Glucose infusion partially attenuates glucose production and increases uptake during intense exercise

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Manzon, Anthony, Simon J. Fisher, José A. Morais, Lorraine Lipscombe, Marie-Claude Guimond, Sharon J. Nessim, Ronald J. Sigal, Jeffrey B. Halter, Mladen Vranic, and Errol B. MarliSS. J. Appl. Physiol. 85(2): 511–524, 1998.—Glucose infusion can prevent the increase in glucose production (Ra) and increase glucose uptake (Rd) during exercise of moderate intensity. We postulated that 1) because in postabsorptive intense exercise (>80% maximal O2 uptake) the eightfold increase in Ra may be mediated by catecholamines rather than by glucagon and insulin, exogenous glucose infusion would not prevent the Ra increment, and 2) such infusion would cause greater Rd. Fit young men were exercised at >85% maximal O2 uptake for 14 min in the postabsorptive state (controls [Con], n = 12) or at minute 210 of a 285-min glucose infusion. In seven subjects, the infusion was constant (C1; 4 mg·kg-1·min-1) and in seven subjects it was varied (VI) to mimic the exercise Rα response in Con. Although glucose suppressed Rα to zero (with glycemia ∼ 6 mM and insulin ∼ 150 PM), an endogenous Rα response to exercise occurred, to peak increments two-thirds those in Con, in both CI and VI. Glucagon was unchanged, and very small increases in the glucagon-to-insulin ratio occurred in all three groups. Catecholamine responses were similar in all three groups, and correlation coefficients of Rα with plasma norepinephrine and epinephrine were significant in all. In all CI and VI, Rα at rest was 2 × Con, increased earlier in exercise, and was higher for the 1 h of recovery with glucose infusion. Thus the Rα response was only partly attenuated, and the catecholamines are likely to be the regulators. This suggests that an acute endogenous Rα rise is possible even in the postprandial state. Furthermore, the fact that more circulating glucose is used by muscle during exercise and early recovery suggests that muscle glycogen is spared.

norepinephrine; epinephrine; glucose turnover; insulin; glucagon

The relative importance of the multiple regulators of energy-fuel homeostasis during exercise varies with the intensity of exercise. One view regarding glucose regulation holds that, at lower exercise intensities, signals generated from the exercising muscle are translated into changes in secretion of insulin and glucagon (3, 12, 31) that result in increases in the glucagon-to-insulin ratio that favor increased hepatic glucose production (Rα). However, in intense exercise (>80% of maximal O2 uptake [V̇O2max]) in human subjects, the changes in insulin and glucagon are likely of insufficient magnitude to be responsible for the up to eightfold increase in Rα that occurs (21, 22–24, 28, 33, 34). Indeed, plasma insulin either remains constant or declines slightly, and glucagon increases less than twofold (21, 23, 24, 28, 33, 34). Portal vein measurement of both hormones would be required to prove this contention.

Nonetheless, a signal for rapid hepatic glycogenolysis has been invoked, which anticipates the need for the marked increase in Rα. In contrast to the “feedback” signal at lower exercise intensities, this has been suggested to be “feedforward” (16, 40). The precise nature of this signal(s) is not known. Irrespective of the site of origin of the signal, we (21–24, 28, 33) and other investigators (5, 16) have proposed that it is the marked catecholamine response during intense exercise that is the prime regulator of Rα. Circulating norepinephrine (NE) and epinephrine (Epi) concentrations both increase at least 15-fold (16, 21, 23, 24, 28, 32). A regulatory role is suggested by the highly significant correlations between the individual catecholamines and corresponding values of Rα during >85% VO2max exercise (16, 21–24, 28, 33). Such Rα responses and correlations with the catecholamine responses have been shown to persist, despite prevention of the insulin and glucagon changes, during “islet cell clamp” experiments with octreotide (synthetic somatostatin) and exogenous hormone infusions (33). Indeed, such responses occurred even with increases in plasma insulin during exercise (33). This is consistent with but does not prove the cause-effect relationship postulated. The same can be stated regarding the Rα responses during experiments with either β-adrenergic blockade with propranolol (34) or α-blockade with phentolamine (32).

We hypothesized that if the proposed catecholamine mechanism is necessary for the Rα response to intense exercise and independent of a glucose feedback mechanism, such a response should occur even if preexercise endogenous Rα were completely suppressed by continuous intravenous glucose infusion and its accompanying hyperinsulinemia. Indeed, it should occur even if an amount of glucose equivalent to the normal Rα increment were infused exogenously during exercise, in addition to the constant infusion begun before exercise. This would be a further contrast to the feedback mechanism for glucose regulation in lower intensity exercise in which attenuation or complete prevention of the endogenous Rα increment has been shown (3, 13, 14, 36, 40). The attenuation of the Rα increment was shown to
be due to insulin and glucagon in experiments in which the hormone responses were not perturbed, as well as in somatostatin studies in which levels were adjusted by endogenous hormone replacement. The glucose uptake (Rₙ) responses in all of these experiments showed greater dependence of muscle on glucose as substrate, presumably because of the combination of higher insulin levels and their effects on free fatty acid (FFA) release from adipose tissue.

