

# Synergistic Interaction between Exercise and Insulin on Peripheral Glucose Uptake

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**ABSTRACT** The interaction of exercise and insulin on glucose metabolism was examined in 10 healthy volunteers. Four study protocols were used: study 1: plasma insulin was raised by  $\sim 100 \mu\text{U/ml}$  while plasma glucose was maintained at basal levels for 2 h (insulin clamp). Study 2: subjects performed 30 min of bicycle exercise at 40% of  $\text{VO}_2$  max. Study 3: an insulin clamp was performed as per study 1. Following 60 min of sustained hyperinsulinemia, however, subjects exercised for 30 min as per study 2. Study 4: subjects were studied as per study 3 except that catheters were inserted into the femoral artery and vein to quantitate leg glucose uptake.

During the 60–90-min period of hyperinsulinemia (study 1), glucose uptake averaged  $8.73 \pm 0.10$  mg/kg per min. With exercise alone (study 2), the increment in peripheral glucose uptake was  $1.43 \pm 0.30$  mg/kg per min. When hyperinsulinemia and exercise were combined (study 3), glucose uptake averaged  $15.06 \pm 0.98$  mg/kg per min ( $P < 0.01$ ) and this was significantly ( $P < 0.001$ ) greater than the sum of glucose uptake when exercise and the insulin clamp were performed separately. The magnitude of rise in glucose uptake correlated closely with the increase in leg blood flow ( $r = 0.935$ ,  $P < 0.001$ ), suggesting that the synergism is the result of increased blood flow and increased capillary surface area to exercising muscle. More than 85% of total body glucose metabolism during studies 1 and 3 was accounted for by skeletal muscle uptake.

These results demonstrate that (a) insulin and exercise act synergistically to enhance glucose disposal in man, and (b) muscle is the primary tissue responsible for the increase in glucose metabolism following hyperinsulinemia and exercise.

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Received for publication 14 February 1981 and in revised form 31 July 1981.

## INTRODUCTION

Exercise has long been known to have a beneficial effect on blood glucose control in insulin-dependent diabetics with moderate fasting hyperglycemia (1–6). Several studies have documented that exercise per se is capable of promoting glucose uptake by muscle (7–10). This stimulatory effect on glucose metabolism occurs despite a decline in basal plasma insulin levels (7–10), but appears to be dependent upon some minimal circulating insulin concentration (11). Thus, in juvenile-onset diabetics who have been withdrawn from insulin for 48 h or more, and in poorly controlled insulin-dependent diabetics, the hypoglycemic effect of exercise may not be demonstrable and, in fact, a worsening of the diabetic state with hyperglycemia and hyperketonemia may ensue (5, 6, 8). It is well known that acute exercise enhances the disposal of an oral glucose load (12, 13) and decreases the daily insulin requirement (2, 14). In fact, hypoglycemia is a well-known complication of exercise in the insulin-dependent diabetic (1).

Previous studies in rats (15), dogs (16), and man (17–19) have demonstrated that exercise enhances the absorption of insulin from subcutaneous injection sites. The resultant increase in circulating plasma insulin levels could then exert a blood-glucose lowering effect either by inhibiting hepatic glucose production or by stimulating peripheral glucose uptake, or both. These observations raise the possibility that exercise and insulin may act in concert to enhance cellular uptake of glucose. In perfused rat muscle preparations (11), the effects of isometric exercise and insulin (at high concentrations, 10 mU/ml) on glucose uptake are distinct and additive. In man, exercise enhances the disposal of an oral glucose load (12, 13), and can accentuate the hypoglycemic effect of subcutaneously administered insulin in the absence of an augmented rise in plasma insulin levels (18). The fol-

lowing questions thus arise: (a) does exercise alter insulin-induced glucose uptake in man when the plasma insulin concentration is not allowed to change but is maintained constant at some hyperinsulinemic level, (b) if exercise has an enhancing effect on insulin-mediated glucose uptake, is this effect additive or synergistic, and (c) does exercise alter the metabolic clearance rate of insulin? To answer these questions, we used the insulin clamp and hepatic venous catheter techniques under conditions of rest and exercise.

