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Insulin binding to monocytes in trained athletes: changes in the resting state and after exercise.

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Research Article

Insulin binding to monocytes was examined in trained athletes (long distance runners) and in sedentary control subjects in the resting state and after 3 h of exercise at 40% of maximal aerobic power. At rest, specific binding of 125-I-insulin to monocytes was 69% higher in athletes than in sedentary controls and correlated with maximal aerobic power. The increase in insulin binding was primarily due to an increase in binding capacity. During acute exercise, insulin binding fell by 31% in athletes but rose by 35% in controls. The athletes had a smaller decline in plasma glucose and a lower respiratory exchange ratio during exercise than did controls. We conclude that physical training increases insulin binding to monocytes in the resting state but results in a fall in insulin binding during acute exercise. Changes in insulin binding in athletes thus may account for augmented insulin sensitivity at rest as well as a greater shift from carbohydrate to fat usage during exercise than is observed in untrained controls.

Insulin Binding to Monocytes in Trained Athletes

CHANGES IN THE RESTING STATE AND AFTER EXERCISE

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ABSTRACT Insulin binding to monocytes was examined in trained athletes (long distance runners) and in sedentary control subjects in the resting state and after 3 h of exercise at 40% of maximal aerobic power.

At rest, specific binding of ^{125}I-insulin to monocytes was 69% higher in athletes than in sedentary controls and correlated with maximal aerobic power. The increase in insulin binding was primarily due to an increase in binding capacity. During acute exercise, insulin binding fell by 31% in athletes but rose by 35% in controls. The athletes had a smaller decline in plasma glucose and a lower respiratory exchange ratio during exercise than did controls.

We conclude that physical training increases insulin binding to monocytes in the resting state but results in a fall in insulin binding during acute exercise. Changes in insulin binding in athletes thus may account for augmented insulin sensitivity at rest as well as a greater shift from carbohydrate to fat usage during exercise than is observed in untrained controls.

INTRODUCTION

Physical training markedly decreases the insulin response to glucose administration (1). Because glucose tolerance remains unimpaired, an increase in total body sensitivity to insulin characterizes the well-trained athlete (1). Despite the augmented insulin sensitivity, during submaximal exercise athletes derive more energy from fat and less from carbohydrate than do sedentary subjects (2). Neither the mechanism of the augmented insulin sensitivity that occurs in the resting state nor the factors regulating the greater shift of fuel metabolism toward fat utilization occurring during exercise in athletes have been established. Because changes in insulin binding to monocytes have been observed to correlate with changes in insulin sensitivity in a variety of conditions (e.g., obesity [3, 4], maturity onset diabetes [5, 6], and growth hormone deficiency [7]), and inasmuch as acute exercise increases insulin binding to monocytes (8), we examined insulin binding at rest and after 3 h exercise in athletes and sedentary control subjects.

METHODS

10 well-trained male athletes (long distance runners) (age, 28.5±1.5 yr, weight, 68.2±1.7 kg, mean±SE), and 15 untrained, age- and weight-matched male control subjects (age, 25.8±1.4 yr, weight, 71.7±1.9 kg) participated in the study. All subjects were within 10% of their ideal body weight (Metropolitan Life Insurance Tables, 1959). The athletes engaged in regular exercise consisting of running 7 miles or more per day six to seven times per week for 5 yr or more before study. The control group did not engage in athletics on a regular basis. In each subject the maximal aerobic power ($\dot{V}O_{2\,max}$)[1] was determined by means of a standard incremental exercise test on a cycle ergometer (9). $\dot{V}O_{2\,max}$ in athletes (66.0±1.4 ml/kg·min) was 55% higher than in the control subjects (42.6±1.4 ml/kg·min, $P < 0.001$). For 3 d before the study, all subjects ingested a weight-maintaining diet containing 250–300 g carbohydrate. The nature, purpose, and possible risks of the study were explained to all subjects before they gave their written, voluntary consent to participate.

Each subject was studied in the postabsorptive state after a 12- to 14-h overnight fast. An indwelling catheter was inserted in an antecubital vein for obtaining blood samples before, during, and after exercise. After base-line blood samples were obtained, the subjects performed 3 h continuous cycle ergometric exercise at a relative intensity approximating 40% of their $\dot{V}O_{2\,max}$. In the athletes, the relative and absolute intensity of the exercise were, respectively, 38.5±1.8% and 610±20 kilopondmeters per minute; in controls the cor-

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[1] *Abbreviation used in this paper*: $\dot{V}O_{2\,max}$, maximal aerobic power.

responding values were 41.3±1.0% and 402±22 kilopondmeters per minute.