We therefore studied three groups of healthy, fit young subjects at >85% Vₒ₂max: one postsabsorptive group without glucose infusion (control or Con), the second group after 210 min of constant 4 mg·kg⁻¹·min⁻¹ glucose infusion (continued during exercise and for 60 min of recovery), and the third group with the same continuous infusion but with a stepwise increment during exercise and decrement early postexercise (variable) that mimicked the endogenous Rₙ response of the control subjects. Results of these studies have been presented in part in abstract form (19).

METHODS

Participants in the study were 26 lean, weight-stable, fit men (ages 18–36 yr), one of whom was studied twice. All engaged in regular activity, such as running, cycling, soccer, and/or rowing, combined in some subjects with resistance training. Anthropometric and exercise data are presented in Table 1. Screening before the study included medical history, physical examination, complete blood count, blood biochemistry, urinalysis, hepatitis B and HIV serology, electrocardiogram, and chest roentgenogram to exclude any significant diseases. Subjects were informed of the purpose of the study and of the possible risks, and subjects gave signed consent as prescribed by the institutional human ethics committee. To minimize amounts of blood taken and radioactivity administered to each person, we studied different subjects in each of the three protocols.

Vₒ₂max was determined with breath-by-breath analysis during an incremental workload test (starting at 0 and increasing by 20 W/min) with the subject sitting on an electrically braked cycle ergometer (Collins Metabolic Cart, Collins, Braintree, MA). O₂ uptake (Vₒ₂; STPD), CO₂ output (STPD), ventilation (in l/min, BTPS), and respiratory exchange ratio were calculated and recorded at 30-s intervals. Heart rate was displayed electrocardiographically. Exhaustion was defined by the subject at the time at which he was unable to continue cycling; this point was uniformly reported as being due to leg muscle fatigue. On a separate occasion at least 2 days after the Vₒ₂max test, each subject underwent a test without blood sampling at 50% for 30 s, followed by ~80% of the previously established maximal workload. This test was done to familiarize the subjects with the workload protocol, to assure a uniform 12- to 15-min duration, and to assure that subjects would reach ~85% Vₒ₂max within 6–7 min. The workloads that achieved these end points were then used for the subsequent study involving glucose turnover.

Three different protocols for studies of glucose turnover were employed in subject groups that were well matched (Table 1). In the first Con experiment, the subjects received no exogenous glucose. In the second, the constant-infusion (CI) group, 10% dextrose in water was infused (4 mg·kg⁻¹·min⁻¹ iv) via an infusion pump (IVAC, San Diego, CA) beginning at 210 min before and during exercise and for 60 min of recovery. The third group of subjects received the same rate of infusion for the same interval, except that additional stepwise increments of 50% dextrose in water (by using a syringe infusion pump; Harvard Apparatus, South Natick, MA) were given during exercise and with stepwise decrements to reach the constant rate of 4 mg·kg⁻¹·min⁻¹ at 16 min of recovery. This variable infusion (VI) resulted in rates of glucose infusion that approximated the pattern of response of endogenous glucose appearance (Rₙ) in the Con subjects (Fig. 1A).

The studies with glucose turnover measurements began between 0800 and 0900; subjects were in the fasting state for 12 h overnight and had not performed any significant exercise in the preceding 24 h. A 20-gauge Cathlon IV intravenous cannula (Critikon Canada, Markham, ON, Canada) was inserted into one antecubital vein for sampling, and another was inserted into a forearm vein of the other arm for infusion. After 20–30 min, a preinfusion blood sample was drawn. A priming bolus of 22 µCi of HPLC-purified [3-3H]glucose tracer (DuPont-NEN, Billerica, MA) was followed by a constant infusion of 0.22 µCi/min in 0.9% saline for 150 min in Con and 120 min in glucose-infused subjects before exercise and continued for 120 min after exercise. Blood was sampled at seven 10-min intervals before time 0 (beginning of exercise) to assure a steady state of plasma [3H]-glucose specific activity (sp act). Glucose sp act was adequately maintained by increasing and decreasing the tracer infusion incrementally during the exercise and the immediate recovery period only, then returned to the preexercise rate until 120 min of recovery. The goal was to introduce labeled glucose into the circulation at a rate proportional to endogenous Rₙ, thereby attenuating changes in [3H]glucose sp act to <2% during the rapid changes in glucose kinetics (23, 24, 28, 31, 33–35). This assures the validity of glucose turnover calculations (10). In the 12 Con subjects, the tracer infusion was increased 7.5-fold (in five 3-min steps: 2, 2.75, 4, 5.4, and 7.5× the initial rate) followed by the same stepwise decreases beginning at 3 min of recovery. In the second group (7 subjects who received the CI glucose), the tracer infusion was increased by fourfold in three 4-min steps (2, 2.75, and 4× the initial rate), followed by similar decrements in recovery. In the third group (7 VI subjects), the tracer infusion was increased 5.4-fold in four 3-min steps (2, 2.75, 4, and 5.4× the initial rate), followed by similar decrements beginning at 4 min of recovery. Blood samples were drawn at 2-min intervals during exercise and at exhaustion, also defined as time 0 of recovery, such that samples were drawn at 2, 4, 6, 8, 10, 15, 20, 30, 40, 50, 60, 70,
80, 100, and 120 min thereafter for measurements of glucose and radioactivity.