## METHODS

**Subjects.** The study group consisted of 10 healthy male volunteers ranging in age from 23–42 yr (mean  $\pm$  SEM =  $29 \pm 2$ ) and in ideal body weight from 87–111% (mean =  $99 \pm 3\%$ ) (based on Metropolitan Life Insurance Tables, 1959). Subjects were consuming a weight-maintaining diet containing at least 200 g/d of carbohydrate for 3 d before study. None were taking any medications and none had a family history of diabetes mellitus. All subjects were studied in the postabsorptive state at 8 a.m. after a 12–14-h overnight fast. In six subjects catheters were inserted under local anesthesia into an antecubital vein for the administration of insulin and/or glucose and into a brachial artery and a hepatic vein as previously described for the determination of splanchnic glucose production (20). These six subjects were studied with three different protocols as described below. The purpose, nature, and potential risks of the study were explained to all subjects and written consent was obtained before their participation. The protocol was reviewed and approved by the Ethics Committee of the Karolinska Institute.

### Experimental protocol

Six subjects participated in the first three experimental protocols and thereby served as their own controls.

**Study 1.** The insulin clamp technique (21) was used to produce a steady-state plateau of hyperinsulinemia. After a 60-min control period, a primed-continuous (40 mU/m<sup>2</sup> per min) intravenous infusion of insulin (Eli Lilly & Company, Indianapolis, Ind.) was administered for 120 min, and the plasma glucose concentration was maintained constant at basal levels by the periodic adjustment of a variable glucose infusion. Under these steady-state conditions of euglycemia, all of the infused glucose is taken up by cells and provides a measure of the total amount of glucose metabolized by the entire body in response to the infused insulin. In this and in the subsequent two studies, net splanchnic glucose production was quantitated as described in the Calculation section.

**Study 2.** After a 60-min control period, the same six subjects performed 30 min of bicycle exercise at ~40% of their estimated maximal aerobic capacity (22) to examine the effect of exercise alone on peripheral glucose uptake. The 30-min exercise period was followed by a 30-min postexercise recovery period. Since the glucose concentrations remained unchanged throughout the 60-min study period, the total amount of glucose metabolized by the body must be equal to the rate of splanchnic glucose production as measured by the hepatic venous catheter technique (20). Catheters were also inserted into the femoral artery and femoral vein to allow quantitation of leg glucose exchange.

**Study 3.** The same six subjects as in studies 1 and 2 received a 2-h euglycemic insulin clamp (21) as per study 1. The continuous insulin infusion during study 3 was administered

at a rate of 30 mU/m<sup>2</sup> per min to ensure that the steady-state plasma insulin levels would be less than in study 1 (insulin clamp alone). After 60 min of sustained hyperinsulinemia, subjects performed 30 min of bicycle exercise at 40% of their VO<sub>2</sub> max as per study 2, and this was followed by a 30-min postexercise recovery period. During the exercise and postexercise periods, the plasma glucose concentration was maintained constant at the basal level by the periodic adjustment of a variable glucose infusion.

**Study 4.** In an additional four subjects, catheters were also inserted into a femoral artery and femoral vein (in addition to the antecubital vein, hepatic vein, and brachial artery) to quantitate leg glucose exchange (20). These subjects were studied as per protocol 3 above.

**Analytical procedures.** Plasma glucose concentration was determined by the glucose oxidase method (Glucostat, Beckman Instruments, Inc., Fullerton, Calif.). Methods for the determination of blood glucose (20), plasma immunoreactive insulin (23), and hepatic and leg blood flow (20, 24) have previously been described. Leg volume was determined by the volume displacement of water.

