24 ± 2; UT: 1 ± 1, 6 ± 1, 14 ± 2, and 20 ± 2 ml·min^{-1}·kg leg^{-1}) and young men (T: 1 ± 1, 12 ± 3, 23 ± 3, and 26 ± 3; UT: 1 ± 1, 8 ± 2, 17 ± 2, and 21 ± 2 ml·min^{-1}·kg leg^{-1}). Therefore, insulin action in muscle is not reduced by aging. At high insulin concentrations, the leg blood flow is lower, whereas glucose extraction is higher in aged compared with young men. Training increases overall insulin action on glucose clearance in skeletal muscle identically in aged and young subjects.

WHOLE body insulin action is reduced with increasing age, although variability in insulin action among older subjects is substantial (Davidson, 1979; Rosenthal et al., 1982; Jackson, 1990). The reduction has indirectly been attributed to decreased insulin action in aged skeletal muscle (DeFronzo, 1979; Fink et al., 1983). However, aging per se is probably not the cause of insulin resistance. Alternatively, the diminished whole body insulin action seen with advancing age could be due to a relative increase in body fat (Davidson, 1979; Coon et al., 1992; Kohrt et al., 1993). Also, a decreased level of physical activity with advancing age has been suggested to contribute to decreased whole body insulin action (Davidson, 1979). Physical activity increases insulin action in young people predominantly by effects in the skeletal muscle, and a decrease in whole body insulin action in aged people might reflect a decreased insulin action in skeletal muscle. Against this, it has been reported that in the forearm, insulin-stimulated glucose uptake rates (Kalant et al., 1980) and skeletal muscle glycogen synthase activity (Gumbiner et al., 1992) are similar in young and elderly healthy people. However, skeletal muscle in the forearm would probably not be representative for a decrease in physical activity with aging.

Whole body insulin action in aged people is improved with physical training (Torino, 1989; Kahn et al., 1990; Rogers et al., 1990; Yamanouchi et al., 1992). Furthermore, aged people exhibit the same histochemical and morphological adaptations and increases in glycolytic and mitochondrial enzyme activities in skeletal muscle in response to training as young people do (Coggan et al., 1992). However, the effect of training on insulin action in muscle has not yet been specifically investigated in healthy, aged people.

The present study was carried out to further characterize the interaction between aging and physical activity on the effect of insulin in human skeletal muscle. We used a one-legged training model and measured insulin-stimulated glucose uptake rates simultaneously in the trained and in the untrained leg of both healthy young subjects and healthy aged subjects. Some of the data from the young subjects has previously been reported separately (Dela et al., 1992).

Materials and Methods

Subjects. — Seven healthy young men (23 ± 1 yr, mean ± *SE*; range, 21–24 yr) and eight healthy aged men (59 ± 1 yr; range, 58–64 yr) participated in the study, which was approved by the local ethical committee. None of the subjects had any family history of diabetes or other endocrinological disorder, and none were taking any medication. All the aged subjects had normal glucose tolerance (assessed by a 75-g oral glucose tolerance test). Characteristics of the study groups are shown in Table 1.

Table 1. Characteristics of the Study Groups

	Young (n = 7)	Aged (n = 8)
Age (yr)	23 ± 1	59 ± 1‡
Fasting plasma glucose (mM)	5.3 ± 0.1	5.7 ± 0.1‡
Fasting plasma insulin (pM)	64 ± 10	70 ± 7
Waist circumference (cm)	77.7 ± 0.8	99.1 ± 1.5‡
Waist-hip ratio	0.94 ± 0.01	1.00 ± 0.01‡
Body weight (kg)	69.5 ± 1.0	83.2 ± 2.3‡
Body mass index (kg/m²)	20.9 ± 0.3	25.7 ± 0.7‡
Body fat (%)	7.5 ± 0.8	20.0 ± 2.1‡
Leg volume (l)		
UT-leg	10.1 ± 0.3	9.8 ± 0.4
T-leg	10.5 ± 0.3*	10.3 ± 0.4*
$\dot{V}O_2$ peak (ml•min^{-1}•kg b.w.$^{-1}$)		
UT-leg	44 ± 2	27 ± 2‡
T-leg	52 ± 2*	30 ± 2‡*

Note. Values are mean ± *SE*. Subjects performed one-legged bicycle training 30 min/day, 6 days/week for 10 weeks at 70% of the maximal oxygen uptake obtained during a graded one-legged bicycle test ($\dot{V}O_2$ peak). T and UT denote trained and untrained legs, respectively. Significant difference ($p < .05$): *, from UT leg; ‡, from young subjects.