Samples for measurements of glucose turnover were placed into tubes containing heparin and sodium fluoride and were processed as described previously (23). Heparinized plasma was collected with aprotinin (Trasylol; 10,000 kallikrein inhibitor U/ml; FBA, New York, NY) in a volume 1/10 that of the added blood for subsequent immunoreactive insulin (IRI), immunoreactive glucagon (IRG), and FFA assays. For catecholamine measurements, blood was added to EGTA- and reduced glutathione-containing tubes, and the plasma was frozen at -270°C until assay. One aliquot of whole blood was immediately deproteinized in an equal volume of cold 10% (wt/vol) perchloric acid, kept on ice until centrifuged at 4°C, and then frozen at -20°C for later lactate and pyruvate assays.

Glucose was measured by the glucose oxidase method with the use of a Glucose Analyzer II (Beckman, Fullerton, CA). Blood lactate and pyruvate were measured by enzymatic microfluorometric methods previously detailed (33). Plasma insulin was determined by RIA, using an anti-beef insulin antiserum, purified human insulin standard (27.3 µU/ng), 125I-labeled human insulin (Linco, St. Louis, MO), and dextrancoated charcoal separation. Pancreatic IRG was measured on plasma by double-antibody RIA (Linco). FFAs were estimated by the method of Ho (12a) as used previously (24, 28). All assays that were performed on aprotinin-containing plasma were corrected for the plasma dilution introduced by the concurrently measured hematocrit. Plasma NE and Epi concentrations were measured by using a radioenzymatic technique (sensitivity <50 pM) (9). The intra- and interassay coefficients of variation for all assays were <10%; for the enzymatic assays, they were <5%. R₈ and R₉ were calculated from the variable isotope infusion protocols according to the one-compartment model (29), with data systematically smoothed by using the optimized optimal segments program (4). Glucose metabolic clearance rate (MCR) was calculated for each time point by dividing R₉ by the plasma glucose concentration.

Baseline characteristics were analyzed by using one-way ANOVA. Plasma glucose, sp act, glucose turnover, MCR, lactate, pyruvate, FFA, and hormone results were analyzed.
by ANOVA for repeated measures. Intergroup differences found to be significant (taken at \( P < 0.05 \)) were subsequently analyzed by the Student-Newman-Keuls t-test. Paired Student's t-tests were used for analysis of some differences within the same group over time. Linear correlations were calculated by using the Pearson correlation coefficient. Individual correlation coefficients were calculated for each individual by using all 13 data points at which catecholamines, glucagon, and insulin were measured. This correlation coefficient was then treated as a continuous variable for which means and SE were calculated, and intergroup differences were assessed using one-way ANOVA, ANOVA for repeated measures, and the Student-Newman-Keuls tests. The SAS-STAT software package (SAS Institute, Cary, NC), SPSS-Windows release 6.0 software package (SPSS, Chicago, IL), Microsoft Excel 5.0 Analysis ToolPak (GreyMatter International, Cambridge, MA), and Primer Biostats (McGraw-Hill, New York, NY) were used. Data are presented as means ± SE.

RESULTS

No untoward effects were experienced during or after any of the infusion protocols or exercise tests. There were no statistically significant differences in anthropometric measures, \( \dot{V}O_2 \text{max} \), workload, or exercise duration data (Table 1). The plasma glucose sp act levels were at steady state in all three groups before exercise, rose slightly during exercise, and returned to baseline in the recovery period in CI and VI, but sp act declined only transiently in Con subjects immediately after exercise. None of the exercise-related changes in sp act within subject groups exceeded 25% (Fig. 1B).

The principal findings in the CI and VI subjects were as follows. 1) The \( R_a \) response was still rapid and marked, although \( R_a \) was attenuated compared with the response in Con subjects. 2) \( R_d \) was higher before
exercise, rose earlier in exercise (although to a similar peak value), and remained higher in recovery. 3) The catecholamine responses were not statistically significantly different compared with those in Con subjects. 4) There were some differences between CI and VI subjects’ responses, especially plasma glucose and insulin responses.

