Intense Exercise Has Unique Effects on Both Insulin Release and Its Roles in Glucoregulation

Implications for Diabetes

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In intense exercise (>80% $V_{O_{2max}}$), unlike at lesser intensities, glucose is the exclusive muscle fuel. It must be mobilized from muscle and liver glycogen in both the fed and fasted states. Therefore, regulation of glucose production (GP) and glucose utilization (GU) have to be different from exercise at <60% $V_{O_{2max}}$, in which it is established that the portal glucagon-to-insulin ratio causes the less than or equal to twofold increase in GP. GU is subject to complex regulation by insulin, plasma glucose, alternate substrates, other humoral factors, and muscle factors. At lower intensities, plasma glucose is constant during postabsorptive exercise and declines during postprandial exercise (and often in persons with diabetes). During such exercise, insulin secretion is inhibited by β-cell α-adrenergic receptor activation. In contrast, in intense exercise, GP rises seven- to eightfold and GU rises three- to fourfold; therefore, glycemia increases and plasma insulin decreases minimally, if at all. Indeed, even an increase in insulin during α-blockade or during a pancreatic clamp does not prevent this response, nor does pre-exercise hyperinsulinemia due to a prior meal or glucose infusion. At exhaustion, GU initially decreases more than GP, which leads to greater hyperglycemia, requiring a substantial rise in insulin for 40–60 min to restore pre-exercise levels. Absence of this response in type 1 diabetes leads to sustained hyperglycemia, and mimicking it by intravenous infusion restores the normal response. Compelling evidence supports the conclusion that the marked catecholamine responses to intense exercise are responsible for both the GP increment (that occurs even during glucose infusion and postprandially) and the restrained increase of GU. These responses are normal in persons with type 1 diabetes, who often report exercise-induced hyperglycemia, and in whom the clinical challenge is to reproduce the recovery period hyperinsulinemia. Intense exercise in type 2 diabetes requires additional study. *Diabetes* 51 (Suppl. 1):S271–S283, 2002

With increasing emphasis on fitness and competitive sports, more diabetic individuals are engaging in intense physical activity with greater frequency. It is essential, therefore, to appreciate the fundamental differences in the metabolic responses to intense exercise compared with moderate or mild exercise. Intense exercise [>80% of maximum oxygen consumption ($V_{O_{2max}}$) or even exceeding 100% $V_{O_{2max}}$ for brief periods] may occur in sports involving sprints or repeated short bouts with brief intervals of rest, such as baseball and hockey. This type of exercise is considered "anaerobic," despite the huge accompanying increment in V_{O_2}. Therefore it is almost entirely dependent on glucose and glycogen for energy, irrespective of the time interval from the last meal. Typically, increments in lactate production markedly exceed those in uptake, resulting in blood lactate concentrations increasing from 10- to 20-fold to >10 mmol/l. This indicates that the muscle is unable to oxidize all of the pyruvate generated by glycolysis via the tricarboxylic acid cycle. This necessitates greater availability of carbohydrate fuel in absolute terms (and relative to other fuels) because only a small fraction of the potential ATP from complete oxidation is available when lactate is the end product. Such carbohydrate is derived from both intramuscular glycogen and circulating glucose. Because fatty acid utilization is aerobic, a much smaller proportion of total fuel used is from this source. Indeed, typical respiratory quotients during intense exercise are at, or even above 1.0, reflecting primarily carbohydrate as the major fuel source for the whole organism. In contrast, in lower-intensity fasting exercise, early glucose use is progressively supplanted by fatty acids, and blood lactate rises much less. At these lower exercise levels, glucose is used as primary fuel only when lipolysis is inhibited by the insulin response to a recent meal or to ongoing carbohydrate ingestion during exercise.

Because insulin is the primary mediator of carbohydrate fuel fluxes under most circumstances, one might expect it to be involved in the responses during intense exercise. Were this the case, it would follow that diabetic persons, especially those with type 1 diabetes, would be unable to generate a normal metabolic response, as is well documented at lower intensity exercise. However, intense exercise is the exception to this primacy of insulin as regulator during exercise. The consensus from the few laboratories studying glucoregulation in this type of exer-

cise is that catecholamines are the primary regulators of glucose homeostasis during and for the first few minutes following a bout. A number of studies have suggested that insulin cannot be a key regulator, as the huge glucose production (GP) and glucose utilization (GU) responses occur whether plasma insulin remains unchanged, falls, or even rises. Furthermore, in subjects with type 1 diabetes, at both euglycemia and hyperglycemia, normal magnitudes of the increment and subsequent decrement of GP still occur.

Insulin does play the major role in the response during recovery. In normal subjects there is a small hyperglycemic response during exercise that increases substantially immediately at exhaustion and persists for up to 1 h. This is accompanied in recovery by hyperinsulinemia. It could be argued that a hyperglycemic-hyperinsulinemic response after glycogen-depleting exercise creates the appropriate milieu for at least partial restoration of muscle glycogen. The absence of this physiological hyperinsulinemia in the early recovery period in type 1 diabetes can result in greater or more sustained hyperglycemia. This is in marked contrast to the conventional notion, based on clinical observations and laboratory studies of exercise of lower intensity, that exercise is generally beneficial for glycemic control in both type 1 and type 2 diabetes [reviewed in (1)]. The therapeutic approaches that derive from the latter observations, i.e., to increase consumption of rapidly assimilated carbohydrate in the period around which exercise is performed and/or to adjust insulin doses downward in anticipation of exercise, could actually exacerbate the hyperglycemia that follows intense exercise. Though not quantified, many diabetic athletes report hyperglycemia following intense exercise (E.B.M., personal communication). As will be seen below, because of the nature of the normal insulin response and its effects, a simple or empirical strategy to normalize metabolic responses in persons with diabetes is more challenging to devise. Indeed, most of the research to date has involved exercising in the postabsorptive state, yet most exercise is not performed in this state. Therefore, we devised studies to determine responses at other times in the feeding-fasting cycle in normal subjects, to provide further insights into mechanisms and eventual therapeutic strategies.

We will review the effects of intense exercise on insulin levels as well as its metabolic effects in nondiabetic subjects. Because catecholamines play a pivotal glucoregulatory role during intense exercise, their effects on insulin secretion and glucoregulatory responses have been studied during α- or β-adrenergic blockade and during infusions of epinephrine (EPI) and norepinephrine (NE) to mimic endogenous plasma concentrations. The effects of intense exercise on insulin disposal could be inferred from levels during a "pancreatic clamp" and during constant-rate insulin infusions in type 1 diabetes. The effects of "feeding" and suppression of GP by its insulin response were studied during glucose infusions and in the postprandial state. Glucoregulatory defects were demonstrated in type 1 diabetic subjects exposed to basal insulin infusion. Thus, the two main questions regarding insulin we address are: *1*) What factors modify its secretion? and *2*) What are the effects of insulin secretion during and especially after intense exercise?

Glucoregulatory responses to moderate exercise

Moderate postabsorptive exercise is an extraordinary example of euglycemic homeostasis (Fig. 1*A*). There is a precise match between the increases in GU and GP. This is considered to be feedback-regulated by signals associated with the increased demand by the exercising muscles, causing responses that increase GP to match GU. Insulin secretion is inhibited to below fasting levels (Fig. 1*B*) by α-adrenergic receptor activation (2,3), both via the sympathetic innervation of the islets and by circulating catecholamines (Figs. 1*C,D*). This decrease of insulin secretion is important because it increases GP by the liver by sensitizing it to glucagon (4–6). It is established that the decreases in insulin and unchanged or increased glucagon account for the corresponding increases in GP (7,8) (Figs. 1*B* and 2*A*). Thus, the ratio of glucagon to insulin is the main regulator of GP during moderate exercise (5,9) (Fig. 2*B*). Catecholamines play a role in increasing GP, presumably through gluconeogenesis, only during prolonged exercise >2 h duration (10–12). Their increases during 40 min of moderate exercise (Fig. 1*C* and *D*) are modest and predicted to have small GP effects based on results in animal studies. The increment of GU (Fig. 2*D*) is precisely adapted to the increment of GP (Fig. 2*C*). The signal(s) coordinating these liver and muscle responses, and whether insulin plays any role, remain unknown. What has been known for many years is that muscle GU increases despite decreased insulin, because exercise causes translocation of GLUT4 glucose transporters from a different pool than insulin (13,14), and the exercise-induced signaling of GU is independent of insulin signaling (15). Also, increased peripheral blood flow augments total insulin delivery to muscle and thus compensates at least in part for the decreased plasma insulin concentrations. This also explains why the insulin and exercise effects are additive (16). The effects of both insulin and exercise counteract the effect of catecholamines, which under most conditions inhibit muscle GU.

