Glucose Turnover in Type I Diabetic Subjects During Exercise

Effect of selective and nonselective β-blockade and insulin withdrawal

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OBJECTIVE — To assess the effect of selective β_1-blockade (atenolol and betaxolol) and nonselective β-blockade (propranolol) on glucose turnover in subjects with insulin-dependent (type I) diabetes mellitus during moderate exercise.

RESEARCH DESIGN AND METHODS — Five subjects with type I diabetes were infused with insulin and then exercised for 1 h, after pretreatment with each of the three drugs or saline and, on a separate day, after withdrawal of insulin. Glucose turnover was measured using tritiated glucose.

RESULTS — Plasma glucose, initially 9.2 ± 0.5 mmol/L (mean ± SE) when insulin infused and 14.0 ± 0.8 when insulin was withdrawn, fell on exercise by 3.4 ± 1.1 mmol/L ($P < 0.05$) saline, 4.0 ± 0.8 mmol/L ($P < 0.01$) with betaxolol, 3.8 ± 0.7 mmol/L ($P < 0.01$) with atenolol, 5.0 ± 0.6 mmol/L ($P < 0.005$) with propranolol, and 1.7 ± 1.0 mmol/L (NS) when insulin was withdrawn. Propranolol, but not the other β-blockers, caused a significantly greater fall in glucose on exercise than during the control study. Glucose appearance rate (R_a) was similar basally and rose to an almost identical level in all five groups during exercise. Glucose disappearance rate (R_d) rose similarly during exercise, except after propranolol when the rise was significantly greater than with saline ($P < 0.01$). Failure of glucose to change significantly during exercise when insulin had been withdrawn was associated with the smallest rise in R_d and the highest nonesterified fatty acid concentrations. Propranolol and betaxolol, but not atenolol, reduced nonesterified fatty acids.

CONCLUSIONS — We conclude that the greater fall in glucose on exercise after β-blocking drugs is probably largely a direct effect of β_2-blockade on muscle, increasing the exercise-induced rise in R_d glucose. This offers support to the use of β_1-specific drugs, where β-blockade is necessary in type I diabetes.

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Control of plasma glucose levels during exercise in normal individuals is complex, probably involving changes in insulin and glucagon secretion, and the adrenergic system (1–5). Insulin-dependent (type I) diabetic subjects, without residual insulin secretion, therefore lack one of the main control mechanisms of blood glucose concentration. When type I diabetic subjects are treated with subcutaneous insulin, blood glucose tends to fall during exercise, whereas exercise with insulin deficiency results in little change or even a rise in blood glucose concentration (6). A fall in blood glucose with exercise in type I diabetic subjects has also been shown during infusion of intravenous insulin caused by failure of the hepatic glucose production rate to rise and match the increase in glucose utilization rate (7). These effects of exercise on plasma glucose have been shown to be highly dependent on plasma insulin concentration (8). The mechanism of the changes in blood glucose during exercise under conditions of insulin deficiency has not been studied in man, although in dogs little change in blood glucose was found, caused by almost equal exercise-induced rises in both glucose appearance rate and glucose utilization rate (9). β-Adrenoreceptors are known to play a role in the control of glucose metabolism in diabetes during exercise (7,10) and nonselective β-blockade ($\beta_1 + \beta_2$) with propranolol has been shown to enhance the hypoglycemic effect of exercise, in the presence of insulin, in both dogs (10) and type I diabetic subjects (7), mainly by increasing glucose metabolic clearance rate and utilization rate, although with some reduction in glucose appearance rate (R_a). Propranolol also reduces nonesterified fatty acid (NEFA) levels (10–13), and this may in part account for the increase in glucose utilization (caused by lack of NEFA as an alternative fuel for muscle).