**Calculations.** During the insulin clamp and insulin clamp plus exercise studies, the mean glucose infusion rate was calculated for 15- or 20-min intervals and was assumed to be equal to the rate of glucose uptake by the entire body since net splanchnic glucose production was completely suppressed. During the exercise alone study, the rate of total glucose uptake was assumed to be equal to the rate of splanchnic glucose production since the plasma glucose concentration did not change during exercise. Net splanchnic glucose balance was calculated from the product of the arterio-hepatic venous blood glucose concentration difference times the hepatic blood flow and is expressed in milligrams per kilogram per minute. Glucose uptake by the leg was calculated as the arterio-femoral venous blood glucose concentration difference multiplied by the leg blood flow. The extraction ratio of glucose by the leg was calculated as the arterio-femoral venous blood glucose concentration difference divided by the arterial glucose concentration multiplied by 100. The steady-state plasma glucose and insulin concentrations during the insulin infusion were calculated as the mean of values obtained at 5-min intervals over time periods as specified in the Results. The metabolic clearance rate (MCR) of insulin was calculated by dividing the constant insulin infusion rate by the mean increment above basal in plasma insulin concentration during the specified time interval. All data are presented as the mean  $\pm$  SEM. Statistical comparisons between mean values were performed by the paired or the unpaired *t* test as applicable (25).

## RESULTS

**Study 1.** The basal plasma insulin concentration was  $18 \pm 2$   $\mu$ U/ml; during the continuous insulin infusion, this rose to a steady-state plateau (10–120 min) of  $115 \pm 7$   $\mu$ U/ml. The stability of the plasma insulin concentration is indicated by the coefficient of variation which was  $8 \pm 1\%$ . The calculated MCR of insulin (10–120 min) was  $435 \pm 42$  ml/m<sup>2</sup> per min. The basal arterial plasma glucose concentration,  $83 \pm 1$  mg/dl, was maintained at  $82 \pm 1$  mg/dl throughout the period of hyperinsulinemia with a  $3.9 \pm 0.2\%$  CV. The total amount of glucose infused during the 120-min clamp period averaged  $7.37 \pm 0.11$  mg/kg per min. The time-related change in glucose metabolism is shown in Table I. Net

TABLE I  
Glucose Uptake

Time, min	0-20	20-40	40-60	60-75	75-90	90-105	105-120	0-60	60-90	90-120	0-120
	<i>mg/kg/min</i>										
Insulin clamp Study 1	3.65 ±0.26	6.27 ±0.34	7.74 ±0.27	8.58 ±0.15	8.87 ±0.09	8.97 ±0.15	9.01 ±0.14	5.88 ±0.15	8.73 ±0.10	8.99 ±0.14	7.37 ±0.11
				Exercise		Postexercise					
Exercise alone* Study 2				1.03 ±0.12	1.83 ±0.49	0.91 ±0.24	0.39 ±0.16	—	1.43 ±0.30	0.65 ±0.19	—
Insulin clamp and exercise. Study 3	3.99 ±0.23	6.33 ±0.44	8.30 ±0.38	13.32 ±0.98	16.81 ±1.02	12.65 ±0.79	10.56 ±0.62	6.23 ±0.27	15.06 ±0.98	11.60 ±0.54	9.83 ±0.49

Time-related increase in glucose uptake during the euglycemic clamp alone, exercise alone, and the combined insulin clamp plus exercise.

\* Represents the increment in splanchnic glucose production above the basal level. Basal net splanchnic glucose production was  $1.91 \pm 0.25$  mg/kg per min.

splanchnic glucose production averaged  $1.93 \pm 0.26$  mg/kg per min in the basal state, decreased by 85–90% at 30 min ( $P < 0.001$ ), and became slightly positive by 120 min (Fig. 1).