Plasma glucose was determined by the glucose oxidase procedure (10) and plasma insulin by radioimmunoassay (11). We isolated mononuclear cells by the method of Boyum (12) and determined the specific binding of [^{125}I]monoiodoinsulin to monocytes by the method of Bar et al. (13) as previously described (4, 7, 8). Oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were determined during exercise by continuously recording the expired ventilatory volume and the fractions of O_2 and CO_2 in mixed expired air (electronic analyzers calibrated against manometric analysis). The values were corrected to standard temperature and pressure and the respiratory exchange ratio was calculated as $\dot{V}CO_2$:$\dot{V}O_2$ (9). The insulin binding data were analyzed by Scatchard analysis (14). In the statistical analysis of the data we used the unpaired or paired *t* test, as applicable, and linear regression analysis (15).

RESULTS

In the resting state, plasma glucose in athletes (85±2 mg/dl) was lower than in controls (93±2 mg/dl, $P < 0.005$), and plasma insulin levels also tended to be lower in athletes (12±1 μU/ml) than in control subjects (16±2 μU/ml, $0.05 < P < 0.1$). Before exercise, total specific binding of ^{125}I-insulin to monocytes in athletes (14.0±1.4%) was 69% higher than in untrained subjects (8.3±0.5%, $P < 0.01$) (Fig. 1). Scatchard analysis of the insulin binding data (not shown) revealed curvilinear plots in both groups and an increase in the number of binding sites in athletes (22,600±1,800 sites/monocyte) as compared with controls (14,500±900, $P < 0.001$). To evaluate the binding affinity of insulin receptors, the concentration of unlabeled insulin necessary to decrease specific binding of ^{125}I-insulin by 50% was determined. In the resting state, the 50% inhibition of ^{125}I-insulin binding occurred in athletes at a concentration of unlabeled insulin (5.3 ng/ml) that tended to be lower than in control subjects (6.4 ng/ml) (Fig. 1).

An inverse correlation was observed between insulin binding and plasma insulin levels in athletes ($r = -0.63$, $P < 0.05$) as well as controls ($r = -0.62$, $P < 0.02$). Among the athletes, insulin binding correlated with $\dot{V}O_{2\,max}$ ($r = 0.63$, $P < 0.05$) (Fig. 2). However, no correlation between insulin binding and $\dot{V}O_{2\,max}$ was observed in untrained subjects ($r = 0.16$, $P > 0.5$).

After acute exercise, total specific binding of ^{125}I-insulin to monocytes rose by 35% in untrained subjects, to 11.2±1.4% ($P < 0.025$) (Fig. 3A), thus confirming previous findings from our laboratory (8). In marked contrast, the athletes demonstrated a 31% fall in specific insulin binding after acute exercise, reaching values of 9.7±2.1% ($P < 0.01$) (Fig. 3B). In both groups the changes in insulin binding induced by exercise were observed only at concentrations of insulin of 5 ng/ml or less (Figs. 3A and B). In the controls as well as the athletes the number of binding sites remained unchanged during exercise (controls: 14,500±900 sites/cell vs. 14,200±1,100; athletes: 22,600±1,800 sites/cell vs. 22,400±1,500). In contrast, the concentration of unlabeled insulin needed for 50% inhibition of ^{125}I-insulin binding fell with acute exercise in controls (from 6.4 to 4.0 ng/ml) (Fig. 3A), but rose with acute exercise in athletes (from 5.3 at rest to 10.0 ng/ml after exercise) (Fig. 3B). The percentage of monocytes in the peripheral leukocyte population remained unchanged during exercise in the athletes (7±2% before and 6±1% after exercise) and in the control subjects (8±1 vs. 8±1%). Nor was there any change in the percentage of monocytes in the mononuclear cell preparations used for the binding studies (athletes, 16.0±1.4% before and 15.5

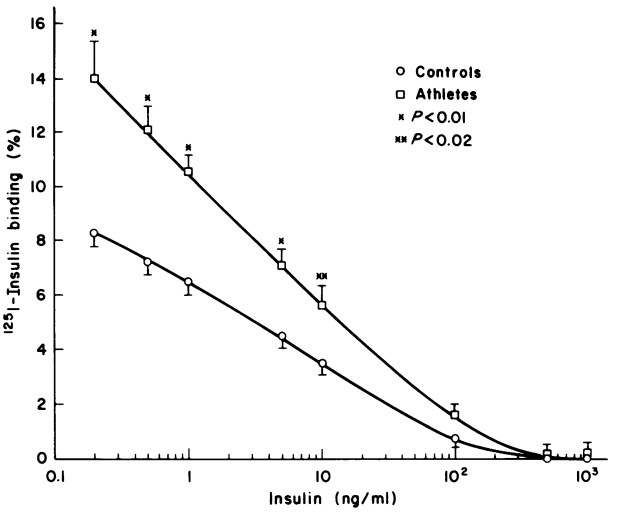

FIGURE 1 Specific binding of ^{125}I-insulin to monocytes in control subjects and athletes in the resting state. Mononuclear cells (4×10^7/ml) were incubated with ^{125}I-insulin (0.2 ng/ml) at 22°C for 180 min in the absence (initial point of the curve) and presence of increasing concentrations of unlabeled insulin. Data are expressed per 1×10^7 monocytes/ml.