It is uncertain whether these adrenergic controls of glucose metabolism

during exercise are β_1- or β_2-mediated. In normal subjects, the β_1-specific drug metoprolol had an effect between propranolol and placebo in lowering blood glucose during exercise at 50% of $\dot{V}O_{2\ max}$ (13). The effects of β_1-blockade alone on glucose metabolism during exercise have not been investigated in diabetic man. We have chosen to investigate two β_1-specific drugs: atenolol, which is relatively lipid insoluble and betaxolol, which is highly lipid soluble (this property might lead to different effects on NEFA and glucose metabolism).

The aims of this study were to:

1. Establish the mechanism of the changes in plasma glucose concentration seen in moderate exercise in insulin-deficient type I diabetic subjects.

2. Compare the effects of β_1-blockade, with atenolol or betaxolol with that of nonselective β-blockade, on the control of glucose metabolism in prolonged moderate exercise in moderately controlled, insulin-infused type I diabetic subjects.

RESEARCH DESIGN AND METHODS

— This study was approved by St. Thomas's Hospital ethical committee, and five men with type I diabetes gave written informed consent to take part. They were within 20% of their ideal body weight and had no clinical evidence of neuropathy, nephropathy, proliferative retinopathy, or ischemic heart disease. They were not taking any medication apart from insulin. C-Peptide did not rise above 0.20 nM/L in response to 1 mg i.v. of glucagon (14). Further clinical details are given in Table 1.

Each subject had five studies in random order after an overnight fast and at least 1 wk apart. Subjects came to the hospital on the evening before the study, having taken no insulin since before breakfast. A cannula was inserted into a forearm vein, and soluble insulin was infused at a variable rate to maintain the blood glucose at around 9 mM/L. The next morning, the infusion rate was fixed at a rate that maintained this blood glucose and was not altered again during the study. On each occasion, a primed continuous infusion of [1-^{3}H]glucose was started at 0800 on the morning of the study. After a 2-h equilibration period, they were injected intravenously with either normal saline (0.5 ml/kg), propranolol (0.2 mg/kg), atenolol (0.15 mg/kg), or betaxolol (0.15 mg/kg) as a bolus. Doses were chosen, based on previous work, to have equipotent β-blocking effects in terms of heart rate reduction (15,16). Thirty min after the drug, subjects undertook a 60-min period of exercise, at 35% of their previously determined $\dot{V}O_{2\ max}$, on an exercise bicycle. No subject became hypoglycemic during the study. The fifth study was identical, except that they were not infused with insulin overnight and had no further insulin until the end of the study. One subject was withdrawn from this part of the study because he did not feel well before the exercise period.

Respiratory measurements were made, by standard methods, at 15-min intervals during exercise, measuring inspired and expired O_2 (using a Servomex oxygen analyzer) and CO_2 (using an infrared analyzer [Godart]), together with inspired gas volumes using a turbo transducer.

Blood samples were taken from a cannula in an antecubital vein on the contralateral arm. The cannula was kept patent by intermittent flushing with normal saline (154 mmol/L sodium chloride solution); no heparin was used. Blood samples for glucose and glucose specific activity were taken at 10-min intervals from the time of injection of drug or saline and placed in fluoride oxalate tubes and the plasma separated after centrifugation at 4°C. Samples were taken every 30 min for measurement of lactate and NEFA concentration. Samples for lactate were taken directly into ice cold 10% perchloric acid and immediately frozen and kept at −70°C until assayed. Blood for NEFA concentrations was taken into EDTA tubes, the plasma separated, and frozen. An aliquot of the infusate was taken and frozen to allow calculation of the isotope infusion rate.

Table 1—*Clinical details of the subjects*

Patient	Age (yr)	HbA_1 (%)	Insulin dose (U/day)	Years of diabetes	Weight (kg)	Body mass index (kg/m^2)
1	33	9.3	41	1	78	23.0
2	22	9.4	82	20	74	25.0
3	35	8.9	27	16	64	21.1
4	36	7.9	30	2	73	21.1
5	21	8.1	96	10	66	21.6
Mean ± SD	29 ± 7	8.7 ± 0.7	55 ± 32	10 ± 8	71 ± 6	22.4 ± 1.7

Normal range for HbA_1 is 6.0–8.7%.

