Regulation of Glucose Kinetics During Intense Exercise in Humans: Effects of α- and β-Adrenergic Blockade

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This study examined the effect of combined α- and β-adrenergic blockade on glucose kinetics during intense exercise. Six endurance-trained men exercised for 20 minutes at approximately 78% of their peak oxygen consumption (V_{O_2}) following ingestion of a placebo (CON) or combined α- (prazosin hydrochloride) and β- (timolol maleate) adrenoceptor antagonists (BLK). Plasma glucose increased during exercise in CON (0 minutes: 5.5 ± 0.1; 20 minutes: 6.5 ± 0.3 mmol · L^{-1}, $P < .05$). In BLK, the exercise-induced increase in plasma glucose was abolished (0 minutes: 5.7 ± 0.3; 20 minutes: 5.7 ± 0.1 mmol · L^{-1}). Glucose kinetics were measured using a primed, continuous infusion of [6,6-^{2}H] glucose. Glucose production was not different between trials; on average these values were 25.3 ± 3.9 and 30.9 ± 4.4 μmol · kg^{-1} · min^{-1} in CON and BLK, respectively. Glucose uptake during exercise was greater ($P < .05$) in BLK (30.6 ± 4.6 μmol · kg^{-1} · min^{-1}) compared with CON (18.4 ± 2.5 μmol · kg^{-1} · min^{-1}). In BLK, plasma insulin and catecholamines were higher ($P < .05$), while plasma glucagon was unchanged from CON. Free fatty acids (FFA) and glycerol were lower ($P < .05$) in BLK. These findings demonstrate that adrenergic blockade during intense exercise results in a blunted plasma glucose response that is due to enhanced glucose uptake, with no significant change in glucose production.

DURING INTENSE exercise in humans, circulating plasma glucose levels are elevated as the rate of glucose production exceeds glucose uptake.[1-5] It has been suggested that under such conditions, adrenergic mechanisms mediate this rise in plasma glucose by an increase in glucose production and/or a reduction in peripheral glucose uptake.[1-5] However, studies in adrenaline-deficient bilaterally adrenalectomized humans,[6] as well as in liver transplant patients who have no sympathetic neural innervation to the liver,[7] have demonstrated that glucose production and uptake are not impaired during intense exercise. It appears that adrenergic mechanisms may not play an essential role in regulating glucose kinetics during intense exercise, although the use of patient populations makes it difficult to extrapolate these findings to normal healthy individuals. In light of this, anaesthetic blockade of the celiac ganglion has been employed to impair sympathetic activity to the liver and adrenal medulla in normal subjects.[8] Under these conditions glucose kinetics during intense exercise were not affected, but this experimental approach does not provide optimal conditions as insulin and glucagon were infused as anaesthesia also results in sympathetic neural blockade to the pancreas.[8]

An alternative approach to examine adrenergic regulation of glucose kinetics during intense exercise in normal healthy individuals has been to employ adrenoceptor antagonists. However, the limited studies that have utilised this approach have employed either α- or β-adrenoceptor antagonists individually.[4,5] Compared with a control trial, β-adrenoceptor blockade resulted in a significant increase in both glucose production and uptake,[4] whereas α-adrenoceptor blockade had no significant effect on glucose kinetics.[5] Interpretation of these studies is complicated, as blocking the β-adrenoceptor results in high circulating catecholamine levels that may "unmask" the α-adrenergic effects[4] and vice versa.[5] Therefore, the aim of the present study was to examine the effect of combined α- and β-adrenergic blockade on glucose kinetics during intense exercise in healthy trained males.

MATERIALS AND METHODS

Subjects

Six endurance-trained males (26 ± 2 years, 71 ± 3 kg, mean ± SEM) volunteered to serve as subjects for the experiment. The experimental procedures and possible risks of the study were explained to each subject verbally and in writing. All subjects gave informed, written consent and the experiment was approved by The Alfred Hospital Research Ethics Committee. Screening before the study included a medical history, physical examination, electrocardiogram (ECG), and blood chemistry.