Experimental design. — Peak oxygen uptake ($\dot{V}O_2$ peak) was measured during a one-legged graded bicycle test to exhaustion before and after training (see below). $\dot{V}O_2$ peak was identified as the highest oxygen uptake obtained. Because only a few of the aged subjects were able to achieve maximal steady-state oxygen uptake during one-legged bicycling before training, $\dot{V}O_2$ peak was used instead of the conventional maximal oxygen uptake. Body weight, percent body fat (by skinfold measurements), leg volume (by water displacement), and waist (at the level of the umbilicus) and hip circumference (at the level of the anterior superior iliac spine) were measured before and after the training program. The training leg was randomly determined.

The one-legged training program has been described previously (Dela et al., 1992). In short, it consisted of 30-min one-legged supervised bicycling on an ergometer bicycle, 6 days/week for 10 weeks at a work load corresponding to 70% of $\dot{V}O_2$ peak.

Three days before the clamp, the subjects abstained from alcohol intake and consumed a diet consisting of a minimum of 250 g of carbohydrate/day. On the day of the experiment, the subjects arrived in the laboratory at 8:00 a.m., 16 hr after the last training bout. They had fasted since 10:00 p.m. the day before and arrived by car to minimize physical activity prior to the clamp. A three-step hyperinsulinemic (insulin infusion rates: 28, 88, and 480 mU•min•min^{-1}•m^{-2}) isoglycemic clamp was performed in combination with catheterization of a radial or brachial artery and both femoral veins. Blood flow was measured by thermodilution, and arterial and venous blood samples were drawn in duplicate (before insulin infusion) or triplicate (at t = 85, 100, and 115 min of each 120-min lasting clamp step) while pneumatic cuffs around the ankles were inflated to systolic blood pressure +50 mmHg. Details of the clamp procedure and blood flow measurements have been reported elsewhere (Dela et al., 1992, 1995).

Analytical procedures. — Blood samples for determination of whole blood (arterial and venous) and plasma (arterial) glucose was collected in iced tubes containing potassium-fluoride and heparin (20 μmol and 10 IU/ml blood) or heparin (10 IU/ml blood), respectively. Measurements were obtained by use of an automated glucose analyzer (Model YSI 23 AM; Yellow Springs Instruments). Blood for determination of insulin in plasma was stabilized with 500 kallikrein inhibitory units aprotinin (Trasylol) and 1.5 mg EDTA/ml blood and centrifugated at 4 °C. Plasma was stored at –20 °C until analysis (radioimmunoassay kit; Novo Nordisk, Denmark). Blood for determination of oxygen content was sampled anaerobically in heparinized syringes, then kept on ice and analyzed on an ABL4 blood gas analyzer (Radiometer, Copenhagen, Denmark) within 1 hr. Expiratory air was collected in Douglas bags through a mouthpiece before and at the end of the clamp. Subjects were accustomed to the mouthpiece for at least 4 min before collection of air (≈10 min). Volume of expired air was measured in a giant spirometer, and fractions of O_2 and CO_2 were analyzed by paramagnetic (Servomex OA 189) and infrared (Capnograph Godard 146) electronic gas analyzers, respectively.

Calculations. — Volume of the leg was calculated as total leg volume minus volume of the foot. Leg weight was calculated assuming a specific gravity of 1. Glucose infusion rates were averaged for 10-min periods. Whole body glucose uptake during steady state was calculated as the mean of glucose infusion rates during the last 30 min in each clamp step, corrected for loss of glucose in the urine. Glucose and oxygen arterio-venous extraction in percent was calculated as $(C_a - C_v)/C_a \times 100$, where C_a and C_v are the concentrations in arterial and femoral venous blood, respectively. Leg glucose clearance rates were calculated as glucose extraction × blood flow.