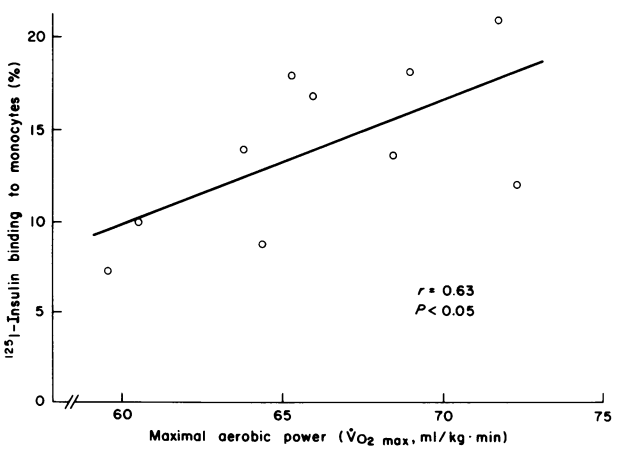

FIGURE 2 The relationship between specific ^{125}I-insulin binding to monocytes and $\dot{V}O_{2\,max}$ in athletes in the resting state.

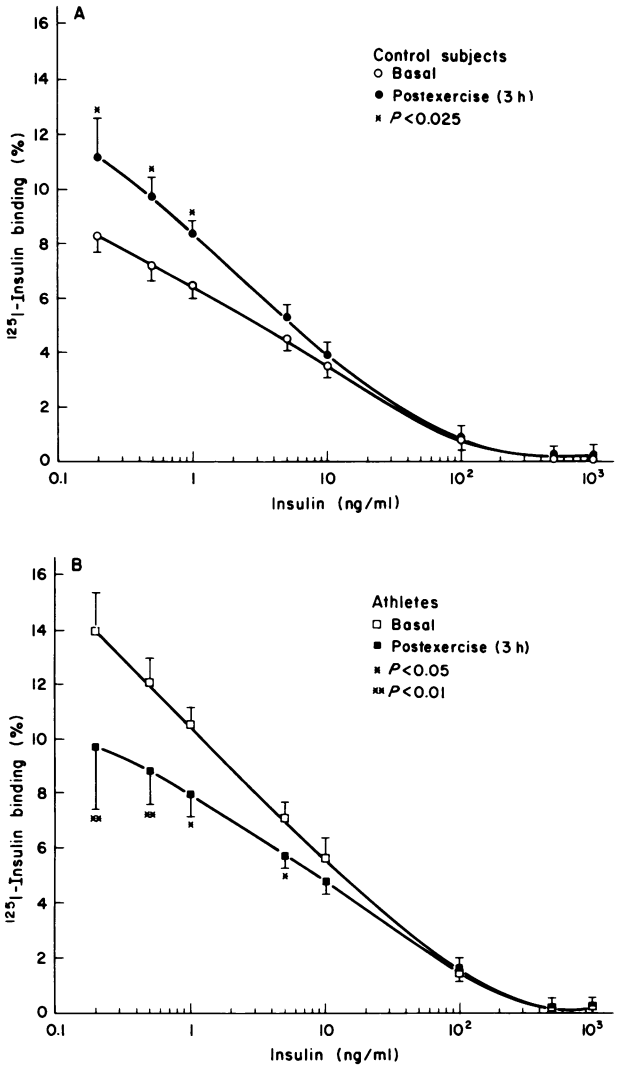

FIGURE 3 Specific binding of ^{125}I-insulin to monocytes before and at the end of 3 h ergometric exercise in control subjects (A) and athletes (B). Controls demonstrated a rise in insulin binding (A), whereas a fall in insulin binding was observed in athletes during exercise (B).

±2.0% after exercise; controls, 14.8±1.2% before and 15.6±1.4% after exercise).

The oppositely directed changes in insulin binding during acute exercise in the untrained and trained subjects were accompanied by differences in fuel metabolism. During exercise, the fall in plasma glucose in athletes (−12±3) mg/100 ml) was 40% less than in controls (−20±2 mg/100 ml, $P < 0.05$). In the resting state the respiratory exchange ratio was the same in control subjects (0.86±0.02) and athletes (0.86±0.03). However, at the termination of exercise, the respiratory exchange ratio was unchanged from resting values in controls (0.85±0.01) but had fallen significantly below resting values in the athletes (0.79±0.02, $P < 0.05$). Based on the respiratory exchange ratio (16), one can estimate that at the end of exercise, the athletes used 72% of extracted oxygen for fat catabolism and only 28% for carbohydrate oxidation, whereas the corresponding fractions in untrained subjects were 51% for fat and 49% for carbohydrate oxidation.