Plasma glucose concentrations in CI and VI were significantly higher than in Con subjects during the infusion in the baseline (preexercise) period, but the concentrations were not different between the two infused groups (Fig. 2A). There was a significant trend downward in mean glucose in CI and VI before exercise. Mean values at time 0 of exercise were 4.98 ± 0.41, 5.18 ± 0.24, and 5.91 ± 0.17 mM in Con, CI, and VI groups, respectively. The mean value in the VI group was significantly greater (P = 0.002) than in Con and CI subjects. In both Con and VI, mean values increased significantly (P = 0.002) during exercise, to 6.80 ± 1.06 and 7.13 ± 0.41 mM at exhaustion, respectively. Surprisingly, values in CI decreased progressively to 4.24 ± 0.27 mM at 14 min of exercise (P < 0.05 vs. time0), then increased in the first 4 min of recovery to values not different from those at time0, and remained unchanged until 60 min of recovery. In Con and VI subjects, plasma glucose concentrations remained elevated from exhaustion to 30 min of recovery, returning to baseline values by 60 min of recovery. During this period of recovery, mean glucose values in Con were not different from those in VI, but both were significantly higher (P <
0.001) than in CI subjects. In both CI and VI subjects, glucose decreased to levels similar to or somewhat lower than in Con subjects on cessation of the exogenous infusion at 60 min of recovery.

The total $R_a$ measures the sum of exogenous glucose infusion plus endogenous glucose $R_a$. During the baseline period, total $R_a$ was almost identical, and was constant in the two infused groups, and, as expected, was significantly higher ($P < 0.001$) than in Con subjects (in mg·kg$^{-1}$·min$^{-1}$: 2.08 ± 0.06 in Con, 3.89 ± 0.07 in CI, and 3.81 ± 0.23 before exercise). Total $R_a$ rose rapidly in all three groups to values of 14.40 ± 1.22, 11.79 ± 0.45, and 18.91 ± 0.52 mg·kg$^{-1}$·min$^{-1}$ in Con, CI, and VI, respectively, at exhaustion. At exhaustion, total $R_a$ in VI was significantly higher than in Con and CI ($P < 0.05$), but the values were not different in the latter two groups. Total $R_a$ decreased rapidly in early recovery, then decreased progressively toward the respective baseline values of each of the groups between 45 and 75 min of recovery. When the exogenous infusion ceased, $R_a$ returned to the levels found in Con subjects.

Endogenous glucose production (total $R_a$ minus the exogenous infusion rates) was constant at baseline in Con subjects, their values representing total $R_a$ as given above. In the infused subjects, endogenous $R_a$ was suppressed to values not different from zero during the last 60 min of the baseline period. The progressive,

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Fig. 4. Plasma immunoreactive insulin (IRI; A), immunoreactive glucose (IRG; B), and IRG-to-IRI molar ratio (C) during baseline, intense exercise, and recovery periods. Values left of the −210-min time point are from before glucose infusion (open bar at bottom). Data are presented as in Fig. 1B.
slight decline accounts for the decline in plasma glucose (Fig. 2A). Just before exercise, $R_a$ values were $-0.02 \pm 0.07$ and $-0.01 \pm 0.12 \text{ mg·kg}^{-1}·\text{min}^{-1}$ in CI and VI, respectively. The increments over values before exercise, presented in Fig. 2B, best quantify the effect of exercise on endogenous $R_a$. Rates at time $-10$ and time $0$ min before exercise were set at $0$ for all three groups. All other values shown are differences from these. In Con, values of $0$ thus correspond to absolute rates of $2 \text{ mg·kg}^{-1}·\text{min}^{-1}$, because all $R_a$ was endogenous. Increments are extremely rapid, to peak values of $12.09 \pm 1.24$, $7.88 \pm 0.44$, and $7.31 \pm 0.48 \text{ mg·kg}^{-1}·\text{min}^{-1}$ in Con, CI, and VI, respectively ($P < 0.005$ in Con vs. CI and VI). Repeated-measures ANOVA showed the overall response in Con to be significantly higher over the exercise period ($P = 0.008$), although it is mainly the later exercise time points that were responsible for this difference (Fig. 2B). Despite the greater rate of exogenous glucose infusion in VI subjects, their responses were not different from those in CI subjects. Early in recovery, the increments in endogenous $R_a$ declined rapidly and by $4$ min were no longer greater in Con, but values reached baseline levels somewhat later in the infused subjects. When glucose infusion ceased, values for endogenous $R_a$ in CI and VI subjects were no longer suppressed, and means increased to $2.35$ to $2.70 \text{ mg·kg}^{-1}·\text{min}^{-1}$, values that were not different from preexercise endogenous $R_a$ in Con.