The importance of insulin in moderate exercise can be best illustrated in type 1 diabetes (4,17,18). GP and GU are well balanced in experiments in which basal insulin is infused intravenously at a constant rate appropriate to maintain euglycemia at rest. Under these conditions, plasma insulin does not decrease during exercise, but its relationship to portal glucagon levels is such as to cause increased GP by the liver. However, in severe insulin deficiency the increments in GP with exercise may exceed those in GU and lead to further hyperglycemia. In contrast, in the usual treatment of type 1 diabetes, hyperinsulinemia may ensue because exercise can increase insulin mobilization from its subcutaneous depot, particularly if the injection site is in an exercised region. This results in falling glucose levels that may reach the hypoglycemic range, depending on the pre-exercise concentration, because the rise in insulin blocks the effect of glucagon on liver GP and concurrently amplifies GU even more than that required for the exercise. In contrast, we will describe how the insulin concentration perfusing the liver during intense exercise is of minor importance. We will present data to show that this is because catecholamines, rather than the glucagon/insulin interaction, are the main regula-
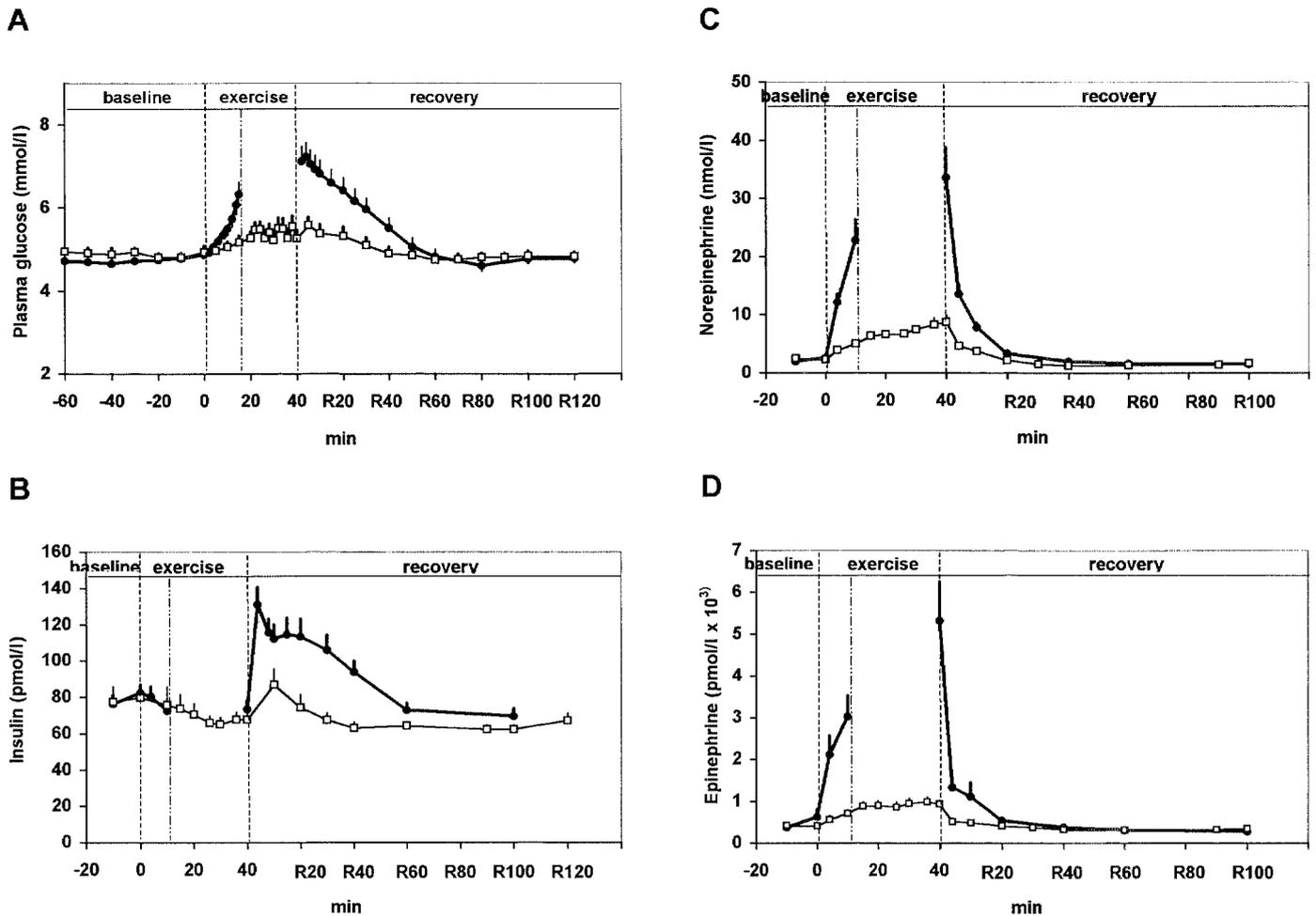
FIG. 1. Comparison of responses during 40 min of moderate intensity exercise (50% Vo_{2max}) ($\square$—$\square$) and 15 min intense exercise (87% Vo_{2max}) ($\bullet$—$\bullet$) in normal young male subjects. A rest period termed baseline was followed by exercise of the two different durations, as shown between the vertical broken lines. The break in the line for intense exercise is to permit plotting the recovery (R) period (R0–R120 min) starting from cessation of exercise. Data are presented as means ± SE. *A*: Plasma glucose, unchanged in moderate and rising with intense exercise, especially in the recovery period. *B*: Plasma insulin, with a significant decline in moderate and trend downward in intense exercise, followed by a marked rise in recovery. *C*: Plasma NE. *D*: Plasma EPI, both catecholamines increasing about threefold in moderate, but markedly in intense exercise, with rapid return to baseline levels.

tors of GP in this special setting. Unless otherwise indicated, "exercise" hereafter refers to intense exercise.

Glucoregulatory responses to intense exercise

Metabolic responses to intense exercise can be divided temporally into those occurring during the muscular work itself, those occurring immediately after exhaustion as the acute and massive changes reverse, and those that occur later in recovery (19). Typically, even very fit persons can sustain exercise at ≥80% Vo_{2max} for periods of only 10–15 min, although elite athletes may do so for longer. Exercise experiment paradigms, as well as certain sports that require this level of exertion, often use exercise that generates maximal or supramaximal Vo_2 for up to 3–5 min. These bouts may be repeated with variable intervening time intervals. If the rest interval is short (e.g., several 5-min bouts) the metabolic responses, especially hyperglycemia, are additive (20). If the intervals are as long as 1 h, most of the components of a single response are repeated (21). These responses to multiple, repeated bouts will not be considered in detail here, in part because existing techniques for studying glucose turnover in this setting

