Role of Insulin and Glucagon in the Regulation of Hepatic Glucose Production During Exercise

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During exercise, muscle consumption of blood-borne glucose increases 7–40 times the basal level, depending on the intensity and duration of the exercise performed.[1–3] Hypoglycemia fails to occur despite the increase in glucose consumption, because there is a simultaneous increase in glucose output from the liver.[1] In short-term exercise the increase in hepatic glucose production represents primarily glycogenolysis, while in long-term exercise gluconeogenesis becomes increasingly more important.[3] With respect to the factors stimulating glucose output from the liver during exercise, a fall in insulin,[1] a rise in glucagon,[2,4] and elevations in plasma catecholamines[5,6] have been observed. The relative importance of these various hormonal changes has not, however, been determined. The present study was consequently undertaken to further evaluate the role of altered insulin and glucagon secretion in the hepatic glucoregulatory responses to exercise. Specifically we examined the effect of maintaining endogenous insulin and glucagon secretion at basal levels by infusing glucose and also the effect of hyperinsulinemia, induced by infusion of exogenous insulin, on splanchnic glucose output during exercise.

METHODS

The subjects were healthy Swedish adults, 18–34 yr of age, who were within 10% of ideal body weight. None participated in a regular exercise training program. All were informed of the nature, purpose, and possible risks of the study before giving their voluntary consent to participate.

All studies were conducted in the morning after an overnight fast. Catheters were placed in a brachial artery, hepatic vein, and peripheral vein, as described previously.[1,2,7] After introduction of the catheters, the subjects were studied at rest in a supine position and during upright exercise for 40–45 min on a bicycle ergometer at a work intensity of 150–200 W (55–65% of maximal $\dot{V}_{O_2}$).

Three different protocols were employed before and during exercise. Group 1 (saline controls, $n = 6$): These subjects received only a saline infusion during the rest and exercise period. Group 2 (glucose infusion, $n = 6$): These subjects received an infusion of glucose at a rate of 2 mg/kg/min. This infusion rate was chosen because it has previously been shown to inhibit splanchnic glucose production by 80–90% without altering peripheral glucose utilization in healthy, resting subjects.[8,9] The glucose was infused for 45 min in the resting state before initiation of exercise and continued throughout the exercise period. Group 3 (insulin-glucose infusion, $n = 4$): This group received an infusion of insulin (1 mU/kg/min) known to produce physiologic hyperinsulinemia[10] together with a glucose infusion at a rate of 5 mg/kg/min in the resting state and 10 mg/kg/min during exercise so as to prevent hypoglycemia. The insulin–glucose infusion was administered for 30 min before the initiation of exercise and was continued throughout the exercise period.

The techniques employed for the determination of hepatic blood flow, oxygen consumption, blood glucose, plasma insulin, and plasma glucagon have been described previously.[1,4,7] The Student's t test was employed for the statistical analyses using the paired t test where appropriate.[11] Mean values ± standard error of the mean are given in the tables and figures.

RESULTS

Oxygen uptake and blood flow (Table 1). Oxygen consumption increased to values sevenfold to ninefold the resting level in all three groups after 40 min of exercise. The respiratory exchange ratio (R) also showed comparable increments during exercise, although the values tended to be highest in the group receiving the combined insulin-glucose infusion (Group 3). Estimated hepatic blood flow fell by 50–60% in all three groups.

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TABLE 1
Oxygen consumption and hepatic blood flow at rest and after 40 min of exercise (mean ± SE)

	Oxygen uptake		Respiratory exchange ratio		Hepatic blood flow	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
	(ml/min)				(ml/min)	
Group 1 (Controls)	250 ± 20	2330 ± 150	0.77 ± 0.01	0.85 ± 0.02	1250 ± 150	662 ± 70
Group 2 (Glucose infusion)	242 ± 17	2250 ± 206	0.78 ± 0.02	0.83 ± 0.04	1360 ± 120	660 ± 80
Group 3 (Insulin-glucose infusion)	286 ± 13	2250 ± 200	0.77 ± 0.02	0.89 ± 0.03	1670 ± 162	713 ± 158