Glucose $R_a$ remained constant in all groups during the baseline period before exercise (Fig. 3A). Both infused groups maintained twice the rates as in Con subjects, levels just before exercise being $1.77 \pm 0.08$, $4.85 \pm 0.30$, and $4.33 \pm 0.35 \text{ mg·kg}^{-1}·\text{min}^{-1}$ in Con, CI, and VI respectively ($P < 0.001$). In both CI and VI, $R_d$ increased at about the same rates as in Con; therefore, the rates remained higher throughout the exercise period. At the point when subjects reached exhaustion, these values had risen markedly to $8.28 \pm 0.63$, $10.05 \pm 0.45$, and $11.23 \pm 0.83 \text{ mg·kg}^{-1}·\text{min}^{-1}$ in Con, CI, and VI, respectively ($P = 0.014$), followed by a gradual decrease during recovery. $R_d$ remained significantly greater in VI than CI for the first $40$ min of recovery ($P < 0.001$). In both VI and CI, $R_d$ remained higher than in Con ($P < 0.001$) until after the glucose infusion was stopped. Thus more circulating glucose was taken up during exercise and for the duration of the recovery period during which exogenous glucose was being infused. Correspondingly, because $R_d$ was lowest throughout the experiment in Con subjects, they demonstrated the lowest MCR (Fig. 3B). Although the $R_d$ was higher in CI than in the Con subjects, because plasma glucose declined with exercise and remained lower, the MCR increased most in CI subjects during exercise and for the first $10$ min of recovery. Exercise MCR was intermediate in the VI subjects (partly because of their higher plasma glucose concentrations). However, from $10$ min of recovery onward, the CI and VI subjects had identical values that remained higher than values in Con subjects even at $60$ min after cessation of the glucose infusion ($P < 0.05$).

The suppressed endogenous $R_a$ and augmented $R_d$ and MCR before exercise in the CI and VI subjects were associated with a sustained near doubling of plasma insulin (IRI) levels compared with the Con subjects ($P = 0.0003$) during the baseline period (Fig. 4A). In all three groups of subjects, exercise induced a significant decrease in IRI, although values were lowest in Con ($P = 0.023$). In all groups, there was a marked, immediate increase during recovery; the highest IRI levels were in the VI subjects ($P = 0.01$). In Con, the increase was sustained for the duration of the postexercise hyperglycemia, returning to preexercise concentrations.
at 60 min of recovery. In marked contrast, the IRI in CI subjects followed the different glycemic response, decreasing again during early recovery and remaining lower than in Con until 40 min recovery. In keeping with the greater recovery hyperglycemia in VI subjects, IRI remained markedly elevated for the first 20 min of recovery and then declined progressively, only reaching values not different from Con and CI subjects at 120 min of recovery.

Figure 4B displays the IRG responses. There was a significant glucose infusion-related suppression of IRG in both CI and VI compared with their own levels at -210 min during the baseline period (P < 0.05). Exercise was associated with no significant change in Con, with a small nonsignificant trend toward an increase in CI and VI subjects, and with return to preexercise levels in recovery. Thus the glucagon-to-insulin ratio was significantly lower (P = 0.005) during the baseline period in CI and VI than in Con subjects (Fig. 4C). The trend toward increase during exercise in all groups was mainly because of the decrease in IRI (Fig. 4A), and the ratio in CI and VI remained below that in Con (P = 0.012). The subsequent marked decrease in early recovery, the return to baseline conditions at 60 min, and the return to identical values at 120 min of recovery were all caused more by the IRI than by the IRG changes. There were significant intergroup differences in recovery.

The plasma catecholamine concentrations are shown in Fig. 5. NE values at time 0 were not different among

Fig. 5. Plasma norepinephrine (A) and epinephrine (B) during baseline, intense exercise, and recovery periods. Values left of -210-min time point are from before glucose infusion (open bar at bottom). Data are presented as in Fig. 1B.
groups. The responses of CI and VI subjects during and after exercise were not significantly different from those of Con subjects (Fig. 5A). In all groups, a very rapid and extremely large increment occurred, from a mean of \( \sim 2.7 \) nM to mean peak values at exhaustion of from 24 to 40 nM, returning by 20 min of recovery to baseline levels. Although there appears to be a lesser mean response in CI subjects (an 8.3-fold increment), this was not statistically significant either by ANOVA or unpaired t-analysis at any time point. When compared with time 0, the increases in Con were 13.7- and 15.3-fold in VI. The considerable interindividual variability, especially in the peak levels achieved, accounts for this result. The same comments apply to the plasma Epi concentrations and responses (Fig. 5B). An extremely large and rapid response, not different among groups, that rapidly returned to baseline levels, was observed. The CI subjects’ peak levels increased less than in the other two groups, by 5.8-fold, compared with 12.0-fold in VI and 13.1-fold in Con. The mean correlation coefficients (r values calculated individually for each subject) of NE and Epi with endogenous Ra are summarized in Table 2 for each protocol. In all cases, there was a significant relationship of the catecholamines to Ra.

Despite the considerable differences in Ra and MCR, there were no differences in the baseline levels or the responses of blood lactate and pyruvate to exercise (Fig. 6, A and B). At the point of exhaustion, the marked increment in lactate at exhaustion (to 11.6 ± 1.0, 10.5 ± 1.1, and 12.7 ± 0.9 mM in Con, CI, and VI, respectively) and in pyruvate (to 256 ± 12, 241 ± 16, and 223 ± 14 µM in Con, CI, and VI, respectively) attests to the intensity of the exercise. The decline in blood lactate in recovery followed a pattern similar to that of plasma glucose in Con and VI (and the responses of the two groups were identical). The response of the CI subjects was initially more rapid. Peak pyruvate concentrations occurred at 4- to 10-min recovery in all groups (393 ± 23, 367 ± 32, and 404 ± 43 µM in Con, CI, and VI, respectively) and also declined more rapidly in CI subjects. Peak lactate-to-pyruvate ratios occurred at exhaustion (46 ± 4, 43 ± 4, and 58 ± 5 in Con, CI, and VI, respectively; \( P < 0.05 \) Con and CI vs. VI).