Analytical procedures

Plasma glucose was measured in duplicate using a glucose analyzer (model 23AM, YSI, Yellow Springs, OH). Tritiated glucose specific activity was measured after separation of other labeled compounds using anion and cation exchange columns, as previously described (17). [1-^{3}H]Glucose would be expected to behave similarly to [6-^{3}H]glucose after the triose isomerase reaction and would lose its label on conversion of pyruvate to oxaloacetate. Aliquots of the infusate were added to nonradioactive

plasma and run with each assay to measure and correct for recovery.

Standard enzymatic spectrophotometric methods were used on the neutralized perchloric acid extract to measure lactate (18) and ketone body (19) concentrations. NEFA concentration was measured by a fluorimetric method (20).

Calculations

R_a and disappearance rate (R_d) were calculated using the one-compartment nonsteady-state model of Steele (21), which has been discussed further by Hetenyi and Norwich (22) and validated by Radziuk et al. (23). Glucose space was taken as 22% of body weight and the pool fraction as 0.65. Metabolic clearance rate of glucose was calculated as R_d divided by glucose concentration at each time point. Respiratory quotient was calculated as the ratio of CO_2 production to O_2 consumption.

Statistical analysis

Results are given as means ± SE, except in Table 1 where mean ± SD is used. Treatment groups were compared using a general linear model analysis of variance (GLM-ANOVA), followed by a Duncan's test to establish where there were significant differences between the treatment groups. This was implemented on the Number Cruncher Statistical System (NCSS) software (Hintze, Kaysville, UT). $P < 0.05$ indicated statistical significance.

RESULTS

Glucose and glucose turnover

The mean initial glucose concentration was 9.2 ± 0.5 mM/L in the insulin-infused studies and fell significantly during exercise in all these studies. The greatest fall was with propranolol, which was significantly different from the control (saline) study ($P < 0.05$). The other drugs were not significantly different when normalized for starting blood glucose (Fig. 1).

The mean glucose turnover results for the 30 min before exercise are shown in Table 2, and those for the 60 min of exercise are shown in Table 3. R_a and R_d were similar in all groups before exercise, as were the glucose appearance rates during exercise. The fall in glucose during exercise in the insulin-infused studies was largely caused by an increase in R_d without a matching rise in R_a. The time course of the changes in glucose, glucose R_d, and glucose R_a are shown in Fig. 1. Glucose metabolic clearance rate during exercise was increased by propranolol ($P < 0.001$) and marginally by atenolol ($P = 0.03$), but not by betaxolol compared with the saline control study. Glucose R_d during exercise was increased after propranolol ($P < 0.01$), but was not significantly changed by the other β-blockers.

When insulin was withdrawn, the initial glucose was 14.0 ± 0.8 mmol/L, and it did not fall significantly during exercise. Glucose metabolic clearance rate was markedly reduced compared with the control study ($P < 0.001$). R_d during exercise rose least when compared with the other studies (although this did not reach statistical significance [$P = 0.07$]).

Metabolites

The mean levels before and during exercise are shown in Tables 2 and 3, and the time course of changes is shown in Fig. 2.

Lactate levels rose during exercise in both the control and treatment studies. However, propranolol significantly blunted the rise ($P < 0.05$), whereas the β_1-specific drugs did not. Insulin withdrawal did not affect lactate levels.

NEFAs were significantly lowered by propranolol before and during exercise ($P < 0.05$), but not by the β_1-specific agents. Insulin withdrawal resulted in higher NEFA levels that rose during exercise ($P < 0.01$).