Statistics. — Results are expressed as mean ± *SE*. Concentrations of substances in blood and plasma are presented as the mean of determinations on two (before insulin infusion) or three (during insulin infusion) blood samples. To detect differences between states of training and between the groups in responses to insulin infusion, a two-way analysis of variance (ANOVA) for repeated measures was performed. If the ANOVA indicated significant differences, these were located by a pairwise multiple-comparison procedure (Student–Newman–Keuls). To detect differences between parameters represented by single measurements, nonparametric tests for unpaired (Mann–Whitney) and paired (Wilcoxon) data were used as appropriate. A p-value of $< .05$ was considered significant in two-tailed testing.

RESULTS

Plasma glucose and insulin concentrations. — Basal plasma glucose was higher ($p < .05$), while insulin concentrations were similar, in the aged compared with the young subjects (Table 1). During insulin infusion, plasma glucose concentrations were maintained at individual basal concentrations with a coefficient of variation of <6% (data from all

clamp steps and aged and young subjects pooled), and plasma insulin concentrations increased similarly in the aged and the young subjects.

Whole body glucose uptake and clearance. — Glucose infusion rates were similar at the lowest insulin concentration (young: 5.5 ± 0.7; aged: 4.9 ± 0.5 mg•min^{-1}•kg^{-1}). At the two subsequent insulin concentrations, glucose infusion rates were higher in young compared with aged subjects ($p < .05$) (11.3 ± 0.6 vs. 9.9 ± 0.7 and 14.8 ± 0.7 vs. 13.2 ± 0.9 mg•min^{-1}•kg^{-1}, respectively). Whole body glucose clearance always increased with increasing insulin (Figure 1). Whole body glucose clearance was lower ($p < .05$) at the two highest insulin concentrations in the aged compared with the young subjects when expressed per kg body weight (Figure 1). However, there was no difference between the two groups when clearance rates were expressed relative to fat-free mass (FFM) (Figure 1).

Bloodflow, glucose extraction, and clearance in the legs. — In response to insulin infusion, leg blood flow increased ($p < .05$), but it leveled off between the two highest insulin concentrations (Figure 2). Blood flow was always higher ($p < .05$) in young compared with aged subjects. Before insulin infusion there was no difference in blood flow between the trained (T) and the untrained (UT) legs in the young subjects. In the aged subjects, blood flow was higher ($p < .05$) in the T vs. UT leg before insulin infusion. Blood flow increased in T and UT legs from basal to maximal insulin concentrations by 97 ± 22% and 73 ± 19% (young; $p > .05$) and by 67 ± 9% and 84 ± 19% (aged; $p > .05$),

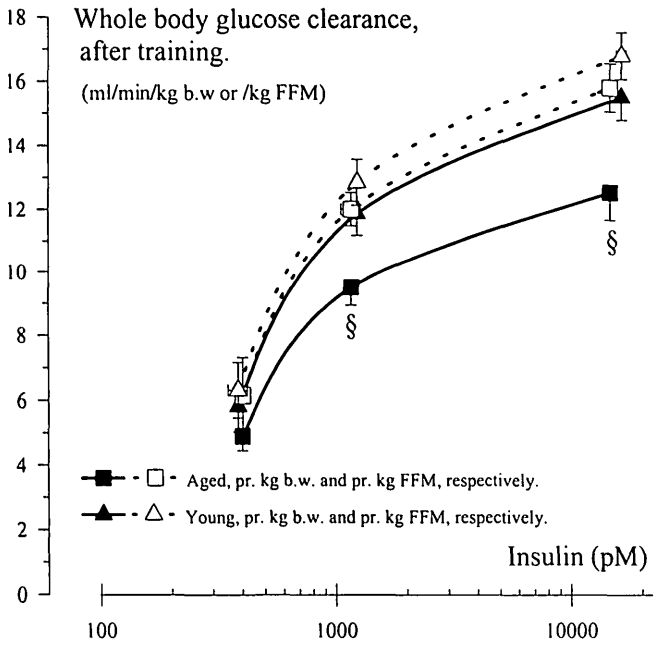

Figure 1. Values are mean ± *SE*. Seven young and eight aged healthy subjects performed one-legged bicycle training for 10 weeks. Insulin-stimulated whole body glucose clearance rates were measured 16 hr after last training session by use of hyperinsulinemic, isoglycemic clamp technique. FFM denotes fat-free mass. Significant difference ($p < .05$): §, from values in young subjects and from values in aged subjects expressed per kg FFM.