Pre-experimental Protocol

All subjects performed an incremental workload test to exhaustion on a modified electromagnetically braked cycle ergometer (Siemens-Elema, Solna, Sweden) to determine their peak pulmonary oxygen uptake (V_{O_2} peak). Subjects lay behind the cycle ergometer on a couch in a supine position. Peak V_{O_2} was the highest V_{O_2} attained during the latter stages of the test and was accompanied by a respiratory exchange ratio (RER) that was greater than 1.1. Mean V_{O_2} peak was 4.18 ± 0.24 L · min^{-1}. For the day preceding each trial the subjects consumed a food package (~14 MJ, 80% carbohydrates) and abstained from exercise, tobacco, caffeine, and alcohol. In addition, they were instructed to consume 5 mL of tap water per kilogram body weight upon waking to ensure euhydration. The subjects reported to the laboratory in the morning after a 10- to 12-hour overnight fast.

Experimental Protocol

Each subject performed 2 exercise trials, separated by at least 7 days. The exercise trials were performed on the same modified cycle ergometer used in the V_{O_2} peak determination test. Subjects performed all exercise tests in the laboratory at a mild temperature (20 to 22°C). Upon arrival at the laboratory, subjects rested quietly in a supine position on the modified cycle ergometer. Chest electrodes were positioned for monitoring of heart rate by ECG. Following local analgesia

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(0.5 mL lidocaine, 10 mg · mL^{-1}), a catheter was introduced percutaneously into the brachial artery for blood sampling and blood pressure measurements. The catheter was kept patent by regular flushing with a small amount of heparinized saline. In addition, a catheter was inserted into a contralateral forearm vein for a primed (3.3 mmol) continuous (41.2 ± 1.0 μmol · min^{-1}) infusion of [6,6-^{2}H] glucose (Cambridge Isotope Laboratories, Cambridge, MA) that was maintained for 2 hours of rest and the duration of exercise. Two hours prior to exercise, subjects ingested either a placebo capsule (CON) or a capsule containing 5 mg of the α_1-adrenergic antagonist, prazosin hydrochloride (half-life = 3 hours) and 5 mg of the nonselective β-adrenergic antagonist, timolol maleate (BLK) (half-life = 5 to 6 hours). These adrenergic antagonists were chosen as adrenoceptors in human liver plasma membranes[9] and skeletal muscle[10,11] appear to be predominately both α_1 and β_2 subtypes. As there was individual variation in exercise tolerance following drug administration in preliminary experiments, BLK was always performed first. Subjects commenced supine cycling exercise at a power output eliciting 82 ± 3% V_{O_2} peak, but due to the earlier onset of fatigue in BLK the power output was reduced to that eliciting 73 ± 3% V_{O_2} peak at 10 minutes, which was maintained until 20 minutes. Two subjects were unable to complete 20 minutes of exercise, fatiguing after 16 and 19 minutes. The time to fatigue was noted and the exercise duration replicated in the subsequent control trial. On average, subjects cycled for 19.2 ± 0.6 minutes at a power output requiring 78 ± 3% V_{O_2} peak. Subjects remained in the laboratory following exercise and were continually monitored for a minimum of 2 hours, and thereafter until no adverse effects of the drugs were detected when subjects were in the upright standing position, which ranged from 2 to 5 hours post-exercise.

Arterial blood samples were obtained at 5-minute intervals for the last 15 minutes of the rest period and throughout exercise for later analysis of plasma glucose, lactate, and ^{2}H-glucose enrichment. Samples were obtained prior to drug administration, immediately prior to the commencement of exercise, at 10 minutes, and at the completion of exercise for analysis of catecholamines. Additional samples were also taken prior to exercise, at 10 minutes, and at the completion of exercise for analysis of insulin, glucagon, cortisol, lactate, free fatty acids (FFA), and glycerol. Blood for glucose, lactate, insulin, cortisol, and glycerol was placed in lithium heparin tubes. For analysis of catecholamines and FFA, blood was placed in plain tubes containing ethylene glycol-bis (ß-aminoethyl ether) N,N,N′,N′-tetraacetic acid and reduced glutathione, and for glucagon in lithium heparin tubes containing Trasylol (Bayer Pharmaceuticals, Sydney, Australia). At the completion of exercise, the blood samples were spun and the plasma removed and stored at −20°C for later analysis. Plasma for catecholamine analysis was stored at −80°C. In preparation for the glycerol assay, 250 μL of plasma was deproteinized in 250 μL of 3 mol/L perchloric acid and spun. The supernatant (400 μL) was then mixed with 100 μL of 6 mol/L KOH, spun again, and the supernatant removed and stored at −80°C.