During exercise plasma insulin fell by 38% in athletes (to 7.2±1.4 μU/ml, $P < 0.05$) and by 45% in controls (to 8.6±1.4 μU/ml, $P < 0.05$). The absolute as well as relative decline in plasma insulin during exercise did not differ between the two groups ($P > 0.1$).

DISCUSSION

The present data indicate that in the resting state specific binding of ^{125}I-insulin to circulating monocytes is higher in athletes than in sedentary subjects. The increase in binding was proportional to the athletes' physical fitness as reflected by their $\dot{V}O_{2\,max}$. The rise in insulin binding was mainly the result of an increase in binding capacity, although a slight rise in receptor affinity may have contributed to the augmentation in total insulin binding. The athletes engaged in regular exercise on the day before the study of insulin binding. The observed rise in insulin binding in the resting state is unlikely to represent a transient acute effect of the previous day's exercise, because our earlier studies indicate that changes in insulin binding induced by acute exercise revert to base line within 20 h after exercise (8). Furthermore, acute exercise caused a fall rather than a rise in insulin binding in athletes.

Although the monocyte is not a target cell for the metabolic actions of insulin, previous studies have shown that altered monocyte binding reflects changes in insulin binding in adipocytes and liver cells (17). Furthermore, in human subjects a close correlation between changes in insulin binding to monocytes and insulin-mediated glucose uptake has been observed in states of insulin resistance such as obesity (3, 4) and maturity onset diabetes (5, 6), and in circumstances of augmented insulin sensitivity such as growth hormone deficiency (7). The current findings thus suggest that increased insulin binding may, at least in part, account for the increased insulin sensitivity demonstrable in the resting state in well-trained athletes (1).

In contrast to the findings in the resting state, acute exercise was associated with a fall in insulin binding in athletes, whereas sedentary subjects demonstrated a rise in insulin binding. These acute changes in insulin binding occurred only at physiologic concentrations of insulin (up to 5 ng or 125 μU/ml), and were the result of changes in receptor affinity rather than alterations in binding capacity. In association with these oppositely directed changes in insulin binding, the athletes had a smaller decline in plasma glucose.

In addition, measurement of the respiratory exchange ratio indicated less usage of carbohydrate and greater dependence on fat during exercise in athletes than was observed in controls. Previous studies have shown that stimulation of glucose usage by exercise is dependent in part on circulating insulin levels (18). Furthermore, glucose usage during exercise is augmented in normal subjects by hyperinsulinemia (19) and is enhanced by increased insulin mobilization from the injection site in insulin-treated diabetics (20). In contrast, in insulin-deficient diabetics, fat oxidation accounts for a relatively larger proportion of total fuel usage by exercising muscle than is observed in healthy controls (21). In the present study, plasma insulin levels were similar in the two groups at the end of exercise. The current findings suggest that during exercise the lesser dependence on carbohydrate and the greater usage of fat observed in athletes as compared with sedentary controls was not a result of variations in plasma insulin levels, but may be caused in part by the fact that insulin binding falls during exercise in athletes whereas it rises in controls.

With respect to the mechanism of the changes in insulin binding in athletes, an inverse relation between circulating insulin levels and insulin binding has been observed in a variety of hyperinsulinemic conditions (3–7). A similar inverse relationship was noted in the present study in the resting state. Thus hypoinsulinemia may be a contributory factor to the increased insulin binding in athletes in the resting state. However, during acute exercise a comparable decline in plasma insulin was associated with oppositely directed changes in insulin binding in athletes and controls. It appears that factors other than circulating insulin concentration are likely to be responsible for the changes in insulin binding observed with acute exercise.

It should be noted that although the athletes and sedentary subjects were comparable in body weight, it is likely that lipid accounted for a smaller proportion of body composition in the athletes than in the controls. The possibility that differences in body composition contributed to the changes in insulin binding and/or plasma insulin observed in athletes cannot be excluded.

Finally, the current findings may have implications regarding the management of diabetes mellitus. In maturity onset diabetes, insulin resistance rather than insulin deficiency is often the major factor responsible for hyperglycemia (5, 6). Furthermore, the decrease in insulin sensitivity in these patients is closely correlated with a reduction in insulin binding to monocytes (6). To the extent that well-trained athletes are characterized by an increase in insulin binding as well as augmented insulin sensitivity, physical training may provide a means of reversing or ameliorating abnormalities of insulin binding and sensitivity in maturity onset diabetes.

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