**Study 2.** Before exercise, basal plasma insulin concentration was  $18 \pm 2$   $\mu$ U/ml. After 30 min of exercise, plasma insulin levels decreased slightly, to  $15 \pm 2$   $\mu$ U/ml, and returned to fasting levels,  $18 \pm 2$   $\mu$ U/ml, at 30 min after stopping exercise. Fasting arterial glucose concentration,  $77 \pm 2$  mg/dl, remained unchanged during the 30-min exercise period,  $76 \pm 3$  mg/dl, and was  $78 \pm 3$  mg/dl at 30 min after stopping exercise.

Basal net splanchnic glucose production,  $1.91 \pm 0.25$

mg/kg per min, rose progressively during the 30-min exercise period to  $3.73 \pm 0.64$  mg/kg per min ( $P < 0.001$ ) and remained elevated during the 15–30-min postexercise recovery period,  $2.30 \pm 0.36$  mg/kg per min ( $P < 0.05$ ) (Fig. 1). The increment in net splanchnic glucose production above basal is shown in Table I. Since the plasma glucose concentration remained constant, the increment in net splanchnic glucose production above basal must be equal to the exercise-related increase in peripheral glucose uptake.

**Study 3.** The fasting plasma insulin concentration was  $11 \pm 2$   $\mu$ U/ml. During the 1st h following insulin infusion, the mean steady-state plasma insulin concen-

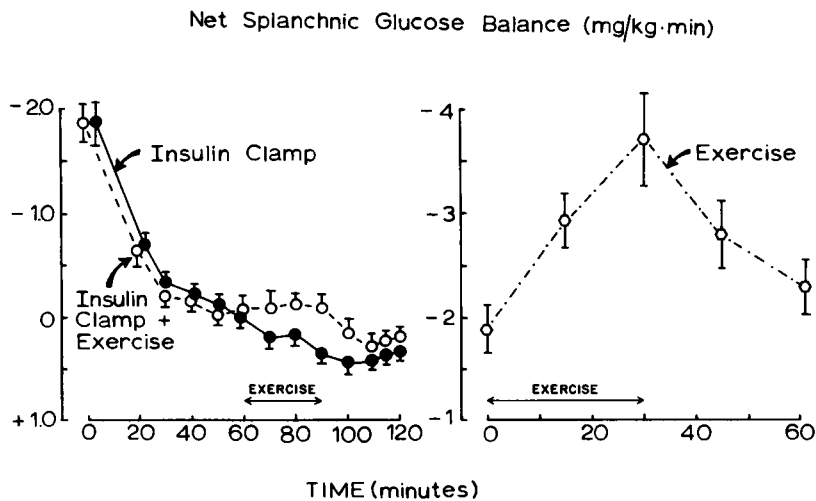


FIGURE 1 Net splanchnic glucose balance during euglycemic hyperinsulinemia (insulin clamp) and combined exercise and hyperinsulinemia is shown in the left panel. Exercise was performed during the 60–90-min time period. The effect of exercise alone is shown in the right panel. Exercise was performed during the 0–30-min time interval and was followed by a 30-min postexercise recovery period.

**TABLE II**  
*Comparisons of Leg Arteriovenous Glucose Difference, Blood Flow, Glucose Uptake, and Extraction Ratio in the Basal State, with Insulin Alone, with Exercise Alone, and with Combined Insulin Plus Exercise (Study 4)*

	Leg A-V difference mg/liter	× Leg blood flow liter/min	= Leg uptake mg/min	Leg uptake mg/kg leg wt per min	Extraction ratio %
Basal	50±7	0.36±0.03	18±2	1.5±0.2	5±1
Exercise*	63±5	2.73±0.27‡	177±14§	15.7±1.1 <sup>  </sup>	9±1
Insulin¶	324±36**	0.41±0.03	106±10**	11.7±1.1**	33±4**
Exercise + insulin§§	189±16‡‡	3.23±0.28‡	604±46‡‡	50.7±3.9‡‡	21±2‡‡

\* Mean value during the 30-min exercise period. These values represent the mean of the six subjects who participated in study 2, since the four subjects who participated in study 4 did not participate in exercise alone protocol (study 2). Therefore, comparisons with this group were performed with the unpaired *t* test.