Expired gases were sampled during exercise for measurement of V_{O_2}, V_{CO_2} and ventilation using an on-line system (Quark b^2 Cosmed, Rome, Italy). Blood pressure was measured and an ECG obtained prior to drug/placebo administration, immediately before the onset of exercise, during exercise, and 2 hours after exercise. Measurements for blood pressure and ECG were digitized at 500 Hz using a 486/50 IBM-compatible PC and a data acquisition system incorporating a 12-bit analogue-to-digital converter (McPherson Scientific, Melbourne, Australia). Systolic, diastolic, and mean blood pressure and heart rate were derived on a beat-to-beat basis from the blood pressure signal using a variable threshold peak-detection technique. Electronic callipers were used to average these signals over appropriate time intervals. During exercise, the intensity of effort was quantified by a rating of perceived exertion on a scale from 6 (minimum effort) to 20 (maximum effort).

Analytical Techniques

Plasma glucose and lactate were measured using an automated glucose-lactate analyzer (EML 105 Radiometer, Copenhagen, Denmark). Plasma cortisol (Diagnostic Products Corp, Los Angeles, CA), insulin (Phadeseph, Pharmacia & Upjohn, Uppsala, Sweden), and glucagon[12] were measured by radioimmunoassay. To express the glucagon-insulin molar ratio, the measured glucagon was divided by 3.485 and then by the corresponding plasma insulin concentration. Plasma catecholamines were determined using a single isotope, radioenzymatic method (TRK 995, Amersham, Buckinghamshire, UK). FFA were measured by an enzymatic colorimetric method (Wako NEFA C test kit, Wako Chemicals, Osaka, Japan) and glycerol by an enzymatic method.[13] Plasma ^{2}H-glucose enrichment was measured as previously described.[14] Rates of plasma glucose appearance (glucose Ra) and disappearance (glucose Rd) at rest and during exercise were calculated using a modified 1-pool non–steady-state model[15] assuming a pool fraction of 0.65 and estimating the apparent glucose space as 25% of body weight. The metabolic clearance rate (MCR) of glucose was calculated by dividing glucose Rd by the corresponding plasma glucose concentration. For the duration of exercise total glucose Ra, Rd, and MCR were determined by calculating the area under the curve. Data from the 2 trials were compared by 2-way analysis of variance (ANOVA) for repeated measures. Specific differences were determined using the Student Newman Keuls post hoc test. Where appropriate, paired comparisons were made using *t* tests. The level of significance was set at $P < .05$. All data are reported as the mean ± SEM.

RESULTS

At rest, prior to drug/placebo administration, arterial plasma epinephrine (CON, 0.56 ± 0.11; BLK, 0.46 ± 0.04 nmol · L^{-1}) and norepinephrine (CON, 1.04 ± 0.16; BLK, 0.95 ± 0.17 nmol · L^{-1}) levels were similar between trials. Ingestion of the adrenoceptor antagonists had no effect on resting catecholamine levels (Fig 1). In CON, exercise resulted in a marked increase ($P < .05$) in circulating levels of catecholamines. However, in BLK the increase in catecholamine levels during exercise was significantly greater than in CON (Fig 1). There were no differences between trials in oxygen uptake, ventilation, or RER (Table 1). Ingestion of the adrenergic antagonists resulted in a reduction ($P < .05$, main effect) in heart rate during exercise (Table 2), but had no effect on heart rate in the resting or recovery period (Table 3). Blood pressure was also significantly reduced during exercise and recovery in BLK (Table 3). The rating of perceived exertion was higher ($P < .05$, main effect) in BLK compared with CON (Table 2).