would be difficult to apply and interpret. Indeed, even for single bouts, it was necessary for us to devise a modified approach to the conventional primed-continuous tritiated glucose infusion method in order to define the rapidity and magnitude of changes in glucose turnover. We therefore used stepwise increments in the 3-[³H]glucose infusion rates by up to 4- to 7.5-fold (21–23) during the exercise, with corresponding steps downward in recovery. Blood samples were taken at 2-min intervals. This approach attenuated the magnitude of changes in circulating glucose specific activity and total radioactivity that otherwise would have rendered estimates of GP and GU less precise. Thus, we were able to define the extremely rapid changes that occurred, in contrast to the more typical 10-min sampling intervals that are satisfactory in lower intensity exercise of longer duration (18). Our studies have been conducted in fit individuals undergoing exercise at >80%, with Vo_{2max} having been previously determined by a test using a progressive increment in resistance (ramp) on a cycle ergometer. The workload selected was subject to minor adjustments that resulted in an initial rapid
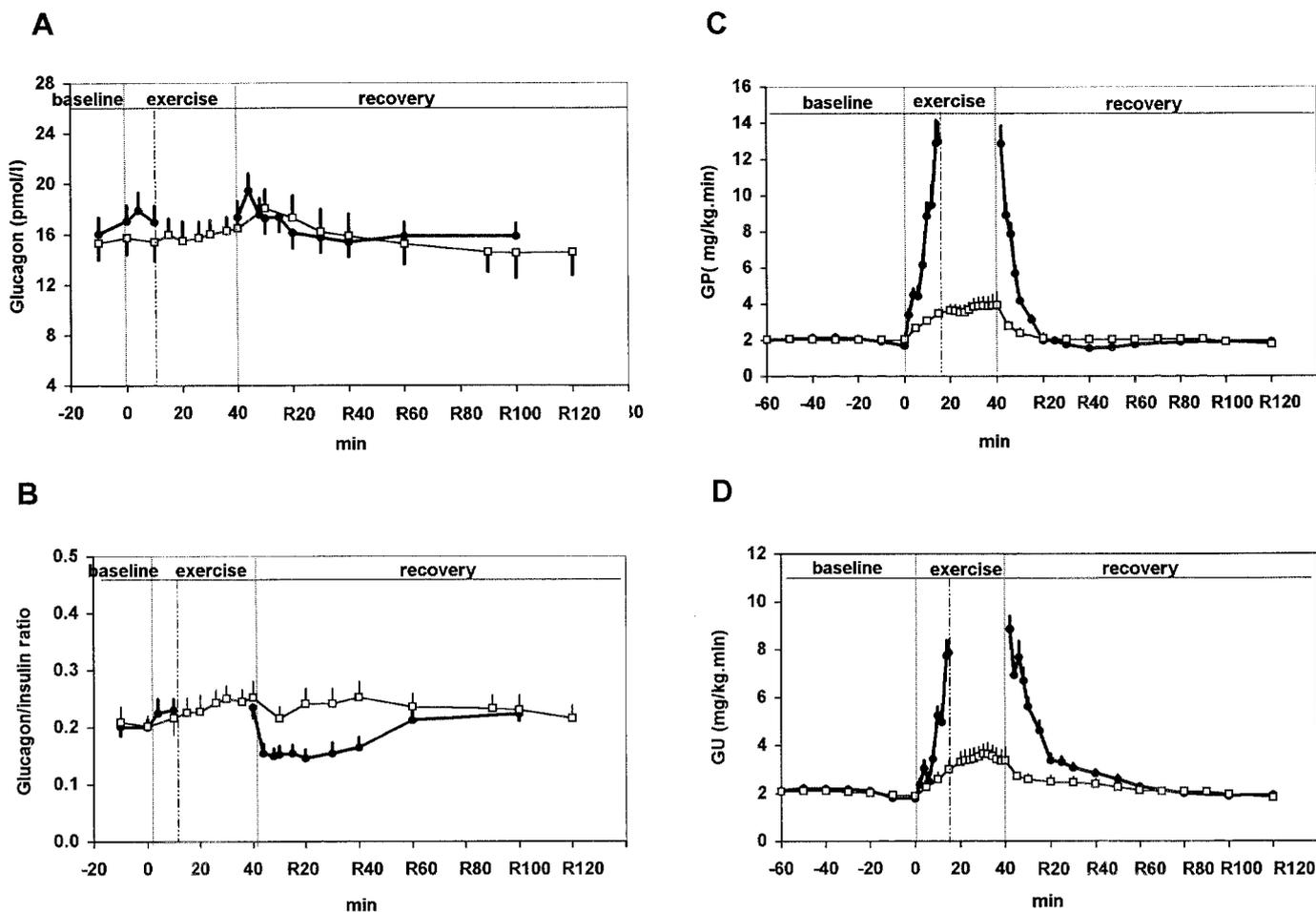
FIG. 2. Comparison of responses during 40 min of moderate intensity exercise (50% Vo_{2max}) (□—□) and 15 min intense exercise (87% Vo_{2max}) (●—●) in normal young male subjects. Data are presented as in Fig. 1. *A*: Plasma glucagon, showing no change at either intensity. *B*: Glucagon/insulin molar ratio, showing a slight rise during exercise, with return to baseline in recovery after moderate intensity, and marked decline after high intensity exercise. The latter is entirely due to the postexercise hyperinsulinemia (Fig. 1*B*). *C*: Rate of GP. *D*: Rate of GU. Both GP and GU double in moderate exercise, whereas GP increases sevenfold and GU fourfold in intense exercise.

increase in Vo_2 to a near steady state, followed by a minor, progressive rise by exhaustion, which in our studies occurred at 14–15 min of exercise.

In intense exercise, a signal for rapid hepatic glycogenolysis has been invoked, which anticipates the need for the marked increase in GP. In contrast to the "feedback" signal at lower exercise intensities, this has been suggested to be "feedforward" (24,25). Irrespective of the site of origin of the signal, we and others (26) have proposed that it is the marked catecholamine response during intense exercise that is the prime regulator of GP. In moderate exercise, plasma catecholamine concentrations increase only two- to fourfold (Fig. 1*C* and *D*) (27,28). In contrast, in intense exercise there is a marked 14- to 18-fold increase of both EPI and NE (Fig. 1*C* and *D*) (e.g., 19,21–23,25,26) to levels seen in pheochromocytoma. This induces a seven- to eightfold increase in GP (Fig. 2*C*), the largest increases seen under any physiological or pathophysiological condition. In contrast to moderate exercise, the increase in GU, though very large, is less than the increase in GP. This restraint in GU increment (Fig. 2*D*) is due to the largely catecholamine-mediated stimulation of muscle glycogenolysis. Despite the increase of plasma glucose that this GP-GU difference causes, plasma insulin

concentration does not change or may even increase slightly. There are two contributing factors. The first is that the high concentrations of catecholamines (acting through a dominant α-adrenergic effect) can prevent glucose stimulation of insulin secretion. The second may be a decrease in insulin disposal (see below). These glucoregulatory responses and their regulation during intense exercise are shown in schematic fashion in Fig. 3.

Further marked changes ensue at exhaustion. Notable is the marked increase of plasma insulin that lasts up to 60 min during recovery (Fig. 1*B*) (e.g., 19,21,22), starting with the immediate and rapid decrease of NE and EPI concentrations. This reflects a rapid waning of the α-receptor–mediated inhibition of the β-cell response to hyperglycemia (with a probable return toward resting rates of insulin disposal). The simultaneous increases of glucose and insulin concentrations create a milieu that should favor repletion of at least part of the muscle glycogen mobilized during the exercise. Such rapid replenishment of muscle glycogen is important because in many such activities there is frequent repetition of short bouts of intense exercise. That the recovery hyperinsulinemia is a physiologically essential early recovery response is illustrated by results in diabetic subjects, as described below.
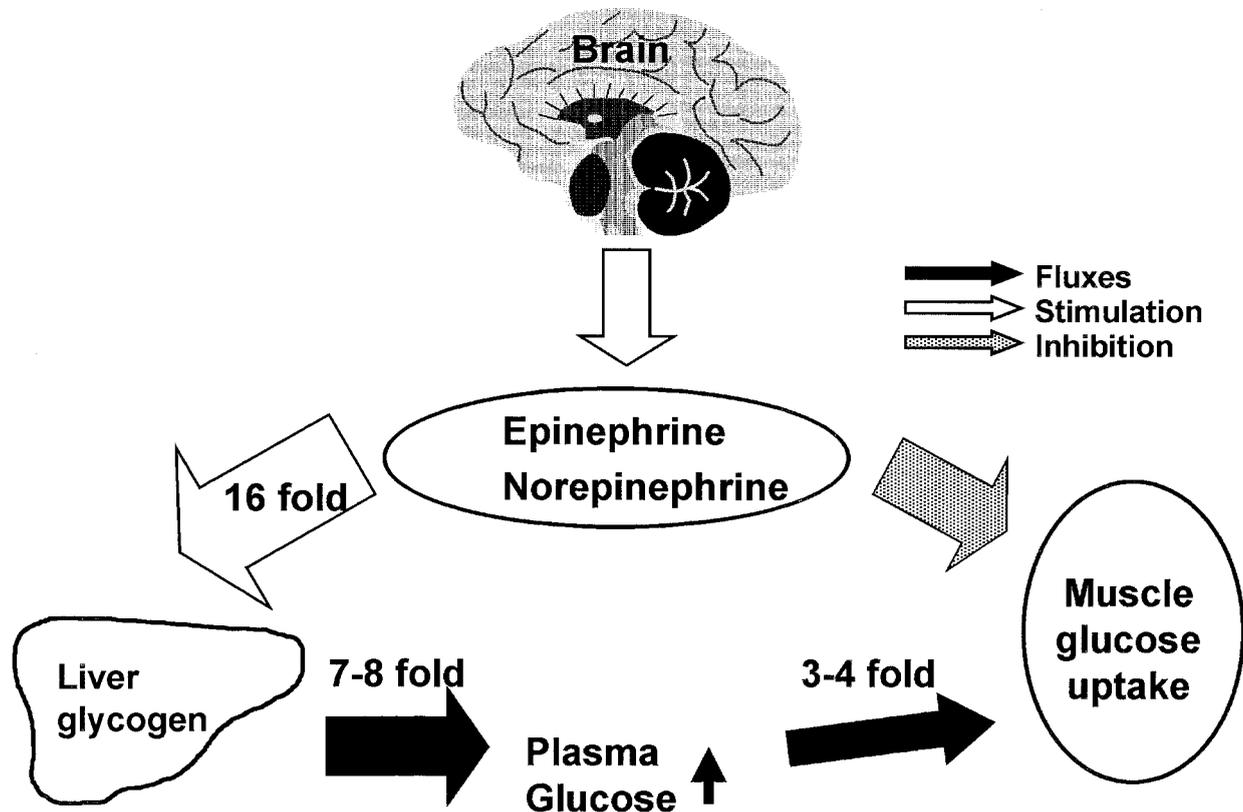
FIG. 3. Schematic representation of the current concept of glucoregulation during intense exercise (>80% Vo$_{2max}$). A "feed-forward" signal originating in the brain is viewed as causing the increased sympathetic outflow that results in 14- to 16-fold increases in circulating EPI and NE (open arrow). The solid arrows and their widths indicate the increases in GP and GU; the difference between their increments accounts for the hyperglycemic response. The wide shaded arrow indicates that at the same time that adrenergic stimulation of the contracting muscle contributes to glycogenolysis (not shown), it restrains the increase in GU from the circulation. Plasma insulin either declines minimally or remains constant during exercise, but increases rapidly and considerably the postexercise period, mediated by the hyperglycemia and release of adrenergic inhibition (not shown).