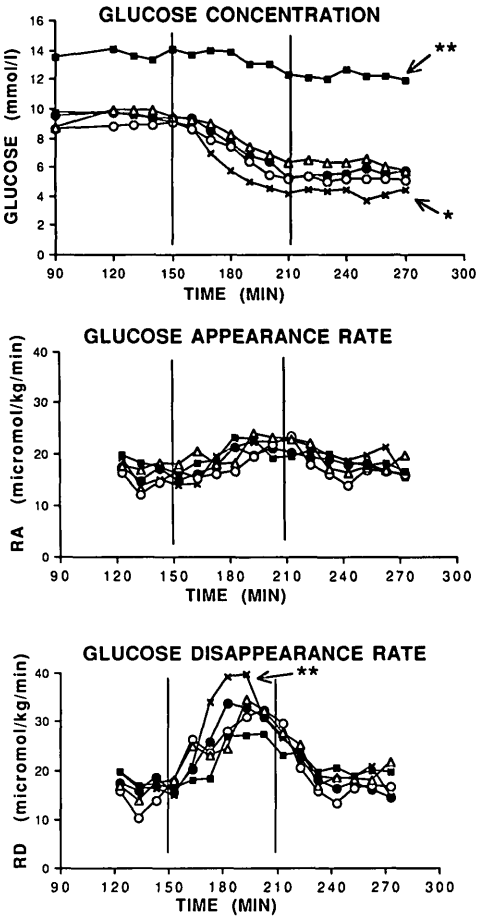

Figure 1—*Time course of changes in glucose, glucose appearance rate (R_a), and glucose disappearance rate (R_d). △, Saline; ●, betaxolol; ○, atenolol; ×, propranolol; and ■, insulin withdrawn. Vertical lines represent the period of exercise. *P < 0.05 and **P < 0.01 refer to significant differences between the curve indicated and saline study (by analysis of variance).*

Glycerol concentrations rose during exercise on the control day, but this rise was significantly blunted by both propranolol and betaxolol ($P < 0.01$). Atenolol and insulin withdrawal did not significantly affect the rise in glycerol concentration.

Ketone body levels were significantly higher when insulin was withdrawn. They tended to rise during all the studies when insulin was infused, although they fell during exercise in the insulin-withdrawn study.

Table 2—*Glucose appearance rate (R_a), disappearance rate (R_d), metabolic clearance rate (MCR), and metabolite values for the 30-min period (120–150 min) after drug injection and before exercise*

	Saline	Betaxolol	Atenolol	Propranolol	Insulin withdrawal
Preexercise					
R_A (mM/kg/min)	16.6 ± 1.7	14.4 ± 1.2	13.3 ± 1.2	13.2 ± 1.3	16.1 ± 1.9
R_D (mM/kg/min)	15.2 ± 1.2	15.5 ± 1.5	12.8 ± 1.1	14.7 ± 1.5	15.7 ± 1.4
MCR (ml/kg/min)	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.2	1.6 ± 0.2	1.2 ± 0.1
NEFA (mM/L)	0.70 ± 0.13	0.57 ± 0.08	0.69 ± 0.12	0.52 ± 0.05	0.87 ± 0.08
Lactate (mM/L)	0.86 ± 0.24	0.83 ± 0.15	0.63 ± 0.08	0.70 ± 0.11	0.75 ± 0.10
Ketones (mM/L)	0.15 ± 0.03	0.16 ± 0.03	0.26 ± 0.05	0.11 ± 0.01	0.36 ± 0.07
Glycerol (mM/L)	0.20 ± 0.03	0.14 ± 0.02	0.20 ± 0.02	0.16 ± 0.02	0.18 ± 0.02

Values are means ± SE.
NEFA, nonesterified fatty acid.

Neither the drugs nor insulin-withdrawal significantly altered the respiratory quotient during exercise from the values seen on the saline control day (Table 3).