Plasma glucose levels were similar between CON and BLK at rest (Fig 2). In CON, plasma glucose increased ($P < .05$) during exercise. In contrast, the exercise-induced increase in plasma glucose was abolished ($P < .05$) in BLK (Fig 2). Glucose Ra and Rd were not different between trials at rest (Fig 3). During exercise there was an increase ($P < .05$, time effect) in both glucose Ra and Rd; however, as glucose Ra during exercise was not different between trials, the blunting of the plasma glucose response in BLK was due to a higher ($P < .05$, main effect) glucose Rd in BLK compared with CON (Fig 3). MCR was also greater ($P < .05$, main effect) in BLK compared with CON (Fig 3). Resting plasma lactate levels were similar between trials (Fig 2); however, during exercise plasma lactate was higher ($P < .05$) in BLK than CON (Fig 2).

Plasma insulin was greater ($P < .05$) in BLK compared with

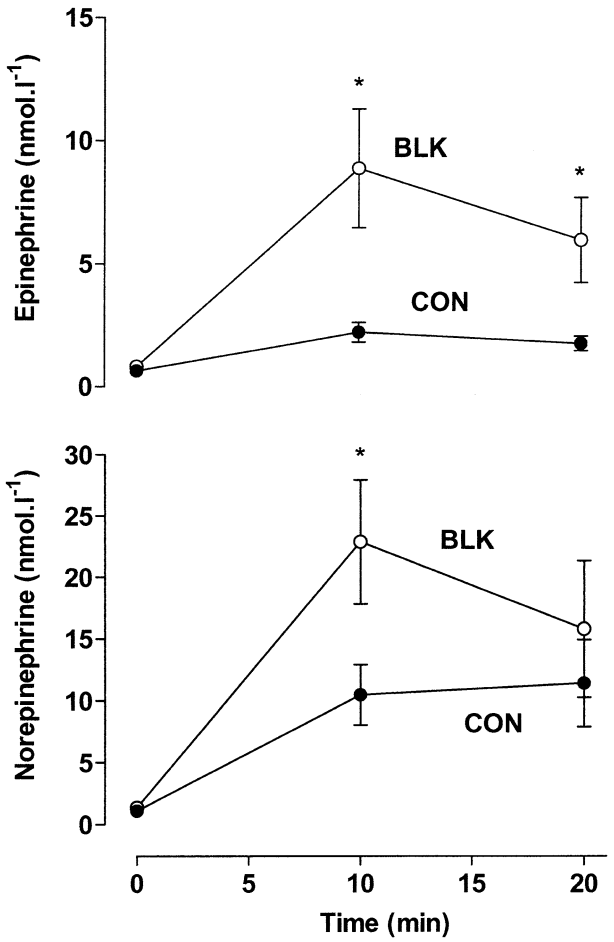

Fig 1. Plasma epinephrine and norepinephrine at rest and during 20 minutes of intense exercise without (CON) and with (BLK) α- and β-adrenergic blockade. Values are mean ± SEM (n = 6 subjects). *Significant difference ($P < .05$) from CON.

Table 1. Oxygen Uptake Ventilation, and Respiratory Exchange Ratio During 20 Minutes of Intense Exercise Without (CON) and With (BLK) α- and β-Adrenergic Blockade

	10 Minutes	20 Minutes
V_{O_2} (L · min^{-1})		
CON	3.47 ± 0.30	3.18 ± 0.23
BLK	3.42 ± 0.30	3.07 ± 0.29
Ve (L · min^{-1})		
CON	104 ± 11	99 ± 15
BLK	109 ± 7	106 ± 15
RER		
CON	1.03 ± 0.01	0.93 ± 0.01
BLK	1.09 ± 0.02	0.95 ± 0.02

NOTE. Values are mean ± SEM (n = 6 subjects). No significant difference between CON and BLK.