‡ *P* < 0.02 vs. basal and *P* < 0.001 vs. insulin.

§ *P* < 0.01 vs. basal, insulin, and exercise plus insulin.

<sup>||</sup> *P* < 0.01 vs. basal and exercise plus insulin, and *P* < 0.02 vs. insulin.

¶ Mean value during the 30–60-min time period of the insulin clamp (study 4).

\*\* *P* < 0.001 vs. basal and *P* < 0.01 vs. exercise plus insulin.

‡‡ *P* < 0.01 vs. basal, vs. exercise, and vs. insulin.

§§ Mean value during the 30-min period of combined hyperinsulinemia and exercise (study 4).

tration was 76±5 μU/ml and the MCR of insulin was 474±40 ml/m<sup>2</sup> per min. Following the initiation of exercise (60–120 min), the steady-state plasma insulin concentration, 77±5 μU/ml, and MCR, 467±23 ml/m<sup>2</sup> per min, did not change significantly.

Basal net splanchnic glucose production, 1.91±0.25 mg/kg per min, declined by >95% at 60 min (*P* < 0.001) and remained suppressed throughout the exercise and postexercise period (Fig. 1). During the 0–60-min time period, glucose uptake averaged 6.23±0.27 mg/kg per min (Table I.) During exercise (60–90 min), glucose uptake increased to 15.06±1.00 mg/kg per min (*P* < 0.01 vs. insulin clamp alone) and remained elevated during the postexercise control period, 11.60±0.50 mg/kg per min (*P* < 0.01 vs. insulin clamp alone).

*Leg glucose uptake.* Simultaneous measurements of leg blood flow, leg uptake of glucose, and total glucose uptake were performed in the six subjects who performed exercise alone (study 2) and in four different subjects during combined hyperinsulinemia and exercise (study 4).

During exercise alone (study 2), leg glucose uptake increased 10-fold from 1.5±0.2 to 15.7±1.1 mg/kg leg wt per min (*P* < 0.001); this was accompanied by a large increase in blood flow with little change in the arterio-venous glucose concentration difference (Table II). The leg glucose extraction ratio, 9±1%, rose slightly, although significantly, over that during the basal state, 5±1% (*P* < 0.02).

In the four subjects who participated in the combined exercise-hyperinsulinemia protocol (Study 4), basal leg blood flow was 0.36±0.03 liters/min (Table II and Fig.

2). Leg blood flow was unchanged by insulin, 0.41±0.03 liters/min, but increased ninefold, to 3.23±0.28 liters/min, during exercise plus insulin. With insulin, leg glucose uptake increased sixfold, 11.7±1.1 mg/kg leg wt per min, compared with the basal state, 1.5±0.2 mg/kg leg wt per min (*P* < 0.01). The effect of insulin on leg glucose uptake was associated with a sixfold increase in the extraction ratio, 33±4% (*P* < 0.001 vs. basal and *P* < 0.02 vs. exercise alone). This increase in the extraction ratio was entirely the result of a widening of the arterio-venous glucose concentration difference (Table II). When exercise was combined with insulin, leg glucose uptake, 50.7±3.9 mg/kg leg wt per min, increased three- to sixfold over that with exercise or insulin alone (*P* < 0.001) (Table II). This increase in leg glucose uptake was associated with a three- to fourfold increase in the arteriovenous glucose concentration difference and a ninefold increase in leg blood flow. The extraction ratio, 21±2%, actually fell compared with insulin alone (*P* < 0.01), but was greater than with exercise alone or that in the basal state (*P* < 0.001). During the 0–60-min period of hyperinsulinemia and during the 60–90-min period of combined hyperinsulinemia and exercise, net splanchnic glucose production was not significantly different from zero.