Plasma FFA levels and responses were markedly influenced by the glucose infusion (Fig. 6C). The preexercise concentrations were suppressed to 39% in CI and 33% in VI of those in Con subjects (\( P < 0.05 \)). In the CI and IV groups, there was no response to exercise, a small and transient increment in early recovery, and then, after glucose infusion was stopped, there was a rebound at 120 min of recovery. The Con subjects showed a dramatic decline in FFA during exercise (\( P < 0.05 \)), partial return after exhaustion, a second decline, to levels like those of the CI and VI subjects by 60 min of recovery, and then a similar rebound at 120 min.

**DISCUSSION**

The Con subjects demonstrated the well-recognized metabolic responses during and after intense exercise (5, 16, 21–24, 28, 33–35). In our Con subjects, a trend upward in plasma glucose was followed by a marked increment at exhaustion (first shown in Refs. 11 and 30) that lasted up to 60 min of recovery and was associated with a corresponding pattern of hyperinsulinemic response. The rapidity and magnitude of both the increase and decrease in Rₐ are perhaps the largest observed in physiological glucoregulation and are highly correlated with the catecholamine responses. The glucagon levels did not change, and the rise in glucagon-to-insulin ratio was entirely caused by the decrease in insulin. This change was not of sufficient magnitude to have caused, although it probably contributed to, the Rₐ rise.

The principal aim of the present study was to test whether the mechanisms that increase Rₐ in intense physical exercise would be able to overcome the prior and sustained suppression by exogenous glucose infusion and its accompanying hyperinsulinemia. The glucose infusion rate of 4 mg·kg⁻¹·min⁻¹ was chosen because this rate can completely suppress endogenous Rₐ (8, 37). This was achieved in the present experiment: the metabolic “set” of the infused subjects was one of mild hyperglycemia, hyperinsulinemia, suppressed glucagon, completely suppressed endogenous Rₐ, and Rₐ greater than in subjects who were not infused. This is what would be expected in the fed state after a meal, i.e., during absorption of ingested carbohydrate. Nevertheless, a rapid and marked increase in Rₐ occurred with the onset of exercise. The magnitude of the peak increment over baseline was less than in the postabsorptive subjects; mean values in CI were 65% of values in Con subjects. Nonetheless, this is still an extremely large increment, four times that typically found in moderate-intensity exercise (14, 31, 37). Furthermore, VI subjects, who received exogenously all the glucose that they would ordinarily have produced endogenously and maintained even higher insulin levels during exercise, produced as much endogenous glucose as the CI subjects, with peak increment 60% that found in Con. This suggests that, above some rate of exogenous glucose infusion that is sufficient to attenuate the Rₐ rise, greater rates cannot suppress the Rₐ response further.

In both CI and VI subjects, the Rₐ response was rapid and the curves of the incremental responses were superimposable from 6 min of exercise onward. We are unaware that exogenous glucose effects on Rₐ have

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Table 2. Correlation between endogenous glucose production rate and plasma catecholamines

<table>
<thead>
<tr>
<th>Group</th>
<th>Norepinehrone r</th>
<th>P</th>
<th>Epinephrine r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.94</td>
<td>&lt;0.01</td>
<td>0.88</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Constant infusion</td>
<td>0.75</td>
<td>&lt;0.03</td>
<td>0.73</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Variable infusion</td>
<td>0.76</td>
<td>&lt;0.04</td>
<td>0.69</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Correlation coefficients (r) were calculated for each subject over the period of increases and decreases in glucose production rate and catecholamines associated with exercise and recovery periods. The r value presented is mean for each subject; P value is that of subject with highest value (least significant) in each group.
been tested previously in human subjects in this manner and with exercise of this intensity. The failure of glucose infusion to fully suppress endogenous Ra in exercise of greater than moderate intensity has been shown previously only in rats (40). The pertinence of such results in rats could not have been extrapolated to humans because there are many important protocol and species differences between the experiments. In the rat study (40), the relative exercise intensity was likely less, the sources of circulating glucose included the gut, and glucose infusion began with exercise.

In contrast with both our findings in the present study and findings in rats (40), exogenous glucose can totally suppress the Ra increment of moderate exercise in human and animal experiments (3, 13, 14, 36). In three of these experiments (3, 13, 36), the glucose infusion was started at the same time as the exercise, rather than before exercise, so it was the increment that was affected rather than the total Ra response.

By our use of radiolabeling with tritium on the third carbon of glucose, we may have underestimated the increment in endogenous glucose production in the glucose-infused subjects. This would mean that the attenuation of the response, compared with that of the Con subjects, may have been even less than presented in Fig. 2B, or indeed that there was no attenuation.