Abbreviations: V_{O_2}, oxygen uptake; Ve, ventilation; RER, respiratory exchange ratio.

Table 2. Heart Rate and Rating of Perceived Exertion During 20 Minutes of Intense Exercise Without (CON) and With (BLK) α- and β-Adrenergic Blockade

	5 Minutes	10 Minutes	15 Minutes	20 Minutes
HR (bpm)				
CON	155 ± 4	172 ± 5	168 ± 5	167 ± 4
BLK*	134 ± 7	141 ± 8	136 ± 8	145 ± 8
RPE				
CON	14 ± 1	16 ± 0	14 ± 1	14 ± 1
BLK*	16 ± 1	18 ± 0	18 ± 0	19 ± 1

NOTE. Values are mean ± SEM (n = 6 subjects).

*Significant difference ($P < .05$, main effect) from CON.

Abbreviations: HR, heart rate; RPE, rating of perceived exertion.

CON at rest and during exercise (Table 4). Plasma glucagon increased ($P < .05$, time effect) similarly during exercise in both trials (Table 4). There was a tendency ($P = .06$) for the glucagon-insulin molar ratio to be lower in BLK (Table 4). Plasma cortisol was similar between trials at rest (Table 4). During exercise, cortisol increased ($P < .05$) in both trials, but was lower ($P < .05$) in BLK (Table 4). Plasma FFA decreased ($P < .05$, time effect) during exercise, but were lower ($P < .05$, main effect) in BLK compared with CON (Table 4). Plasma glycerol levels at rest and during exercise were lower ($P < .05$) in BLK compared with CON (Table 4).

DISCUSSION

The findings from this study demonstrate that the combined effects of α- and β-adrenergic blockade abolish the increase in plasma glucose levels during intense exercise in trained males. The blunting of the hyperglycemic response during intense exercise in BLK appears to be due to enhanced glucose uptake, as there was no significant change in glucose production.

In this study, the combination of both α- and β-adrenergic blockade had no significant effects on glucose production at

Table 3. Blood Pressure and Heart Rate Without (CON) and With (BLK) α- and β-Adrenergic Blockade

	Pre-drug	Pre-exercise	Exercise	2-h Post-exercise
Systolic (mm Hg)				
CON	120 ± 6	132 ± 5	173 ± 8	132 ± 8
BLK	124 ± 6	126 ± 8	137 ± 6*	107 ± 6*
Diastolic (mm Hg)				
CON	70 ± 2	73 ± 2	79 ± 3	73 ± 4
BLK	68 ± 2	69 ± 3*	65 ± 3*	59 ± 3*
Mean arterial pressure				
CON	89 ± 2	94 ± 2	110 ± 3	92 ± 5
BLK	88 ± 3	88 ± 4*	88 ± 3*	75 ± 4*
HR (bpm)				
CON	56 ± 3	54 ± 4	Refer to Table 2	59 ± 5
BLK	53 ± 5	53 ± 3		54 ± 4

NOTE. Values are mean ± SEM (n = 5 subjects).

*Significant difference ($P < .05$) from CON.

Abbreviation: HR, heart rate.