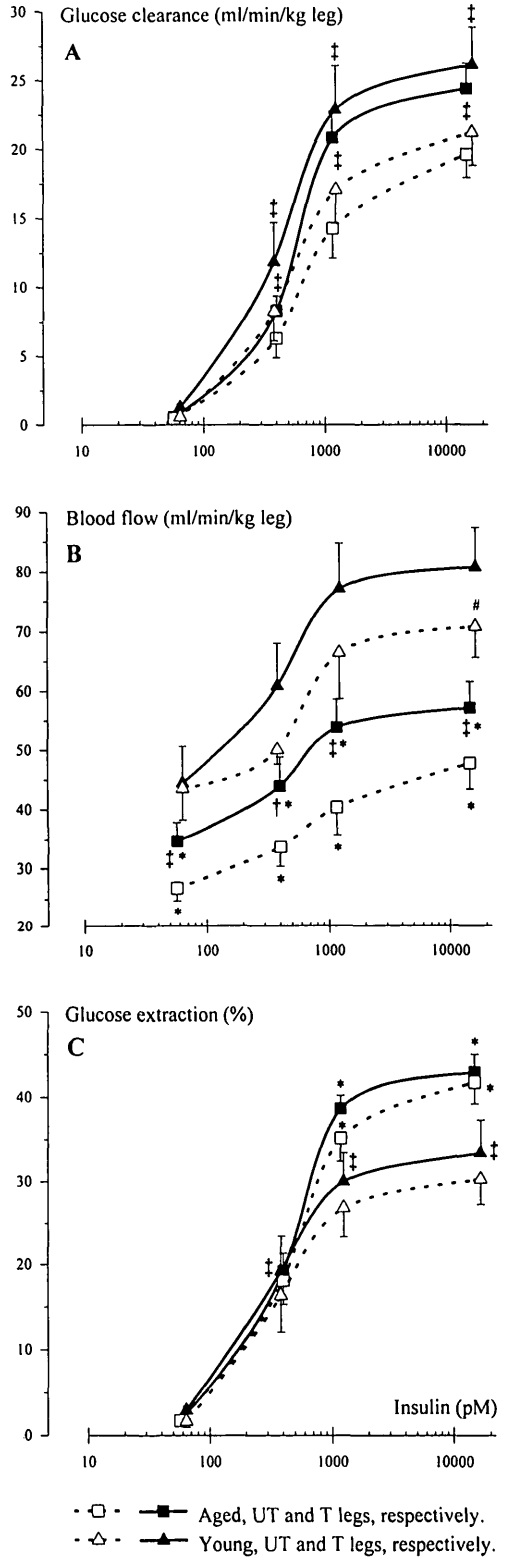

Figure 2. Values are mean ± *SE*. Seven young and eight aged healthy subjects performed one-legged bicycle training for 10 weeks. Sixteen hours after the last training session a hyperinsulinemic, isoglycemic clamp in combination with catheterization of an artery and a femoral vein in both the trained (T) and the untrained (UT) leg were carried out. Basal and insulin stimulated leg glucose clearance rates (**A**) were calculated as blood flow (**B**) × glucose extraction (**C**). Significant difference ($p < .05$): ‡, from UT leg; *, from corresponding leg in young subjects; #, from T leg in aged subjects; †, different from UT leg ($p < 0.1$).

respectively, without a difference ($p > .05$) between the groups.

In the basal state, glucose extraction was similar in T and UT legs in both groups. During insulin infusion, glucose extraction increased and was always higher in the young subjects in T compared with UT legs, whereas glucose extraction did not differ significantly between T and UT legs in the aged subjects. Glucose extraction was higher ($p < .05$) in T and UT legs in the aged subjects compared with the corresponding legs in the young subjects at the two highest insulin concentrations.

In the basal state, leg glucose clearance did not differ between T and UT legs or between aged and young subjects. During insulin infusion, leg glucose clearance was increased ($p < .05$) in T compared with UT legs in both groups. Glucose clearance in both T and UT legs was not different between aged and young subjects. Thus, the increase in response to training was identical in young and aged subjects (at maximal insulin concentrations of 24% and 23%, respectively).