Effect of an "islet-cell clamp" on glucoregulation and insulin disposal in intense exercise

To more precisely define the regulatory contributions of insulin, glucagon, and growth hormone to the metabolic responses to intense exercise, we blocked the endogenous secretion of these hormones with intravenous octreotide and replaced their endogenous secretion by basal-rate infusions (Fig. 4) (22). The roles of the catecholamines could thereby be inferred more robustly, because their responses were not altered (not shown). GP increased normally (Fig. 4A), strongly suggesting that it's main regulators are catecholamines and not insulin and glucagon. GU likewise increased normally (Fig. 4B). Interestingly, despite continuing the insulin infusion at a constant rate, its plasma concentration increased threefold (Fig. 4C), indicating that intense exercise decreases insulin disposal. Furthermore, decreasing its infusion rate by half was associated with a lesser increase in plasma levels, and again the catecholamines and GP responses were the same (22). That GP was not attenuated by this hyperinsulinemia indicates that the stimulus for GP increase was able to overcome any suppressive effects of insulin and a decreasing glucagon-to-insulin ratio. As noted above, these responses of insulin suggest that the failure of intense exercise to suppress insulin without the islet clamp is not only due to the hyperglycemia overcoming its α-adrenergic suppression, but also to the effect of intense exercise to

decrease insulin degradation. Finally, there appears to be little role for growth hormone in these metabolic responses, because they were the same with both the normal >10-fold increase as well as with the maintenance of its levels during infusion of octreotide (22).

Effects of α- or β-receptor blockade

Previous studies at rest and during moderate exercise to define the roles of hepatic α- and β-adrenergic receptor activation in stimulation of GP have yielded inconsistent results and species differences (29–31). Many different experimental approaches have been used. Factors in interpretation of in vivo studies include concurrent effects on insulin and glucagon secretion, and NE delivery to hepatocytes both by local release from sympathetic nerve terminals and via the circulation. The intensity, or perhaps specificity, of the stimulus to increased sympathetic tone and/or circulating catecholamines could also lead to differing interpretations, particularly in human studies (e.g., 32–37). Furthermore, the physiological status of the subjects plays a role—level of fitness and presence of disease determine the absolute as well as relative workloads during exercise. Examples of differing results include the following: α-receptors have been found to be most important in stimulating hepatic GP in rats (38), whereas in dog hepatocytes, β-receptors have been reported to be dominant, and both play a role in cats (reviewed in 30). Propranolol and phentolamine infused together into the
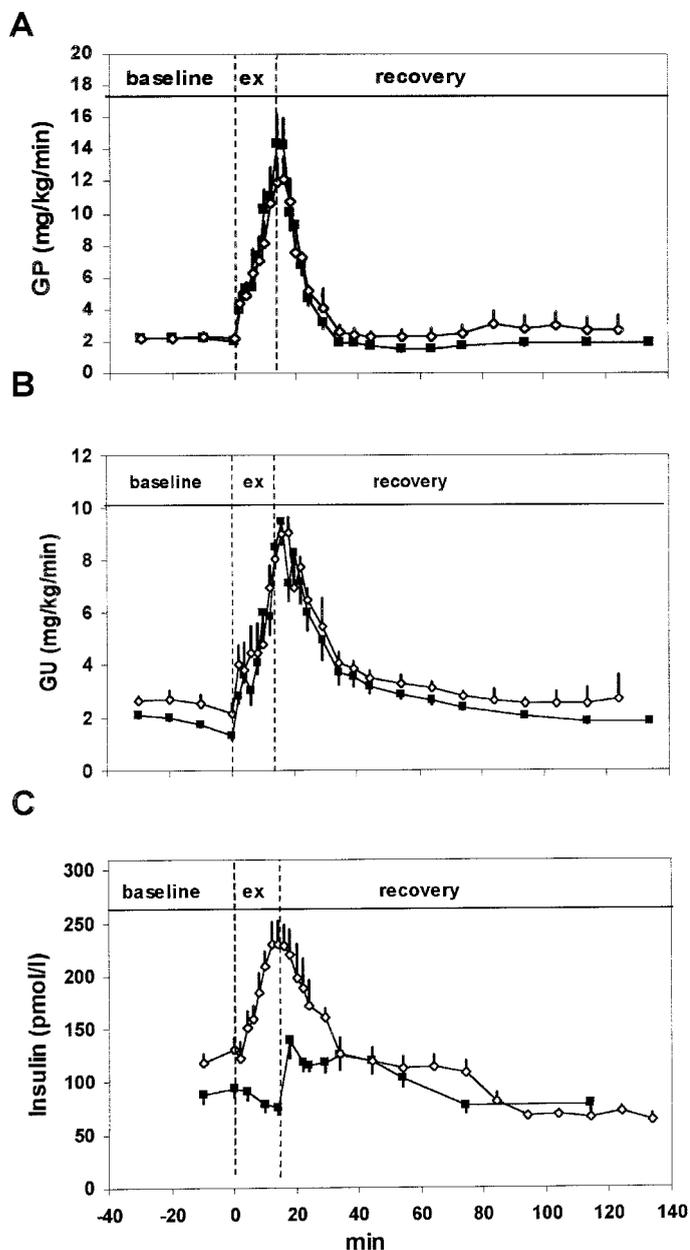
FIG. 4. Glucose turnover and insulin in control (■—■) and "islet cell clamp" (◇—◇) studies with intense exercise in normal subjects. Before, during, and for 60 min following the clamp, octreotide was infused simultaneously with basal infusions of glucagon, insulin, and growth hormone. Despite constant trihormonal infusion, increments of GP (A) and GU (B) are identical to control, as is the plasma glucose response (as in Fig. 1A). There is a twofold increase in plasma insulin during exercise (indicating decreased insulin degradation) (C) and no difference between studies in glucagon (not shown), yet the GP response was unaffected (modified from Sigal et al. [22]).

FIG. 5. The effects of phentolamine infusion on metabolic responses to intense exercise (70 μg/kg bolus + 7 μg/kg/min, from 30 min before 60 min recovery) in normal subjects. α-Blockade (◇—◇) markedly decreases the plasma glucose rise (A) during and after intense exercise, compared with that of controls (■—■), is associated with a substantial rise in insulin (B) and an attenuation of the peak rise of GP (C). There was no effect on glucagon or GU (not shown) (modified from Sigal et al. [36]). As there is not a systematic attenuation of GP with such insulin responses (e.g., Fig. 4C), these results are consistent with an α-receptor role in the GP response.

portal vein were unable to prevent the GP increment in dogs exercised to 85% of their maximum heart rate, which caused a fourfold GP increment (31); however, they were able to block the GP response to portal infusion of NE and EPI, possibly related to the difference between neural and "hormonal" effects.