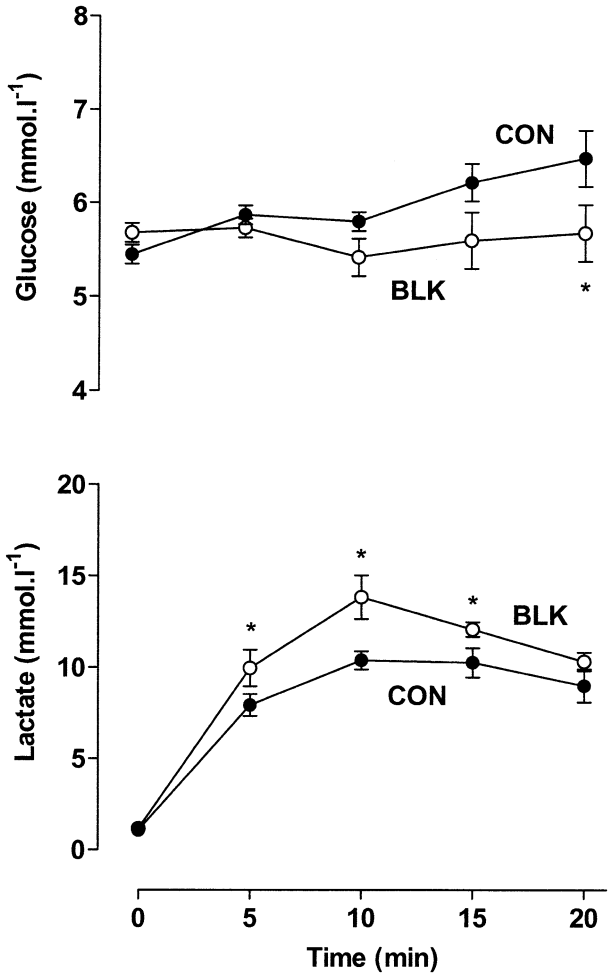

Fig 2. Plasma glucose and lactate at rest and during 20 minutes of intense exercise without (CON) and with (BLK) α- and β-adrenergic blockade. Values are mean ± SEM (n = 6 subjects). *Significant difference ($P < .05$) from CON.

rest and during exercise, which suggests that adrenergic mechanisms may not play an essential role in mediating the increase in glucose production during intense exercise. However, it cannot be ruled out that liver adrenergic blockade was not complete or that there may have been other secondary effects on circulating hormone levels and lipid metabolism that could have influenced glucose production. It is difficult, if not impossible, in humans to ascertain whether the adrenergic antagonists resulted in complete blockade at the liver. There was a significant increase in epinephrine and norepinephrine levels during exercise in BLK, which can mainly be attributed to a decreased clearance rate.[16,17] Plasma FFA and glycerol levels were attenuated in BLK consistent with adrenergic blockade of adipose tissue lipolysis.[18] Furthermore, heart rate during exercise was lower in BLK compared with CON, in line with previous studies using β-adrenergic blockade.[1,4] Although vagal withdrawal can partly account for the increase in heart rate during exercise in BLK, it could be argued that adrenergic blockade was incomplete. In light of the higher plasma catecholamines, it is possible that there may have been some residual adrenergic stimulation, which could have increased glucose output.

The suggestion that adrenergic mechanisms may not play an essential role in regulating glucose production during intense exercise is in agreement with previous studies in humans where adrenergic mechanisms are deficient[6,7] or have been impaired by pharmacological interventions.[5,8]. Although β-adrenergic blockade alone has been shown to result in a marked increase in glucose production during exercise at 100% V_{O_2} peak in healthy individuals, this effect could be accounted for by changes in glucagon and/or insulin, or a result of stimulation via unrestrained α-adrenoceptors at the liver.[4] In further support of findings that argue against an important role for direct adrenergic stimulation in regulating glucose production during intense exercise, infusion of phentolamine and propranolol into the portal vein to selectively block both liver α- and β-adrenoceptors, respectively, was unable to attenuate the rise in