CONCLUSIONS — Previous studies of the effects of propranolol on glucose turnover during exercise in diabetes have given apparently conflicting results that may represent the effects of differing levels of blood glucose control. In the studies of Wasserman et al. (10) in poorly controlled diabetic dogs (blood glucose ~15 mmol/L), the striking finding was an increase in glucose R_d with no effect on R_a and a fall in blood glucose in the propranolol-treated group. Propranolol also caused a fall in NEFA levels and reduced the rise in lactate levels. Simonson et al. (7), in diabetic subjects receiving low-dose insulin infusion, found that propranolol accentuated the fall in blood glucose largely by increasing peripheral utilization, although it also led to a small reduction in hepatic glucose output compared with controls. There was a small but insignificant rise in plasma NEFAs in the control study, which became a significant fall after propranolol and lactate levels were not measured. These subjects had some residual insulin secretion. Tuttle et al. (12) also infused exercising type I diabetic subjects with insulin at a rate such that glucose levels did not change (around 5.5 mmol/L). Propranolol caused a fall in plasma glucose, largely because of the failure of R_a to rise sufficiently early in exercise. The lactate rise was unchanged by β-blockade, and the NEFAs showed a small rise that was abolished by propranolol.

Table 3—*Plasma glucose at the start and end of the exercise period*

	Saline	Betaxolol	Atenolol	Propranolol	Insulin Withdrawal
Exercise					
Initial glucose at 150 min (mM/L)	9.4 ± 1.3	9.3 ± 0.8	8.9 ± 1.2	9.1 ± 0.3	14.0 ± 0.8
Final glucose at 210 min (mM/L)	6.0 ± 1.0	5.3 ± 0.6	5.1 ± 1.2	4.1 ± 0.9	12.4 ± 1.4
R_A (mM/kg/min)	20.0 ± 1.4	18.3 ± 0.9	17.9 ± 0.9	19.4 ± 1.1	19.3 ± 1.5
R_D (mM/kg/min)	26.7 ± 1.9	27.3 ± 1.6	26.2 ± 1.3	30.7 ± 1.9	22.2 ± 2.1
MCR (ml/kg/min)	3.5 ± 0.3	3.8 ± 0.3	4.2 ± 0.3	5.4 ± 0.6	1.7 ± 0.2
NEFA (mM/L)	0.66 ± 0.4	0.47 ± 0.05	0.59 ± 0.10	0.42 ± 0.05	0.17 ± 0.02
Lactate (mM/L)	2.28 ± 0.39	2.12 ± 0.50	1.84 ± 0.32	1.11 ± 0.22	2.00 ± 0.38
Ketones (mM/L)	0.20 ± 0.04	0.08 ± 0.07	0.12 ± 0.01	0.09 ± 0.02	0.17 ± 0.02
Glycerol (mM/L)	0.24 ± 0.04	0.16 ± 0.02	0.27 ± 0.03	0.16 ± 0.03	0.29 ± 0.03
Respiratory quotient	0.92 ± 0.02	0.96 ± 0.02	0.88 ± 0.02	0.96 ± 0.01	0.90 ± 0.02

Values are means ± SE.
Mean glucose appearance rate (R_a), disappearance rate (R_d), metabolic clearance rate (MCR), metabolite values, and respiratory quotient for the 60-min exercise period (150–210 min).

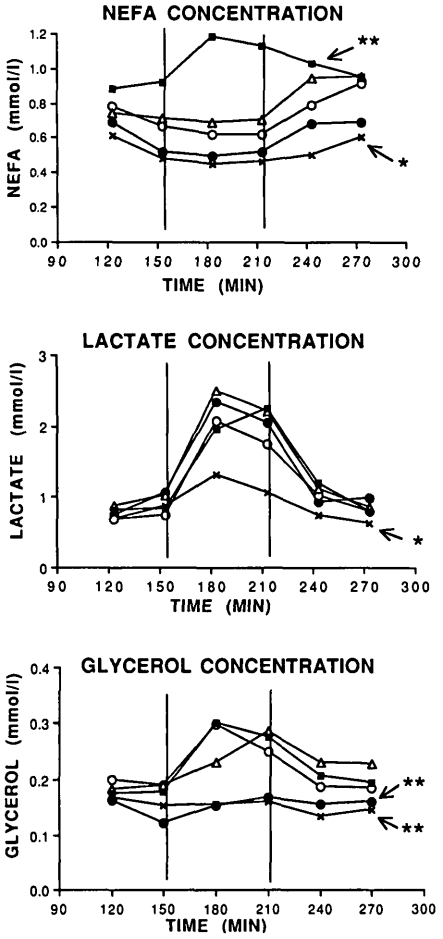

Figure 2—*Time course of changes in nonesterified fatty acid (NEFA), lactate, and glycerol concentrations. △, Saline; ●, betaxolol; ○, atenolol; ×, propranolol; and ■, insulin withdrawn. Vertical lines represent the period of exercise. *P < 0.05 and **P < 0.01 refer to significant differences between the curve indicated and saline study (by analysis of variance).*