Arterial glucose, insulin, and glucagon (Table 2). In the saline controls (Group 1), exercise resulted in an increase in blood glucose (15–25 mg/100 ml, $P < 0.02$), a 50% decline in plasma insulin ($P < 0.01$), and a 30–40% rise in plasma glucagon ($P < 0.05$) (Figure 1). In the group receiving the glucose infusion, blood glucose rose 10–15 mg/100 ml prior to initiation of exercise but fell to resting, preinfusion levels after 40 min of exercise. As a result, blood glucose concentration in the subjects receiving the glucose infusion (Group 2) was 20% lower than in the control group at termination of exercise ($P < 0.01$). Plasma insulin levels rose during the glucose infusion but returned to baseline during exercise. As a result, insulin levels in Group 2 were twofold those observed in Group 1 at the end of exercise ($P < 0.05$). Plasma glucagon levels were unchanged throughout the study. Thus in Group 2 after 40 min of exercise, arterial glucose, insulin, and glucagon had returned to or remained at basal, resting concentrations (Figure 2). In the subjects receiving insulin plus glucose, arterial glucose levels fell during exercise to a nadir of 58 ± 12 mg/100 ml at 10 min and then returned to baseline (Figure 3). Plasma insulin rose, as expected, during the infusion and remained elevated during exercise. Plasma glucagon declined by 30% ($P < 0.05$) prior to the initiation of exercise and then rose to values twice those observed in the resting, preinfusion, basal state ($P < 0.02$) (Table 2).

Splanchnic glucose metabolism. In the controls (Group 1), exercise resulted in a progressive increase in splanchnic glucose production that reached values fourfold the basal rate after 40 min (Figure 1). In the group receiving the glucose infusion (Group 2), splanchnic glucose output fell, as expected,[8] by 85–90% after 45 min of the infusion (Figure 2). Despite ongoing infusion of glucose during exercise, there was a prompt increase in splanchnic glucose output to values threefold the basal rate ($P < 0.01$). However, the overall increase in splanchnic glucose output was 15–60% lower than that observed in the controls throughout the 40-min exercise period ($P < 0.02$, Figure 4). The differences in the rate of rise in splanchnic glucose output were most marked during the first 10 min of exercise, at which time arterial glucose levels showed their most rapid decline in the glucose-infused group, while arterial glucose levels were rising in the controls (Figure 4).

In the subjects receiving the insulin-glucose infusion (Group 3), splanchnic glucose output was completely inhibited during the pre-exercise infusion period (Figure 3). Within 5 min of initiation of exercise, a significant rise in glucose output was observed and it continued to increase, reaching basal values at 45 min despite ongoing hyperinsulinemia (Figure 3). Nevertheless, the rate of splanchnic glucose output at termination of exercise in these subjects (1.3 ± 0.4 mmol/min) was 67% below that observed in the saline controls (Group 1) ($P < 0.01$) and 58% below that observed in the subjects infused with glucose alone (Group 2) ($P < 0.01$).

DISCUSSION

In the present study the importance of changes in insulin and glucagon secretion on hepatic glucose production during exercise was examined. Our findings indicate that, while a fall in insulin and/or rise in glucagon is not essential for exercise to stimulate hepatic glucose production, the magnitude of the increment is dependent on changes in these hormones.

Infusion of glucose (Group 2) was employed so as to prevent the hypoinsulinemia and hyperglucagonemia that

TABLE 2
Arterial glucose, insulin, and glucagon concentrations at rest and after 40 min of exercise (mean ± SE)

	Arterial glucose			Arterial insulin			Arterial glucagon		
	Rest	Post-infusion*	Exercise	Rest	Post-infusion*	Exercise	Rest	Post-infusion*	Exercise
	(mg/100 ml)			(μU/ml)			(pg/ml)		
Group 1	75 ± 2	—	98 ± 3	10 ± 1	—	5 ± 1	65 ± 12	—	90 ± 12
Group 2	77 ± 2	91 ± 1	77 ± 3†	13 ± 3	19 ± 5	13 ± 3‡	53 ± 10	52 ± 8	60 ± 12
Group 3	84 ± 2	96 ± 14	77 ± 14	11 ± 2	106 ± 10	145 ± 20†	60 ± 8	42 ± 8	120 ± 15

* Refers to values obtained after infusion of glucose (Group 2) or insulin plus glucose (Group 3) immediately prior to initiation of exercise. In Group 1 (saline controls) there was no infusion of glucose and/or insulin; resting values were obtained prior to initiation of exercise.

† Significantly different from Group 1, $P < 0.01$.

‡ Significantly different from Group 1, $P < 0.05$.