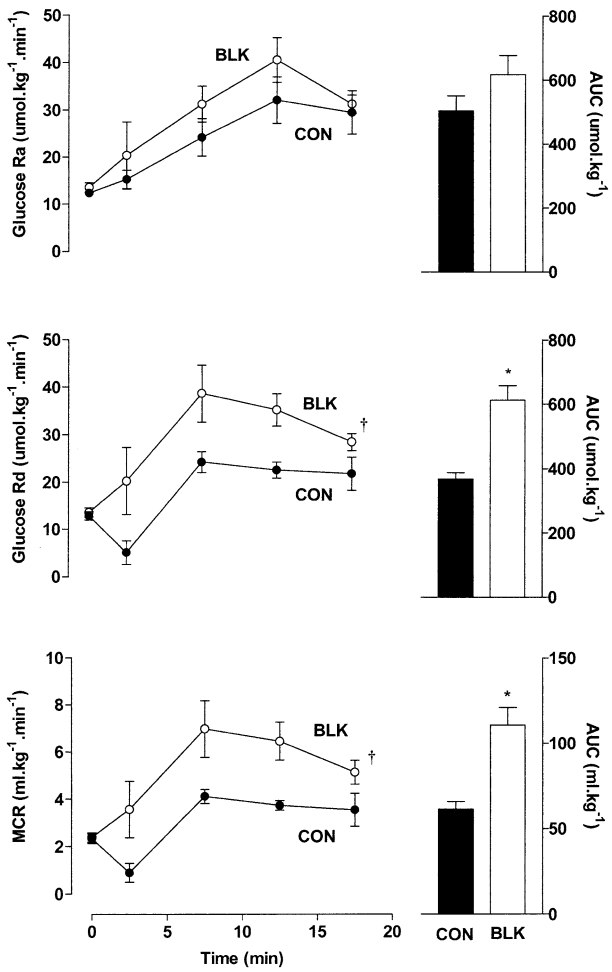

Fig 3. Rates of glucose appearance (Ra) and disappearance (Rd), and metabolic clearance rate (MCR) at rest and during 20 minutes of intense exercise without (CON) and with (BLK) α- and β-adrenergic blockade. Values are mean ± SEM (n = 6 subjects). AUC, area under the curve. †Significant difference ($P < .05$, main effect) from CON. *Significant difference ($P < .05$) from CON.

Table 4. Plasma Hormones and Substrates at Rest and During 20 Minutes of Intense Exercise Without (CON) and With (BLK) α- and β-Adrenergic Blockade

	0 Minutes	10 Minutes	20 Minutes
Insulin (pmol · L^{-1})			
CON	27.2 ± 4.3	21.5 ± 4.0	19.8 ± 5.0
BLK	36.7 ± 5.2*	42.9 ± 6.2*	44.0 ± 7.0*
Glucagon (ng · L^{-1})			
CON	26.3 ± 6.6	27.8 ± 7.9	64.8 ± 17.9
BLK	22.7 ± 2.9	24.8 ± 4.7	42.2 ± 8.2
G-I molar ratio			
CON	0.3 ± 0.1	0.4 ± 0.1	1.5 ± 0.6
BLK	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1
Cortisol (nmol · L^{-1})			
CON	364 ± 34	425 ± 49	552 ± 59
BLK	335 ± 36	377 ± 53*	436 ± 41*
FFA (mmol · L^{-1})			
CON	0.52 ± 0.07	0.27 ± 0.04	0.30 ± 0.04
BLK	0.30 ± 0.05	0.12 ± 0.01	0.11 ± 0.01†
Glycerol (mmol · L^{-1})			
CON	0.07 ± 0.02	0.12 ± 0.01	0.16 ± 0.02
BLK	0.04 ± 0.01*	0.07 ± 0.01*	0.07 ± 0.01*

NOTE. Values are mean ± SEM (n = 6 subjects).
*Significant difference ($P < .05$) from CON.
†Significant difference ($P < .05$, main effect) from CON.

glucose production during intense (85% of maximum heart rate) exercise in dogs.[19]