Whole body oxygen uptake, leg oxygen extraction and uptake. — Whole body oxygen uptake always increased during the clamp (aged: 3.0 ± 0.2 and 3.3 ± 0.1; young: 3.5 ± 0.3 and 4.0 ± 0.2 $ml \cdot min^{-1} \cdot kg^{-1}$) before insulin infusion and at maximal insulin concentrations, respectively.

Leg oxygen uptake always increased with increasing insulin concentrations ($p < .05$) due to increased blood flow, evidently by the lack of changes in oxygen extraction with increasing insulin concentrations ($p > .05$) (Figure 3). Leg oxygen uptake in UT legs was lower in aged compared with young subjects ($p < .05$). Extraction of oxygen in the legs was lower in young compared with aged subjects ($p < .05$) (Figure 3). Furthermore, extraction of oxygen in the legs was lower in T legs compared with UT legs ($p < .05$) (Figure 3).

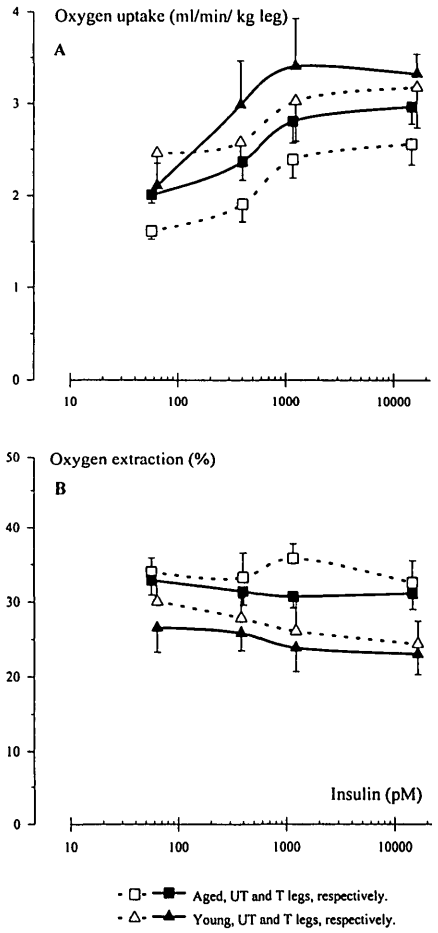

Figure 3. Values are mean ± *SE*. Seven young and eight aged healthy subjects performed one-legged bicycle training for 10 weeks. Sixteen hours after the last training session a hyperinsulinemic, isoglycemic clamp in combination with catheterization of an artery and a femoral vein in both the trained (T) and the untrained (UT) leg were carried out. Oxygen uptake (**A**) was calculated as arterio-venous difference in oxygen concentration × blood flow. Oxygen extraction (**B**) was calculated as $(C_a - C_v)/C_a \times 100$, and is expressed in percent. Oxygen uptake always increased with increasing insulin concentrations ($p < .05$) and in UT legs was lower in aged compared with young subjects (ANOVA). In aged subjects, oxygen uptake was always higher ($p < .05$) in T compared with UT legs (ANOVA). During insulin infusion oxygen extraction was lower in T compared with UT legs ($p < .05$) and was always higher in aged compared with young subjects ($p < .05$) (ANOVA). Oxygen extraction did not change during insulin infusion.

Discussion

The major conclusions in the present study are that young and aged healthy subjects have similar basal and insulin stimulated glucose clearance rates in skeletal muscle. In contrast, aged subjects exhibit decreased blood flow and, at high insulin concentrations, they have higher glucose extraction. Whole body insulin-stimulated glucose clearance in healthy subjects is not reduced by age per se. The reduction may be explained by a relative increase in body fat in aged compared with young subjects. Furthermore, in response to training, insulin-mediated glucose clearance in skeletal muscle increases similarly in young and aged subjects. Finally, in aged subjects, muscle glucose clearance is high relative to aerobic capacity.

The observation that glucose clearance rates are similar in untrained leg muscle in healthy aged and young subjects is in line with previous findings in forearm human muscle (Kalant et al., 1980) and in rats (Ivy et al., 1991). Furthermore, it is compatible with the findings of similar content of glucose transporting protein (GLUT-4) in skeletal muscle in young and aged subjects (Dela et al., 1994). The similar glucose clearance rates at high insulin concentrations in young and aged subjects were based on lower muscle blood flow and higher glucose extraction in aged compared with young subjects (Figure 2). The lower blood flow in the aged subjects, which per se predisposes to a higher glucose extraction, can probably be explained by a lower oxygen uptake (Figure 3).