Subjects in our studies were infused with insulin to achieve a moderately elevated plasma glucose of ~8–9 mM/L, in order to avoid hypoglycemia during exercise. Under these conditions, we found that propranolol accentuated the exercise-induced fall in blood glucose largely by increasing the glucose metabolic clearance rate and peripheral utilization of glucose, but these effects were not seen with the β_1-specific drugs atenolol and betaxolol except that atenolol had a detectable effect on metabolic clearance rate.

β-Blockade may exert its effect on plasma glucose concentration in exercising diabetic patients either by changes in the availability of other substrates for muscle metabolism (both transported in plasma and locally released) or by a direct β-antagonist effect on glucose transport in muscle. NEFAs are used as a fuel by exercising muscle so the reduced NEFA levels available in the blood may play a causal role in the increased glucose utilization seen in nonspecific β-blockade and reduce availability of locally released NEFA. In this study, all three drugs appeared to suppress NEFA levels, but this reached statistical significance only with propranolol. Propranolol is highly lipid soluble, and it is interesting that betaxolol, which is also lipid soluble, had a similar effect as propranolol on NEFA and also like propranolol, significantly suppressed glycerol levels (suggesting inhibition of lipolysis) although not increasing R_d. The lipid-insoluble drug atenolol had less effect on NEFA and no effect on glycerol levels, and yet did have a detectable effect in increasing glucose metabolic clearance rate. This suggests that reduced availability of NEFAs is at least not the sole cause of the glucose lowering effect of propranolol.

We did not detect a significant rise in respiratory quotient, which would be expected if glucose was oxidized at the expense of fat, during β-blockade. This may have been caused by the small numbers and variability in the measurement. Certainly, the respiratory quotient values for propranolol and betaxolol tended to be higher than on the control day (Table 3).

Alternatively, the effect of propranolol on glucose disposal may be mediated by a direct effect on muscle. Catecholamines have been shown to have direct effects on glucose transport in both rat and human adipocytes (24), and rat hindquarters (25,26), although these effects are complex, depending, among other things, on the concentrations of β-agonist and insulin used. Data from this study would be compatible with a direct β_2 effect of catecholamines on glucose uptake in exercising muscles, which is blocked by propranolol but not the other drugs.

Blocking of β-adrenergic stimulation of muscle glycogenolysis (25) may explain the lower rise in lactate concentration with propranolol not seen with the other drugs, again suggesting a β_2 mechanism. Lack of this gluconeogenic precursor (and also glycerol) after propranolol might be expected to result in reduced hepatic gluconeogesis, but the isotope data in this study do not demonstrate any change in hepatic glucose output.

Insulin withdrawal did not result in a significant change in blood glucose during exercise. Glucose metabolic clearance rate was greatly reduced, but glucose R_d was only mildly, and not significantly, reduced compared with the controls, whereas glucose R_a was unchanged. NEFA levels rose considerably during exercise when insulin was withdrawn and this may have spared glucose uptake and elevated ketone body levels. Ketone body levels in this study were considerably lower than those in the study by Berger et al. (6), which may explain why the reported tendency for blood glucose and ketone body levels to rise on exercise was not seen here.

We conclude that propranolol enhances the exercise-induced fall in glucose in insulin-infused type I diabetic men by enhancing glucose utilization, both as a result of reduced substrate availability and a direct β_2-mediated effect on glucose uptake in muscle. The β_1-specific drugs atenolol and betaxolol do not affect the exercise-induced fall in glucose, and are therefore to be preferred for use in diabetic men requiring

β-blockade.

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