In an attempt to define the contributions of α- and β-receptors in intense exercise, we infused the receptor-blocking agents phentolamine (Fig. 5) or propranolol (Fig. 6) intravenously, starting 30 min before the bout and ending at 60 min of recovery (35,36). With phentolamine
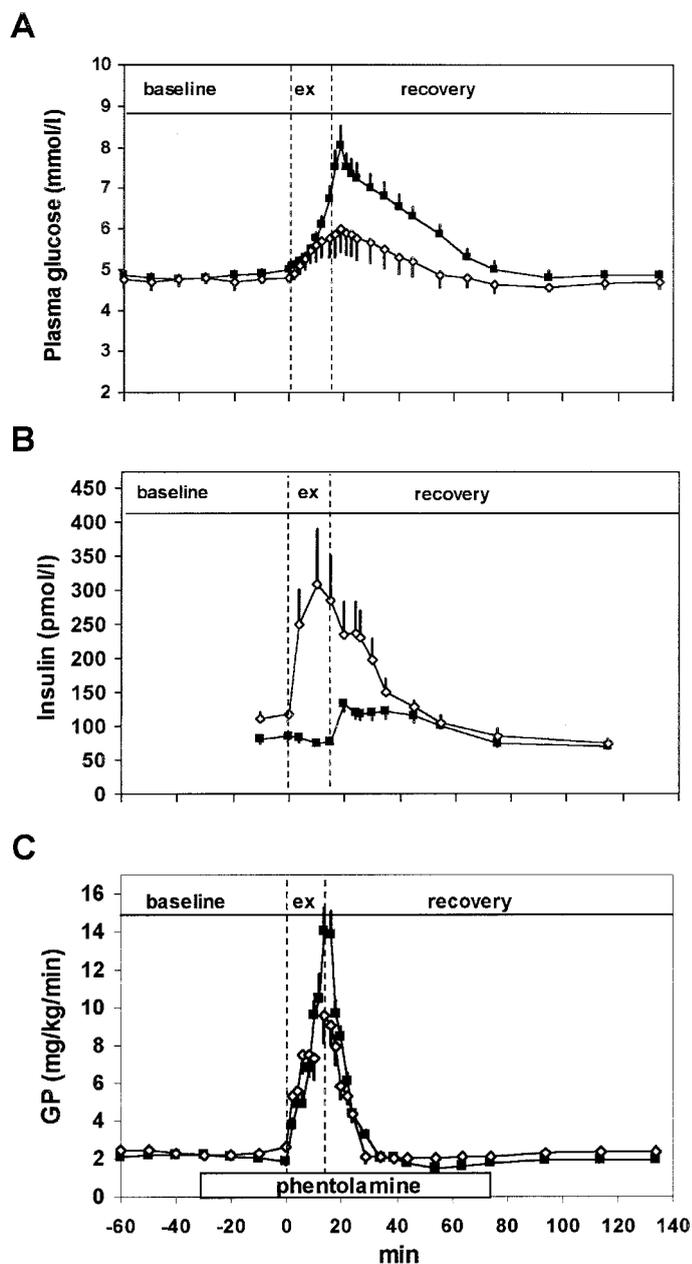
(36), the importance of the usual islet α-receptor effect of inhibiting insulin secretion during exercise (2,3) is clearly illustrated by the threefold increase in insulin (Fig. 5B), despite the fact that the increment of glycemia was substantially decreased (Fig. 5A). Phentolamine thus unmasked the β-receptor–mediated stimulation. Accordingly, because the glucagon response was little altered, the glucagon-to-insulin ratio decreased. The hyperglycemia was less marked because α-blockade decreased the peak increment of hepatic GP (Fig. 5C). This was associated
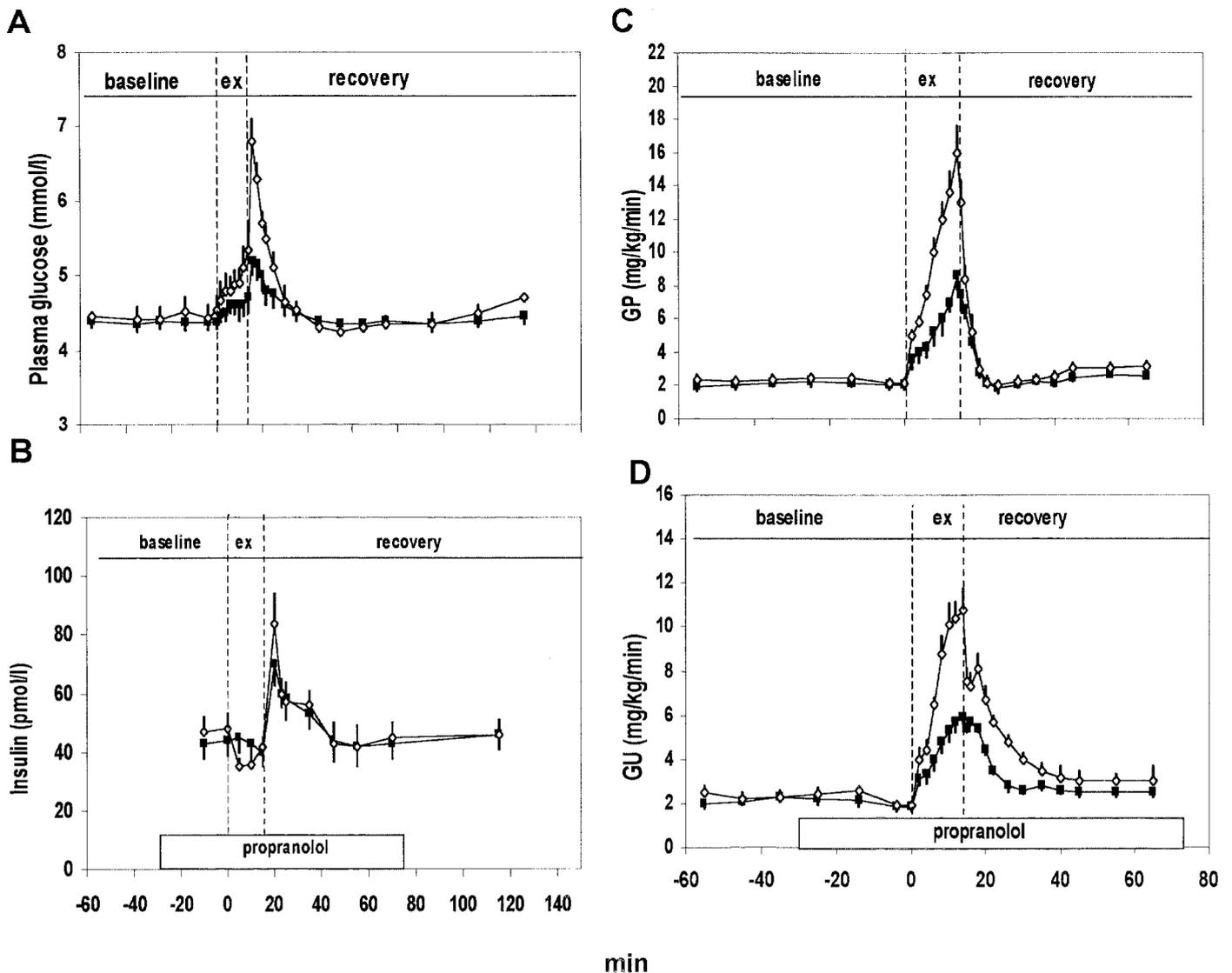
FIG. 6. The effects of β-blockade with propranolol on metabolic responses to intense exercise (150 µg/kg bolus + 80 µg/kg/min infusion, from 30 min before 60 min recovery) in normal subjects. β-Blockade prevented the subjects from performing at as high intensity as in Figs. 1, 2, and 4, so the present control subjects were exercised at this lower rate, accounting for their somewhat smaller metabolic responses (■—■). Greater hyperglycemia with propranolol (A) (◇—◇) is associated with a significant fall in insulin (not present in the control study) (B). Both GP (C) and GU (D) increments are markedly increased by propranolol, but the increment in GP exceeds that in GU, accounting for the hyperglycemia (modified from reference [36]). Catecholamine increments were also markedly greater during β-blockade (not shown). These results are consistent with β-blockade augmenting GU but are consistent with both receptor types being involved in stimulating GP.

with unaltered GU and with markedly enhanced elevations of both NE and EPI, the latter possibly due to decreases in their clearance (see below). These results are consistent with phentolamine blocking part of the GP response to the large rises in catecholamines, and indicate the presence of GP stimulation mediated by α-receptors. That more restraint of the GP increment did not occur could likewise have been due to some β-receptor–mediated stimulation of GP. Though we cannot exclude a partial attenuation of GP related to the effect on the glucagon-to-insulin ratio, the failure of similar changes in other experiments to do so makes this less likely.