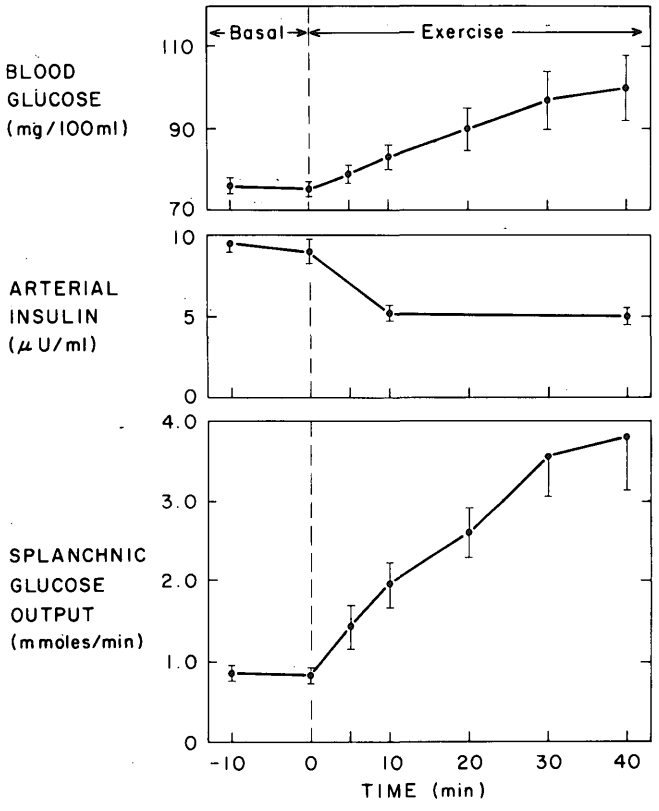


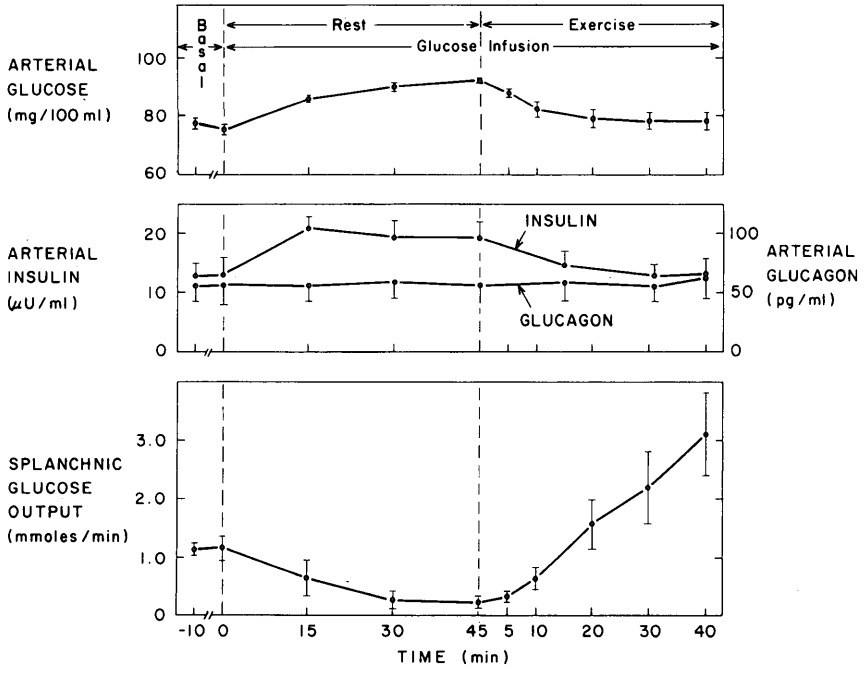
FIGURE 1. Influence of exercise on arterial blood glucose, arterial insulin, and splanchnic glucose output in control subjects receiving the saline infusion (Group 1).

normally accompany moderate or severe exercise (as shown by the controls, Group 1). The dose of glucose (2 mg/kg/min) was chosen because previous studies in resting subjects had shown that such infusion rates inhibit splanchnic glucose output, yet fail to stimulate peripheral glucose utilization.[8,9] The findings in the glucose-infusion subjects (Group 2) indicate that exercise rapidly reverses the inhibition of splanchnic glucose output induced by glucose infusion. Even in the absence of a rise in arterial glucagon or a fall in insulin from basal levels, exercise nevertheless resulted in a threefold rise in splanchnic glucose production (Figure 2). The magnitude of this increment was, however, significantly reduced as compared to that observed in the absence of glucose infusion (Figure 4). This difference was most marked during the initial 10 min of exercise. As a consequence, infusion of glucose at a constant rate during exercise had the seemingly paradoxic effect of causing a fall in arterial glucose concentration, while, in the control studies, arterial glucose levels rose (Figure 4). These data thus indicate that the magnitude of the hepatic glucose response is reduced in the absence of a fall in arterial insulin and a rise in glucagon.