It addition to potential direct adrenergic effects on glucose production, it is also possible that combined α- and β-adrenergic blockade had secondary effects on circulating hormone levels and lipid metabolism that may have influenced glucose production. Plasma FFA and glycerol levels were significantly lower in BLK, which may be due to effects of adrenergic blockade on lipolysis.[18] The lower plasma FFA levels in BLK could also be due to higher insulin levels. Plasma insulin has been shown to decrease with β-adrenergic blockade, as a result of unrestrained stimulation of α-adrenoceptors.[4] However, in the present study combined α- and β-adrenoceptor antagonists resulted in plasma insulin levels that were higher than CON at rest and during exercise. It appears that under these conditions α-adrenergic blockade may play a greater role in controlling insulin secretion. However, C-peptide levels were not measured in the present study, and so it is also possible that adrenergic blockade may have influenced insulin clearance directly or through changes in blood flow distribution. There were no significant effects on glucagon levels at rest or during exercise, which is consistent with previous studies using α- or β-adrenergic blockade during intense exercise in humans.[4,5] The increase in plasma insulin levels and the tendency for the glucagon-insulin molar ratio to be reduced in BLK would be predicted to inhibit glucose production. Despite these pancreatic hormonal changes, glucose production in BLK was not significantly different from CON. The potential inhibitory effect of the changes in pancreatic hormone levels on glucose production could be masked by the effect of some residual adrenergic stimulation. Alternatively, a number of studies in humans suggest that glucagon and/or insulin may not play an important role in regulating glucose production during intense exercise.[20-22] However, these studies in exercising humans, and results from the present study, cannot completely rule out the possibility that changes in the portal vein concentration of pancreatic hormones could have a significant effect on glucose production. Indeed, studies in exercising dogs demonstrate that changes in the portal vein concentration of these hormones can influence glucose production, and that significant changes at the portal vein do not necessarily reflect the level of glucagon and/or insulin measured in peripheral arterial samples.[23,24]

Glucose production was not significantly affected at rest and during exercise in BLK. However, the hyperglycemic response observed during intense exercise in CON was blunted by combined α- and β-adrenergic blockade. Given that small deviations in plasma glucose levels have been implicated in stimulating glucose production during prolonged moderate intensity exercise,[25] it is possible that in the present study changes in glycemia during exercise in BLK may have over-ridden potential inhibitory effects of adrenergic blockade on glucose production. However, as plasma glucose levels in BLK did not fall below resting levels during exercise it is unlikely that this would have had marked effects on glucose production, which is in line with a previous study in phlorizin-treated rats.[26] Furthermore, a significant decrease in plasma glucose below resting levels has failed to show a concomitant increase in glucose production during exercise in humans.[27]

From the present study it can only be speculated as to what other additional factors maybe responsible for the normal increase in glucose production during intense exercise. Hepatic blood flow was not measured, but it is possible that altered splanchnic or hepatic blood flow during high intensity exercise[28] could affect glucose production either directly or indirectly by altering the delivery of hormones and substrates to the liver. There is also the possibility of other, as yet unidentified, factors that may contribute to the increase in glucose output observed during intense exercise. Indeed, during sleep, changes in glucose production can occur despite no detectable change in glucoregulatory hormones.[29] Furthermore, it cannot be excluded that hepatic neural activation may be more important during exercise at higher absolute or relative intensities than that employed in this study.

In the present study the exercise-induced increase in plasma glucose was abolished with combined α- and β-adrenergic blockade. In light of no significant effects on glucose output, the blunting of the hyperglycaemic response during exercise in BLK was due to the higher peripheral glucose uptake. The exact mechanism/s underlying the enhanced peripheral glucose uptake could not be determined in this study, but since epinephrine has been shown to decrease glucose uptake,[6] it is perhaps not surprising that adrenergic blockade has the opposite effect. It is possible that this is mediated via direct effects on sarcolemmal glucose transport[30,31] and/or intracellular metabolism,[32] or by alterations in muscle glycogen utilization and plasma FFA availability, although we are unable to discriminate between the potential mechanisms in the present study. It is also likely that the higher plasma insulin levels in BLK enhanced skeletal muscle glucose uptake during exercise[33] and perhaps by other insulin-responsive tissues. Finally, it cannot be ruled out that blockade of adrenoreceptors on vascular smooth muscle enhanced blood flow and glucose delivery to

skeletal muscle and other tissues, thereby contributing to an increase in glucose uptake, although such an effect may have been offset slightly by the lower plasma glucose levels.

In summary, the findings from this study demonstrate that combined α- and β-adrenergic blockade abolishes the marked increase in plasma glucose levels during intense exercise as a result of enhanced peripheral glucose uptake, with no significant change in glucose production. The effect of adrenergic blockade on glucose kinetics could be mediated by direct effects or indirectly through changes in lipid substrates and/or counter-regulatory hormones.

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