Fig. 6. Blood lactate (A), pyruvate (B), and plasma free fatty acids (C) during baseline, intense exercise, and recovery periods. Values left of -210-min time point are from before glucose infusion (open bar at bottom). Data are presented as in Fig. 1B.
Because this label may be incorporated into hepatic glycogen, the release of some label from glycogen formed during the preexercise period could not be accounted for in our $R_a$ calculations. However, this may be a minor factor, as suggested by the studies by Cherrington’s group in dogs [see Adkins-Marshall et al. (1) and Pagliassotti et al. (26)]. Their studies showed the principal determinant of rates of hepatic glycogen accumulation to be the portoarterial glucose gradient. Because we infused glucose peripherally and the rise in plasma glucose concentration was small, the rate of accumulation of labeled glycogen is likely to have been correspondingly small. Our main conclusion, that the mechanisms for stimulation of a rapid and very large $R_a$ response in intense exercise are not suppressed by provision of exogenous glucose sufficient to completely inhibit $R_a$, is strengthened by this aspect of our experimental design. In contrast, in the rat study cited (40), the facts that glucose was entering via the portal vein during baseline infusion of the same label and that the hyperglycemia was greater would have caused a much larger underestimation of the increment in endogenous $R_a$.

IRI remained elevated in both CI and VI subjects compared with Con subjects throughout exercise, and the minimal increase in IRG was to levels not different from those in Con. Thus the IRG-to-IRI ratio remained below that in Con subjects. Because we have argued previously (21, 22, 28, 33–35) that the IRG and IRG-to-IRI ratio responses in Con subjects were insufficient to cause the $R_a$ response, the lower preexercise levels and small responses in infused subjects suggest that other regulators were primarily responsible. The substantial catecholamine responses that were highly correlated to the endogenous $R_a$ (Table 2) support the possibility that these responses are the main mediators. It is noteworthy that the correlation coefficients during glucose infusion were less than those in Con subjects, but were not lower in CI than in VI subjects, despite the somewhat lesser peak plasma catecholamine levels reached in CI subjects. Indeed, the reason for the lower (although not statistically significant) responses of both catecholamines in CI subjects is not apparent. If the main determinants of the cardiovascular responses to the exercise were the catecholamines, similar responses to the same exercise protocol would be predicted, irrespective of the glucose infusions. Although the plasma glucose concentrations were lower in CI subjects, endogenous $R_a$ increased to the same extent in CI and VI subjects, the latter having higher plasma glucose concentrations. The only explanations that emerge from data available are that the higher insulin level was able to attenuate the response to comparable catecholamine stimulation or that the glucose infusion itself attenuated the response by some other mechanism.

The high circulating levels of NE achieved during intense exercise may include both NE spillover from sympathetic nerve terminals throughout the body as well as direct NE release from the adrenal medulla. However, what is most pertinent to $R_a$ may be the NE release from sympathetic nerve terminals in the liver. Concentrations of NE are considerably higher near activated nerve terminals than in plasma, and the liver is sympathetically innervated, so intrahepatic levels are likely to be even higher than those in plasma during intense exercise. Hepatic NE spillover has recently been shown to increase during heavy exercise in dogs (6). However, it has not yet been established in human...
subjects what the relative roles are of intrahepatic release vs. bloodborne catecholamines during intense exercise. The relative roles of NE and Epi have also not been established. The high levels of Epi predominantly reflect release from the adrenal medulla and likely have direct effects on the liver to enhance $R_d$ in intense exercise. There is an increase in Epi extraction by splanchnic tissue in dogs during heavy exercise (6). There is some disagreement as to the importance of hepatic innervation in rats (cited in Ref. 40) and dogs (39), although the possibility exists that species differences are responsible. The definition of the intensity of exercise in different species probably contributes, at least in part, to the disparities, e.g., $\sim 85\% V_{O2\max}$ exercise in rats (40) gives radically different magnitudes of metabolic responses than in human subjects at this level. Experiments in which $R_a$ responses were not attenuated in liver transplant recipients (17) or after coeliac ganglion blockade (15) were interpreted by the investigators as tending to disprove the hypothesis of catecholamine mediation. However, the blocked subjects (15) were exercised at $< 75\% V_{O2\max}$ and $R_a$ increased considerably less. Furthermore, in the subjects with liver transplant, the absolute level of exercise was considerably less than in intact subjects (68 vs. 123 W) and even these control subjects exercised at one-half the workload of our subjects (Table 1). In unfit subjects, the exercise intensity of even $>80\%$ of a very low $V_{O2\max}$ at such low workloads generated an $R_a$ increase that would not be expected to be dependent on catecholamine stimulation. In another study by the same group (18), sensory blockade by epidural anesthesia similarly had no effect on $R_a$ at $55\% V_{O2\max}$; unfortunately, this result was not tested at maximal exercise. Catecholamine responses were not affected at either level. If these responses can be extrapolated to high-intensity exercise, it would support the notion that the origin of the signal for increase in $R_a$ is in the central nervous system.