When exercise was performed in combination with hyperinsulinemia (study 4), the time-course of increase in leg blood flow closely paralleled the time-course of increase in both leg and total body glucose uptake (Fig. 2). Similarly, the decrease in both leg and total body glucose uptake after cessation of exercise

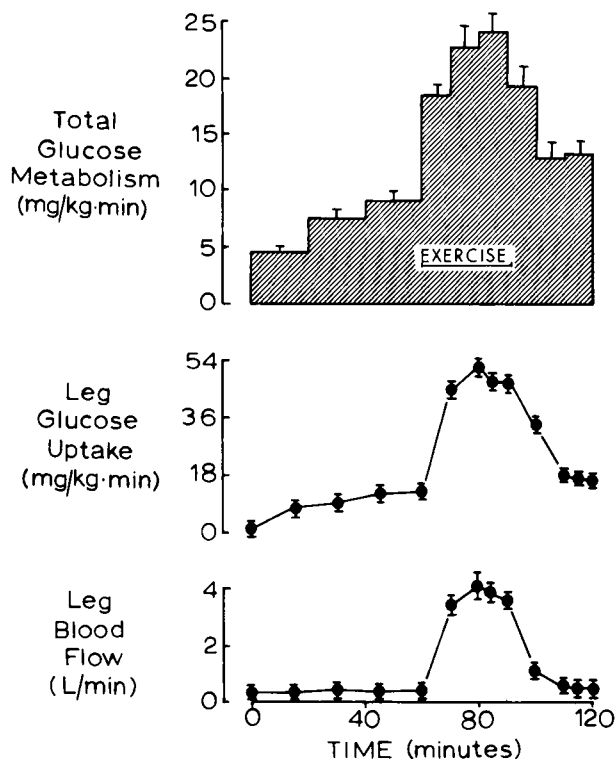


FIGURE 2 Changes in leg blood flow (liters/minute), leg uptake of glucose (milligrams per minute per kilogram of leg weight), and total body glucose uptake (milligrams per minute per kilogram of body weight) during combined hyperinsulinemia-exercise. Exercise was performed during the 60–90-min time period.

closely paralleled the decline in leg blood flow (Fig. 2). During the 60–120-min time period, there was a strong positive correlation between the change in leg blood flow and total glucose uptake ( $r = 0.92$ ,  $P < 0.001$ ).

## DISCUSSION

To examine directly whether exercise is capable of acting synergistically with insulin to enhance glucose uptake by peripheral tissues, we have employed the insulin clamp technique in combination with hepatic and femoral venous catheterization. In the present studies, a dose of insulin was used that was known to completely suppress net splanchnic glucose production. Consequently, the only source of glucose to the body was that administered exogenously through the glucose infusion pump.

During the 60–90-min period of euglycemic hyperinsulinemia, total glucose uptake averaged  $8.73 \pm 0.10$  mg/kg per min. With exercise alone, the increase in glucose uptake above basal was  $1.43 \pm 0.30$  mg/kg per min. The increase in glucose uptake above basal was used since this represents the actual stimulatory effect of exercise on glucose disposal. If the effect of exercise and insulin were purely additive, then the

amount of glucose taken up by the entire body would have been expected to be 10.16 mg/kg per min with combined hyperinsulinemia and exercise (Fig. 3). Instead, the peak increase in glucose uptake was 16.81 mg/kg per min (Fig. 3), and this was 55% higher than predicted if the effects of exercise and insulin were purely additive ( $P < 0.001$ ). The synergistic interaction of exercise and insulin is even more striking when it is considered that the plasma insulin concentration during the combined insulin clamp-exercise study was 33% lower than during the insulin clamp alone. It should be noted that, during the exercise study (study 2), whether the total amount of glucose metabolized or the increase in glucose metabolism above basal is used to evaluate whether the effects of insulin and exercise are additive or synergistic, the conclusion is the same.