Since glucose availability to muscle in the glucose-infused subjects (Group 2) was determined by the infusion rate as well as the rate of release of endogenous glucose from the liver, it is of interest to compare total peripheral glucose delivery (endogenous plus exogenous) in these subjects with glucose delivery (splanchnic glucose output) in the saline controls (Group 1). As shown in Figure 5, total glucose availability in the two groups was virtually identical, particularly during the last 20 min of exercise. These data thus indicate that glucose infusion limits the magnitude of the rise in splanchnic glucose output during exercise only to an amount equal to the infusion rate, so that total glucose availability remains comparable to controls. These data thus demonstrate the exquisite sensitivity of hepatic glucoregulatory mechanisms in exercise.

In the subjects receiving the combined insulin-glucose infusion (Group 3), splanchnic glucose output was completely inhibited in the resting state while arterial insulin levels rose and glucagon fell to values comparable to those observed with a carbohydrate meal. As in the case of infusion of glucose alone, exercise reversed the inhibitory of effects of hyperinsulinemia on splanchnic glucose production (Figure 3). However, despite a twofold rise in plasma

FIGURE 2. Response to infusion of glucose (2 mg/kg/min) before and during exercise (Group 2).



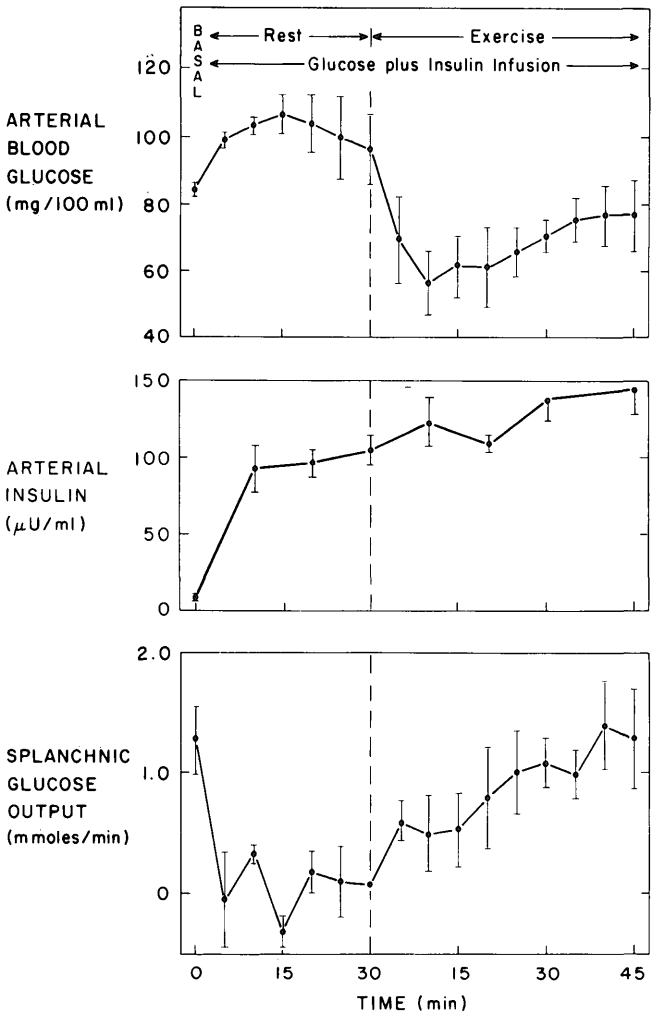


FIGURE 3. Response to infusion of insulin (1 mU/kg/min) plus glucose (5 mg/kg/min) before and (10 mg/kg/min) during exercise (Group 3).