As would be predicted from the exogenous glucose infusion at a rate exceeding endogenous $R_a$ and from the consequent hyperinsulinemia, the $R_d$ and glucose MCR were greater before exercise in the CI and VI subjects than in the Con subjects. They remained greater during exercise, as well, reflecting the interaction of insulin-mediated and exercise-induced effects on increasing glucose disposal. Because $V_{O2}$ and carbon dioxide production responses (the latter not shown) were different between glucose-infused and noninfused subject groups, and because blood lactate and pyruvate responses were identical, the results imply that the total increment in the sums of bloodborne plus muscle glycogen-derived carbohydrate utilization was not different between groups.

Several investigators have shown enhanced utilization of exogenous oral glucose in human subjects during exercise; however, studies during intense exercise are lacking. The experimental paradigm has generally involved starting the glucose at or after onset of exercise (2, 25, 27). In the latter cases, the ability to generate an insulin response would have been affected by the concurrent $\alpha$-adrenergic inhibition of its secretion by the catecholamine responses to exercise. Furthermore, a controversy remains regarding methods of labeling the ingested glucose (25). The pertinence of such results to intense exercise is questionable, as any relative increase in $R_d$ would be contributed to by a decrease in FFA utilization in moderate-intensity exercise; this effect is not an issue in the muscles undergoing intense exercise. Others have explored glucose-insulin-exercise interactions by using the glucose clamp technique, again in exercise of lesser intensity. There is synergism between effects of exercise and insulin on $R_d$ and carbohydrate oxidation in this setting in human subjects (7, 38). In dogs, with an islet cell clamp to keep insulin constant at basal levels, exercise and increased plasma glucose concentration act synergistically on both glucose uptake and metabolism (41). These studies suggest that the combination of high glucose and insulin could, as was the case in the present study, facilitate glucose disposal. However, we cannot exclude another possibility, i.e., with the suppression of FFA levels and the fact that, despite the high $V_{O2}$ observed, some muscles were exercising at relatively lower intensities than were the legs, so that some part of the $R_d$ increment may have been in such other muscles rather than in the legs.

The responses of our subjects during the recovery period were informative. The decline in plasma glucose in CI subjects during exercise, then its return to a plateau not different from fasting glucose for the 60 min of recovery when the infusion was continued, was very different from the pattern of glucose response of the VI subjects. The total $R_a$ response was the same as in Con subjects, so the decline is explained by the higher $R_d$, which remained higher during much of the recovery period despite the lower IRI present until 40 min of recovery. Mean levels of lactate and pyruvate during recovery were also somewhat lower than in Con. The implication is that the sustained prior elevation of IRI was sufficient to have persisting effects on $R_d$ and possibly on the metabolic fate of the additional glucose taken up during recovery. In the CI subjects, the $R_d$ remained at the level of the exogenous infusion rate while endogenous $R_a$ returned to near zero; this effect occurred although these subjects had the lowest IRI during this period. MCR was enhanced considerably.

Because intense postprandial exercise might resemble this situation, with ongoing absorption of meal-derived glucose and increased insulinization, the increased glucose disposal in CI subjects during recovery is potentially relevant to this setting. This would be the first physiological situation in which hyperglycemia does not occur after intense exercise. However, it would be dependent on the prevailing rates of total $R_a$ and on the insulin levels achieved before exercise. We are presently exploring these factors, although, without labeling the meal, it will not be possible to ascertain whether $R_a$ is from exogenous or endogenous sources (25, 27). Our preliminary results suggest that the prediction of attenuated postexercise hyperglycemia
caused by increased $R_d$ is correct (20). If this is confirmed in other studies of postprandial intense exercise, the implication for persons with type I diabetes mellitus could be that they would not develop the greater than normal postexercise hyperglycemia we have shown previously (28, 35) if they were well insulinized and near normoglycemic levels before the exercise bout. This would apply only if total $R_g$ were not greater than found in the CI subjects.

In summary, this study has shown that the physiological stimulus of intense exercise induces a mechanism for rapid and marked stimulation of endogenous $R_a$ that can even overcome complete suppression of hepatic glucose output caused by exogenous glucose infusion and its attendant hyperinsulinemia. This is the case even when the whole $R_g$ increment, which would ordinarily occur in postabsorptive subjects, is provided exogenously. We suggest that the catecholamine response to the intense exercise is a likely candidate to mediate this endogenous $R_g$ response. With prior hyperglycemia and hyperinsulinemia, there is an enhanced $R_d$ before, during, and after intense exercise. This metabolic setting could provide a greater proportion of the muscle energy requirement from circulating glucose rather than from muscle glycogenolysis, and if so, would be glycogen sparing. Our findings in the presence of glucose infusion and increased insulin levels during intense exercise may have implications for the glucoregulatory responses in the postprandial period, both during and after intense exercise, in normal persons and those with diabetes mellitus. Such sparing of muscle glycogen would be particularly important to performance in brief, repetitive bouts of strenuous exercise, such as in sports like hockey or basketball.

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