The rapidity of the rise in glucose uptake with the start of exercise, as well as the prompt decline observed following cessation of exercise, suggest that the synergism may be mediated by changes in blood flow to the exercised extremity. In the four subjects in whom it was measured, leg blood flow increased ~ninefold during exercise and the time-course paralleled the time-course of increase in glucose uptake (Fig. 2). Similarly, the decrease in glucose uptake post-exercise closely paralleled the decline in leg blood flow. It is well known that exercise is associated with a marked increase in blood flow and capillary surface area to working muscle (26, 27). Thus, even in the absence of a change in circulating insulin levels, insulin delivery to muscle would be expected to increase

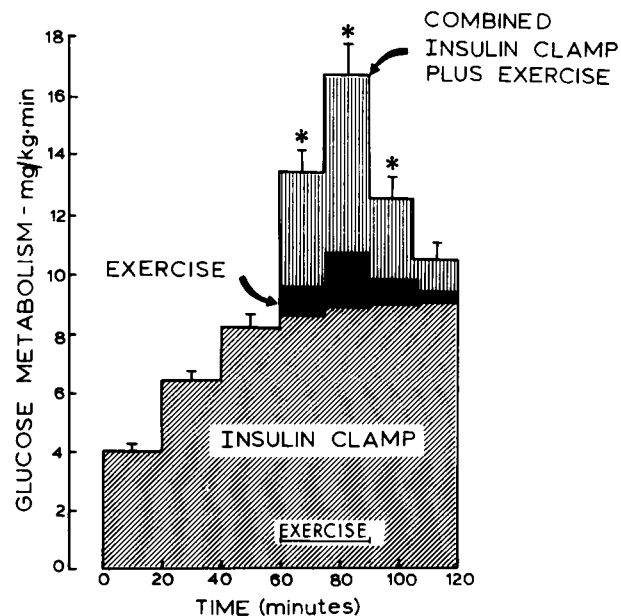


FIGURE 3 Time-related increase in total glucose uptake during the insulin clamp alone, exercise alone, and combined hyperinsulinemia-exercise, showing the synergistic interaction between insulin and exercise.

at least in proportion to the increase in muscle blood flow. In addition, previously unexposed muscle beds would now be exposed to plasma insulin as a result of the opening of non- or hypoperfused capillary beds (27, 28). Recent studies by Kalant et al. (28) have also shown that exercise leads to increased uptake of insulin by exercising muscle, and this may serve to enhance insulin-mediated glucose metabolism. Since insulin was administered by the intravenous route in the present study, and since the plasma insulin concentration and metabolic clearance rate of insulin were unaltered by exercise, the synergistic effect of exercise on glucose metabolism cannot be attributed to changes in insulin delivery or alterations in insulin kinetics. Although previous studies (29) have shown that acute (3 h) exercise in healthy subjects is associated with an increase in insulin binding, the rapidity (within 5 min) of the increase in leg glucose uptake in the present study suggests that increased insulin binding does not play a major role in the stimulation of glucose metabolism following exercise.

Since net splanchnic uptake was negligible, and since brain uptake of glucose is not affected by insulin or exercise (30), the total amount of glucose infused should provide a close approximation of the amount of glucose taken up by peripheral tissues. Furthermore, studies by Björntorp et al. (31) have shown that little glucose is taken up by adipose tissue following glucose administration. Thus, the stimulation of glucose uptake following insulin and exercise in the present study should primarily reflect changes in muscle metabolism. The studies in the four subjects in whom total body glucose uptake, leg glucose uptake, and splanchnic glucose uptake were simultaneously quantitated provide direct support for the importance of peripheral tissues in the disposal of intravenous glucose following both insulin and exercise. During the 0–60-min period of hyperinsulinemia, the mean leg glucose uptake was 8.89 mg/kg leg wt per min. Assuming that muscle tissue represents 64% of the total leg weight (32), glucose uptake per kilogram of leg muscle is 13.9 mg/kg per min. For a 70-kg man, the muscle mass is ~30 kg (33). Since our subjects weighed 72.5 kg on the average, this extrapolates to a mean muscle mass of 31.1 kg. If all muscle tissue in the body responds similarly to leg muscle following insulin, then total muscle glucose uptake would be 432 mg/min or 25.9 g over the 60 min of hyperinsulinemia. During this same time period, total glucose uptake was 6.75 mg/kg per min or 29.4 g. Thus, muscle glucose uptake could account for 88% of the total amount of glucose metabolized. Since no net splanchnic glucose uptake was observed during this same 0–60-minute period, the liver's contribution to insulin-stimulated glucose disposal was negligible. These results are in agreement with previous observations demonstrating that under conditions of euglycemic hyperinsulinemia,