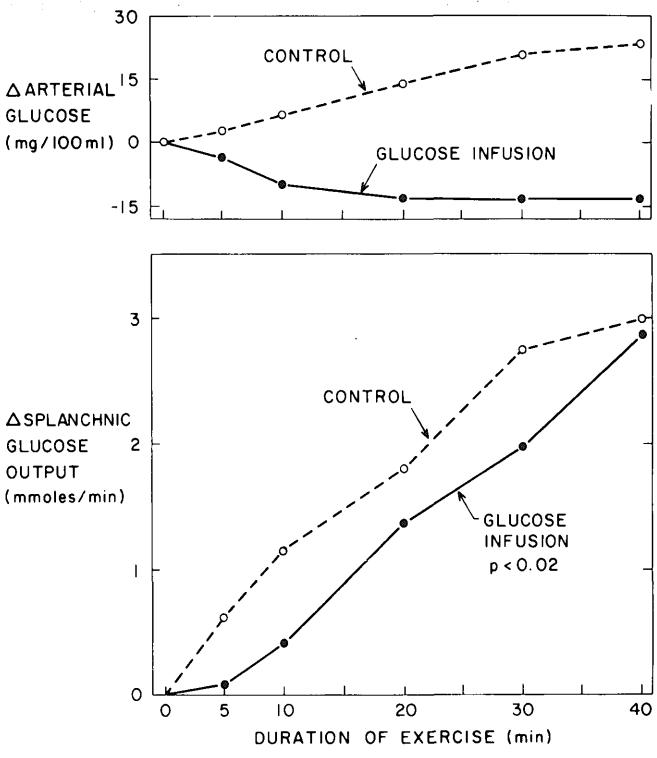


FIGURE 4. Comparison of the changes during exercise in arterial glucose concentration and in splanchnic glucose output in the control group (Group 1) and in the subjects receiving the glucose infusion (Group 2). Statistical analysis of the changes in glucose output was performed by comparing the areas under the curves of glucose output.

glucagon, splanchnic glucose output was 67% less than that observed in the saline controls. These findings thus indicate that hyperinsulinemia markedly blunts (although it does not fully prevent) the stimulatory effects of exercise on hepatic glucose production.

It should be noted that plasma catecholamines, which are known to rise with exercise,[5,6] were not measured in the current study. Inasmuch as the absolute as well as relative workload was comparable in all three groups, it is likely that elevations in plasma catecholamines were no less in the glucose-infused or insulin–glucose-infused subjects than in controls. In fact, the fall in plasma glucose with the continued insulin-glucose infusion to values below 60 mg/100 ml (Figure 3) suggests that the rise in plasma catecholamines may have been exaggerated in these subjects. The blunted splanchnic glucose response in these subjects as well as in those receiving glucose alone (Figure 4) thus underscores the important role of hypoinsulinemia in modulating the hepatic glucose response to exercise.

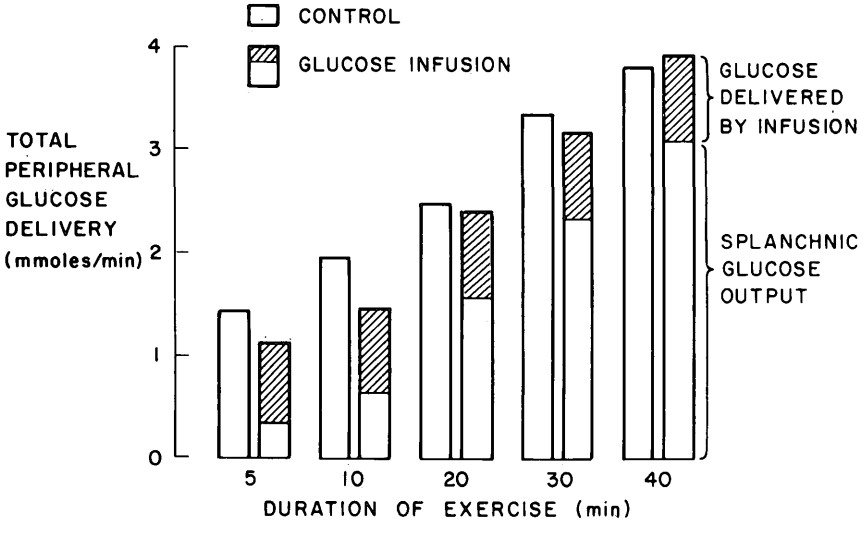


FIGURE 5. Total peripheral glucose delivery during exercise in the controls (Group 1) and in the subjects receiving the glucose infusion (Group 2). In the latter group, total peripheral glucose delivery represents the sum of the infusion rate (2 mg/kg/min) and the splanchnic glucose output. For the controls, total peripheral glucose delivery is equal to splanchnic glucose output.

ACKNOWLEDGMENTS

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