Most human studies have suggested a predominance of β-receptor stimulation of GP (30,39). Were this is the case in intense exercise, β-blockade should decrease GP. However, we found the opposite with the nonspecific β-blocker propranolol (35); at matched exercise intensities, a two-fold higher peak GP occurred versus control responses (Fig. 6C). Interpretation of this response must account of the following. During exercise with propranolol infusion, there was also a greater increase in NE and EPI levels (not shown), along with an early decrease in plasma insulin (Fig. 6B) and an increase in plasma glucagon, resulting in an increased glucagon-to-insulin ratio (not shown). Furthermore, while β-blockade was clearly present because of attenuated increases of heart rates and lipolysis (not shown), it cannot be argued that the blockade was complete, and some β-adrenergic contribution to the increase in GP remains a possibility. In similar studies with β-blockade in type 1 diabetic patients kept euglycemic before exercise by insulin infusion, a similarly enhanced increase in GP was found, which occurred despite increase in plasma free insulin during exercise (40). The increased plasma catecholamine response was also ob-

served. Thus, because the same GP increment occurred with propranolol in the face of both decreased and increased insulin, it seems unlikely that the glucagon-to-insulin responses played a role. Previous studies in humans at rest demonstrated that the increase in NE levels with propranolol infusion (41,42) is due to decreased clearance, rather than increased release, related primarily to increased vasoconstriction (42). This is the likely explanation for the markedly greater response of the plasma catecholamines in our studies.

On the basis of these three studies, we have suggested that during intense exercise both α- and β-receptor effects of catecholamines can increase GP (35,36,40). Because with blockade of either of the receptors the plasma concentrations of catecholamines rose considerably more, this suggests that one system can compensate for the attenuated activity of the other, i.e., there is redundancy in the receptor mechanisms in this specific situation.

The net glycemic effect of propranolol in both diabetic and control subjects was to lessen the magnitude and duration of the exercise hyperglycemia (Fig. 6A) (35,40). This was due to greater enhancement of GU (Fig. 6D) (35,40), likely to occur by inhibition of the well-documented β-adrenergic stimulation of muscle glycogenolysis, thereby allowing for greater uptake of blood-borne glucose. One cannot exclude a contributing role for the concurrent inhibition of lipolysis (leading to a greater decline in plasma free fatty acid) that is normally stimulated by increased β-adrenergic activity at the adipocyte. In the diabetic subjects, this greater GU occurred in the absence of the normal sustained postexercise hyperinsulinemia and returned the glycemia to pre-exercise levels. If it were not for other less desirable effects of β-blockade, this might be part of the strategy for controlling postexercise hyperglycemia in diabetes (see below).

Effects of glucose infusion

We hypothesized that if the proposed catecholamine mechanism is necessary for the GP response to intense exercise independently of a glucose feedback mechanism, such a response should occur even if pre-exercise endogenous GP was completely suppressed by continuous intravenous glucose infusion and its accompanying hyper-

insulinemia. Indeed, it should occur even if an amount of glucose equivalent to the normal GP 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 glucoregulation in lower intensity exercise in which attenuation or complete prevention of the endogenous GP increment has been shown (43–48), due to increase of insulin and decrease of glucagon in experiments in which the hormone responses were endogenous, as well as in somatostatin studies in which levels were adjusted by exogenous hormone replacement. We therefore determined the effects of stepwise increment of glucose infusion during exercise and decrement in the early postexercise period that mimicked the endogenous GP responses of control subjects (Fig. 7) (23). To mimic the fed state, glucose was infused before, during, and after exercise; endogenous GP can thereby be measured accurately by subtracting the known glucose infusion
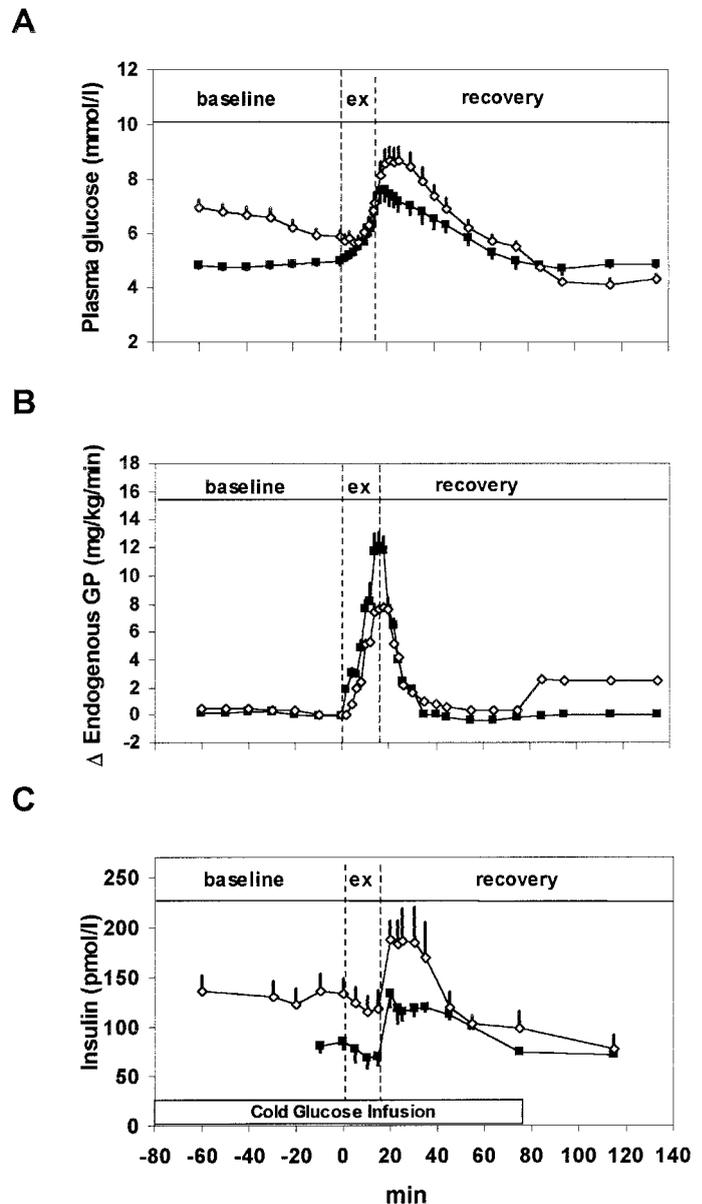

FIG. 7. The endogenous GP response to intense exercise is only partially attenuated with glucose infusion to totally suppress it before exercise. Control postabsorptive subjects received no infusion (■—■). Glucose infusion began at 4 mg/kg/min at baseline, then with exercise was varied (◇—◇) to mimic the endogenous GP response in controls. Glucose infusion increases plasma glucose (A) and insulin (C) at baseline but only partially attenuates the endogenous GP increment during exercise (B) (modified from Manzon et al. [23]). The catecholamine responses were similar (not shown).