The subjects were studied 16 hr after the last training bout. The effect of the last exercise bout (i.e., the effect of acute exercise) most likely had only minor influence on the observed increased insulin action in skeletal muscle. We have previously reported that the effect of acute exercise is negligible compared to that of regular training (Dela et al., 1992, 1995b). Thus, the increased insulin action was the result of local muscular adaptations elicited by regularly repeated exercise bouts.

In the present study, plasma glucose concentrations were clamped at individual fasting plasma glucose concentrations (isoglycemic clamp). This was done to avoid unpredictable and dissimilar hormonal responses to a preclamp reduction in plasma glucose concentration to an identical value (e.g., 5 $mmol \cdot l^{-1}$).

Both glucose clearance and oxygen uptake increased during insulin infusion. The increase in glucose clearance was, however, always more marked than the increase in oxygen uptake. The difference in increases in glucose clearance rates and oxygen uptake rates reflects that the glucose taken up by the leg muscles was predominantly guided into nonoxidative disposal (at maximal insulin concentrations almost 70% as calculated by indirect calorimetry). During insulin infusion, blood flow always closely paralleled metabolic rate which resulted in constant oxygen extraction (Figure 3), as previously noted (Dela et al., 1995a). The lower leg oxygen uptake in the aged rather than in the young subjects is in accordance with the finding of decreased resting oxygen consumption in muscle with aging (McCarter et al., 1992).

Whole body glucose clearance during insulin infusion was determined as the glucose infusion rate relative to the plasma glucose concentration, and comparisons were made with the assumption that hepatic glucose production was inhibited similarly in the two groups (Bonadonna et al., 1994). If anything, it may be reasonable to expect that hepatic insulin sensitivity in the aged subjects was slightly lower compared with the young subjects. Consequently, whole body insulin action may have been slightly underestimated in the aged subjects at the lowest insulin concentrations. This would support the notion that whole body insulin action was not reduced in aged compared with young subjects (expressed relative to to FFM). At the highest insulin concentrations, whole body glucose clearance was lower in aged compared with young subjects (Figure 1), as expected (DeFronzo, 1979; Fink et al., 1983). Interestingly, however, this difference disappeared when glucose clearance was expressed relative to FFM. The matching whole body glucose clearance rates per FFM in the two groups agree with the fact that also muscle glucose clearance was similar in aged compared with young subjects. The combined findings in whole body and leg muscle strongly support the view that the age-induced impairment of whole body insulin action is due to increased amount and localization (i.e., abdominal area) of adipose tissue (Coon et al., 1992; Kohrt et al., 1993) and decreased glucose transport into adipocytes (Fink et al., 1984, 1986).

In response to training, insulin action in skeletal muscle increased identically in aged and young subjects. This finding of identical increases in insulin action emphasizes that the beneficial effects of physical training are not restricted to a young age, and it is in line with other local adaptations in skeletal muscle in aged and young subjects (Coggan et al., 1992). The finding of similar glucose clearance rates, both before and after training [though the young subjects always had higher $\dot{V}O_2$ peak than the aged subjects (Table 1)], indicates that aerobic capacity is more influenced by aging per se than is insulin action. Interestingly, cytochrome *c* oxidase activities in the vastus lateralis muscle were identical in young and aged subjects both before and after training (unpublished observation). This suggests that deterioration of cardiovascular function is responsible for the reduction of aerobic capacity in aged people.

In summary, this study has shown that between young and aged subjects, insulin-stimulated leg glucose clearance does not differ quantitatively. However, leg blood flow was lower in the aged compared with the younger subjects, and at high plasma insulin concentrations leg glucose extraction was higher in the former group. Furthermore, in response to training, insulin action in skeletal muscle increased similarly in the two groups. The increased insulin action in skeletal muscle was due to local adaptations in the muscle elicited by regular exercise training. Finally, whole body insulin-stimulated glucose clearance does not differ between aged and young subjects when corrected for differences in FFM.

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