created by intravenous insulin and glucose infusion, hepatic glucose uptake is small (34).

During combined hyperinsulinemia and exercise, mean leg glucose uptake was 50.7 mg/kg leg wt per min or 79.2 mg/kg of leg muscle per min. The mean muscle mass of each leg was 7.6 kg (64% of leg volume = 11.9 kg) and for both legs was 15.3 kg. Thus, muscle uptake of glucose by both legs was 1,208 mg/min or 36.2 g over 30 min. Non-leg muscle mass (calculated as the difference between total minus leg muscle mass) was 15.8 kg. Assuming that glucose uptake by non-leg (i.e., nonexercising) muscle was similar to that of leg muscle (measured by femoral venous catheterization) at the end of the 60-min period of hyperinsulinemia, 13.0 mg/kg per min, one can calculate that glucose uptake by non-leg muscle was 6.2 g over 30 min. Therefore, total glucose uptake by muscle was 42.4 g. Total glucose uptake by the entire body during the 60–90-min period of combined exercise and hyperinsulinemia was 21.4 mg/kg per min or 46.6 g. Thus, muscle accounted for 91% of total glucose disposal. These calculations emphasize the quantitative importance of peripheral tissues (primarily muscle) compared to the liver in the stimulation of glucose uptake following both exercise and intravenous insulin administration.

Lastly, it is of interest to compare the mechanism of the increase in leg glucose uptake following hyperinsulinemia vs. exercise (Table II). After insulin infusion, there was no change in leg blood flow, and the increase in leg uptake was due entirely to a widening of the arteriovenous difference. This led to a sixfold increase in the extraction ratio (33%), indicating that the primary effect of insulin is to stimulate the intrinsic ability of the muscle to take up glucose.

With exercise alone, the increase in leg glucose uptake was accompanied by a large increase in leg blood flow with little widening of the arteriovenous glucose gradient and a small (4%), though significant, rise in the extraction ratio. There is no physiologic reason to expect an increase in muscle glucose uptake to result as a direct consequence of the increase in leg blood flow. Instead, it is likely that the primary effect of exercise is to directly stimulate glucose uptake by muscle cells (11), while at the same time opening new capillary beds and exposing previously nonperfused muscle tissue to insulin. The fact that the arteriovenous glucose difference increased only slightly means that the rise in blood flow was almost sufficient to keep pace with the increased rate of muscle glucose uptake caused by exercise. Finally, when exercise was performed in combination with hyperinsulinemia, the extraction ratio (21%) fell as compared to insulin alone, presumably because the plasma insulin concentration was proportionately lower. Nonetheless, the uptake of glucose by the leg was markedly enhanced as the result of a ninefold increase in blood flow and a fourfold widening of the arteriovenous glucose concentration

difference. This uptake was significantly greater than the sum of exercise alone and insulin alone, demonstrating that the synergistic interaction between hyperinsulinemia and exercise occurs in muscle tissue.

#### ACKNOWLEDGMENTS

The authors would like to thank Dr. Rosa Hendler for the insulin determinations, the nursing staff of the Clinical Physiology Laboratory at the Huddinge Hospital for their help in performing these studies, and Ms. Barbara Toner for her secretarial assistance.

This work was supported in part by National Institutes of Health grant AM-13526 and grants from the Swedish Medical Research Council (4X-3108) and U. S. Public Health Service International Research Fellowship 1-F05-TW02716-01.

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