rate from total GP. As shown in Fig. 7A, plasma glucose concentration was elevated before exercise and for the first 45 min of recovery, compared with values in uninfused subjects. Despite the total suppression of GP at rest, its endogenous increment was only modestly attenuated during intense exercise (Fig. 7B). This is in contrast to moderate exercise, in which exogenous glucose infusion abolishes endogenous GP (43–48). The endogenous elevation of plasma insulin during glucose infusion appears to inhibit GP only marginally because the huge catecholamine response (which was unaffected, not shown) overcomes the insulin-induced suppression (Fig. 7C). Alternatively, this could be
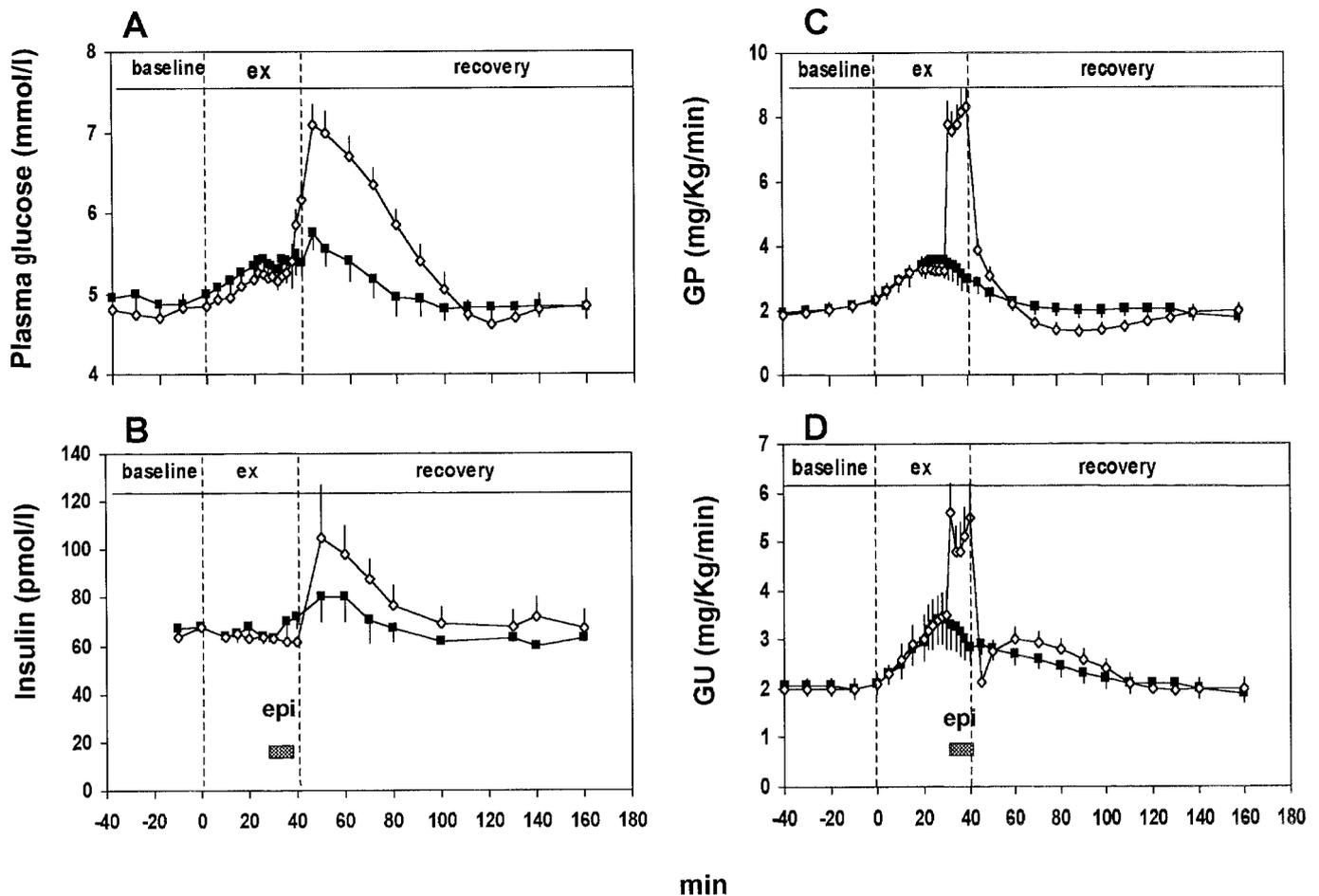
FIG. 8. Glucoregulatory effects of EPI infusion (0.1 µg/kg/min) (◇—◇) during the last 10 min of 40 min of moderate-intensity (50% Vo_{2max}) exercise in postabsorptive normal subjects. Compared with responses without infusion (■—■), EPI increases plasma glucose (*A*), causes recovery hyperglycemia and hyperinsulinemia (*B*), and markedly increases both GP (*C*) and GU (*D*) (modified from Kreisman et al. [27]). The magnitude of the plasma EPI increment achieved (not shown) is consistent with the endogenous response contributing importantly to the GP response in intense exercise.

interpreted as catecholamine-induced hepatic insulin resistance. The markedly greater postexercise increment in plasma insulin (Fig. 7*C*) was parallel to that of the fasted state (albeit even higher) and was associated with increased GU (not shown), probably mostly into muscle.

We subsequently studied the response 3 h following a mixed meal (49). Before exercise, there was elevated glucose appearance into the circulation associated with hyperinsulinemia (and therefore probable suppression of endogenous GP), yet the increase in GP was comparable with that in fasted subjects, and catecholamine responses were the same. It is highly improbable that there would be increase in glucose absorption from the gut during intense exercise. Thus, these results are compatible with those of the glucose infusion, with the same conclusion: that prior suppression of GP by insulin can be overcome by the catecholamine response. In both studies, the GU responses were greater during exercise and persisted during recovery, compatible with the higher insulin levels enhancing glucose uptake into insulin-sensitive tissues, both as primary energy source and substrate for restoration of glycogen depleted during exercise. Accordingly, in the postprandial study, the hyperglycemic response was less than in the fasted state.

Effects of EPI and NE infusion of during moderate exercise

Convincing evidence for catecholamines being the primary mediators of the huge GP response to intense exercise would be if mimicking their plasma levels by exogenous infusion reproduced the response. Such infusions at rest would probably produce unacceptable symptoms. Given the exertion required at 50% Vo_{2max} and that glucoregulation at lower intensities is not primarily catecholamine-mediated, we tested whether infusion of NE, EPI, or both could "convert" the response of moderate to that of intense exercise. Therefore, fit normal subjects were exercised for 40 min at 50% Vo_{2max}, and either the individual catecholamines were infused for the last 10 min or both together were infused during the last 14 min. Figure 8 illustrates the effects of EPI infusion at a constant rate that produced circulating concentrations that peaked in the range found in intense exercise (27). This infusion induced rapid increases in GP from the typical twofold increment over resting rates to over half the peak rate of intense exercise (Fig. 8*C*). Though GU also increased to greater than the twofold rise of moderate exercise, it peaked at less than the GP increment (Fig. 8*D*), so both during the infusion and in early recovery, hyperglycemia occurred (Fig. 8*A*). Unlike after moderate exercise, these effects

were accompanied by recovery hyperinsulinemia (Fig. 8*B*). Thus, most qualitative aspects of the intense exercise response were reproduced, but were quantitatively smaller. Similar observations were also made with infusions of NE that reproduced the plasma levels of intense exercise (28), though the magnitudes of all of the responses were somewhat less than those to EPI. The sum of GP increments achieved separately with EPI and NE (not shown) would approximate that of intense exercise. This would only be a valid calculation if the effects were additive. Therefore, with the knowledge of these effects at the plasma catecholamine concentrations achieved, we performed combined infusions of EPI and NE at incremental rates designed to fully mimic the patterns and magnitudes of intense exercise (50). The latter was achieved, and the increase in GP was indeed predicted by the sum of the two and closely matched that in intense exercise (not shown). Most other hormonal and metabolic responses did likewise. In contrast to both the individual and combined infusions, the catecholamines augmented rather than restrained the increased GU (not shown), although some hyperglycemia did occur because these increments were of smaller magnitude than the increase in GP. We conclude, therefore, that the effects of catecholamines on GU during exercise are different from those during the resting state, in which they are typically reduced. In these experiments, there was a postexercise hyperinsulinemia that corresponded to the magnitude and duration of the hyperglycemia (Fig. 8*B*). Once again, given the absence of "appropriate" changes in insulin and glucagon during the infusions (27,28,50), virtually the whole of the glucoregulatory responses can be attributed to the levels of catecholamines achieved. These results clearly indicate the capacity of NE and EPI to explain the huge increase in GP of intense exercise. That they can do so by peripheral venous infusion implies that they can act as hormones rather than requiring local release of NE to generate the intense exercise response (a contribution of the latter is nonetheless probable). Furthermore, EPI appears to be a more potent stimulator than NE at identical infusion rates and at the circulating levels achieved both endogenously and by infusion. Finally, this infusion model confirms the need for the postexercise hyperinsulinemic response to return plasma glucose to resting concentrations.

Intense exercise in diabetes

Very little research has been done in persons with type 2 diabetes, as most are unlikely to perform strenuous exercise. Given the importance of the increased secretion of insulin in the postexercise period and the relatively small roles of insulin and glucagon during the bout, it would be predicted that persons with type 1 diabetes might have normal GP and GU responses during and immediately following exercise, but abnormal responses for the rest of the recovery period. Our studies in such subjects allow for some compelling inferences with respect to these predictions (40,51,52) (summarized in Fig. 9). Fit, young subjects with no residual subcutaneous insulin received continuous intravenous insulin overnight that maintained either normal or elevated plasma glucose concentrations (Fig. 9*A*). In all three studies, the rates of infusion producing these levels were kept constant during exercise. In one euglycemic study and in the hyperglycemic study these rates were
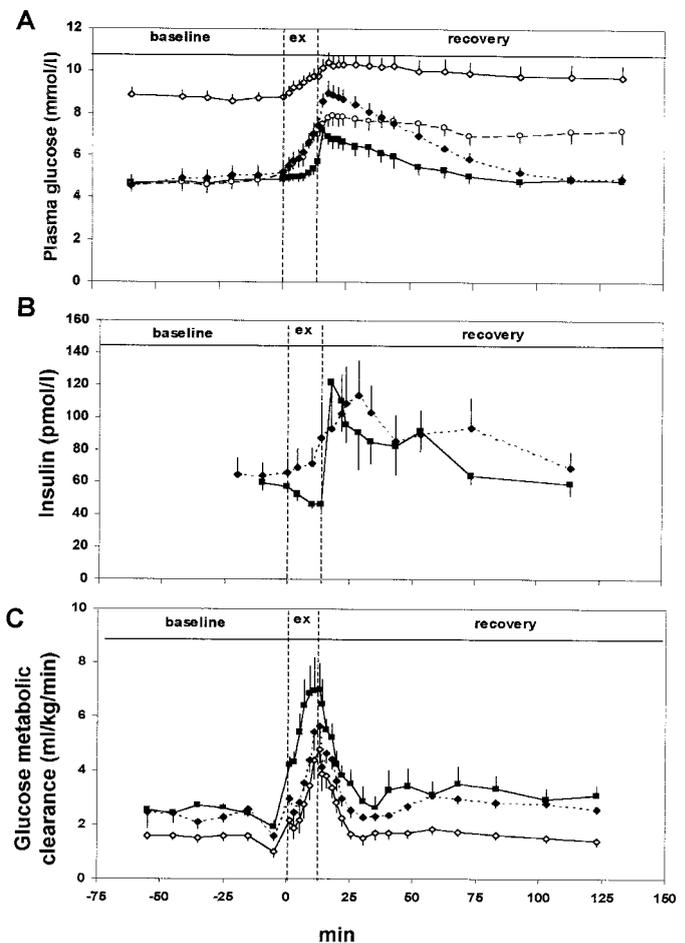

FIG. 9. The effects of postabsorptive intense exercise in subjects with type 1 diabetes, compared with those in nondiabetic control subjects (■—■). Insulin was infused intravenously overnight to result in either euglycemia or steady-state hyperglycemia before exercise. During and after exercise three insulin protocols were employed: infusion kept constant with hyperglycemia (◇—◇) and euglycemia (○—○), and doubled insulin infusion during recovery (◆—◆). For insulin concentration, only groups ◆ and ■ are shown, and for glucose metabolic clearance, ■, ◆, and ◇ are shown. Without extra insulin in both diabetic groups following exercise, plasma glucose remain elevated throughout recovery, but with doubled infusion it declines to baseline as in the control subjects (*A*). With maintained insulin infusion during exercise, levels increase instead of declining as in the control subjects, but with the doubled insulin infusion, the levels approximate those in the control subjects (*B*). With this extra insulin, plasma glucose declines because of improved glucose metabolic clearance (*C*) (modified from Sigal et al. [52]). These results explain the postintense exercise hyperglycemia in some patients and define the requirements for normalization of the response.

maintained during all of recovery, and in one euglycemic study the rate was doubled at the end of exercise. The catecholamine responses and those of GP and GU during exercise and the first minutes of recovery were normal (not shown). Notably, in both studies with constant insulin infusion, the hyperglycemia of exercise continued for the 2-h recovery period (Fig. 9*A*). However, doubling the infusion rate returned glycemia to pre-exercise values, albeit from higher levels and more slowly than occurred in the control subjects. The plasma insulin levels approximated those in control subjects by this simple maneuver (Fig. 9*B*). From this we conclude that in type 1 diabetes the response that is catecholamine-mediated is preserved, but that without extra postexercise insulin, intense exercise can cause sustained hyperglycemia. With repeated

bouts, it is probable that this would progressively worsen. We tested whether inducing an even greater immediate postexercise hyperinsulinemia in the normal subjects could accelerate the decrease in GP—it could not (51). Thus, the decline is due to the drop in catecholamines and therefore a strategy to mimic the normal pattern and magnitude of postexercise hyperinsulinemia may be feasible with available insulins given subcutaneously.

As noted, the increments and early recovery decline of GU were normal (not shown). Noteworthy is that metabolic clearance of glucose was also normal when euglycemia was present at rest. Although in all studies in diabetic subjects it increased somewhat more slowly during exercise, it was much lower postexercise in the hyperglycemic than in the control subjects (Fig. 9C). GU was normal in the latter because increased glucose mass compensates for decreased glucose metabolic clearance. We have speculated that its suppression represents a protective mechanism against hyperglycemia, and that this is the reason that muscle may not have the diabetic complications seen in organs that do not have this mechanism. Most recently, we have shown in the perfused rat hindquarter that this mechanism applies to both hyper- and hypoglycemia, and that it is due to altered translocation and synthesis of glucose transporters (53). Thus, with hypoglycemic and hyperglycemic infusions, the number of glucose transporters in plasma membrane increases and decreases, respectively. This is proportional to changes in GU (53).

As noted, β-blockade before, during, and after exercise normalized the postexercise decrease of plasma glucose (40). This effect is similar to the increment of insulin given in the postexercise period (Fig. 9A) and is due to a marked increase of glucose metabolic clearance. We made a similar observation in diabetic dogs, where stress (intracerebroventricular injection of carbachol) caused hyperglycemia in normal but not in diabetic dogs; this response was prevented by infusion of propranolol (54). The potential role of β-blockade in preventing hyperglycemia following stress or intense exercise remains to be explored.

What are the practical implications of the present findings in type 1 diabetic subjects? One must be circumspect in extrapolating from a small number of fit postabsorptive, complication-free, young diabetic men to the larger number of individuals who would more usually perform exercise in the nonfasting state, be less fit, and not necessarily young, male, and complication-free. There is need to develop strategies for diagnosing and managing exercise-related hyperglycemia (55). From our data, it seems probable that brief intense exercise in the postabsorptive state before insulin injection may lead to prolonged hyperglycemia. Second, if plasma glucose is elevated, it could become more elevated after intense exercise. This would depend on the types of insulin used and the timing of exercise after injection, as well as the type of exercise and its duration. Third, increasing the plasma insulin concentration very soon after intense exercise, even if given in a less-than-physiological fashion, can restore glucose clearance and glycemia toward normal. For the moment, we can only suggest an individualized approach based on blood glucose monitoring before and for several hours following exercise. For those individuals who regularly

and predictably become hyperglycemic after intense exercise, it may be appropriate to recommend a small additional insulin dose immediately after exercise. The optimal agent, dose, and timing to achieve this goal remain to be defined, but one promising approach may be the use of rapidly absorbed monomeric insulin analogs. We would also predict that the approach might need to be different in women than in men with type 1 diabetes. We have shown that for comparable relative exercise intensity based on $V_{O_{2max}}$, normal young women have higher postexercise hyperglycemia and correspondingly greater hyperinsulinemia (56). Finally, it should be reassuring to competitive athletes that their principal fuel-homeostatic responses during the performance of these types of strenuous exercise is, in fact, intact.

There is need for much more study in type 2 diabetes. In obese subjects without diabetes there are abnormal responses, probably related to insulin resistance (57). The hyperglycemic response is prolonged and associated with a much greater and longer hyperinsulinemic period, and while NE responses are normal, EPI responses are half those of lean subjects. The same general pattern of response was found in obese persons during low-energy diets, very-low-energy ketogenic diets, and total fasting, though at different resting levels of all substrates and of insulin (58), perhaps reflecting in part the diets' effects on insulin secretion and action. The combined effects of hypoenergetic diets and diabetes have not been defined. One recent study in type 2 diabetic subjects on diet only addressed postprandial metabolic responses to four bouts of stepped exercise with the highest intensity at 98% $V_{O_{2max}}$ for 4 min (59). Glucose and insulin excursions were lower with exercise because of increased GU and clearance but only after breakfast, not after lunch. Because this absence of a hyperglycemic effect is unusual, it needs confirmation in other protocols before being generalizable to all type 2 diabetes and intense exercise. As with other studies in unfit persons, the absolute workload may have been lower than that which generates the endogenous GP responses described herein, despite being high-intensity relative to these subjects' individual values for $V_{O_{2max}}$.

In conclusion, in intense exercise, insulin secretion does not decrease, or it does so minimally; hyperglycemia occurs because GU increases less than GP. We postulate that the α-adrenergic inhibition of insulin secretion is counterbalanced by hyperglycemia and decreased degradation of insulin. Results of studies with α- or β-blockers suggest that both receptors can stimulate GP and that the lack of one can be compensated for by the other. Compelling evidence that catecholamines are the main regulators of hepatic GP derives from studies in moderate exercise with catecholamine infusions. These mimic all the main parameters of intense exercise, including the responses of insulin, GP, and GU. Hyperglycemia occurs and persists in insulin-infused diabetic subjects in the postexercise period, indicating the need for additional exogenous insulin during this period. Thus, those patients who become hyperglycemic after intense exercise may need an injection of ultra-rapidly acting insulin at a time determined empirically. More study of strenuous exercise in type 2 diabetes is required.

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