Effect of Local Sympathetic Blockade on Forearm Blood Flow and Glucose Uptake During Hypoglycemia

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During hypoglycemia, hepatic glucose production increases and peripheral glucose utilization decreases. Systemic β-adrenergic blockade during hypoglycemia increases peripheral glucose utilization. To explore the local effects of increased α- and β-adrenergic activity on skeletal muscle glucose utilization, we measured arterial and venous plasma glucose concentrations, forearm blood flow (FBF), and forearm glucose uptake (FGU) during a hyperinsulinemic (40 mU/m²/min) stepped-hypoglycemic clamp with intrabrachial artery infusion of saline, phentolamine, propranolol, or combined phentolamine and propranolol. A control study was also performed with a euglycemic clamp and intraarterial saline. During hypoglycemia with saline and phentolamine, there were significant increases in FBF (130% ± 38% and 180% ± 35%, respectively) and FGU (120% ± 51% and 230% ± 150%, respectively). During hypoglycemia with propranolol and phentolamine + propranolol, FBF remained constant. FGU during hypoglycemia with propranolol was not different versus hypoglycemia with saline. No differences were found in these studies for forearm lactate output (FLO) or venous free fatty acid concentrations. These results demonstrate that local, as opposed to systemic, blockade during hypoglycemia does not alter peripheral glucose utilization.

INSULIN-INDUCED hypoglycemia increases both adrenomedullary and nonadrenomedullary sympathetic activity, as evidenced by increases in the plasma epinephrine and norepinephrine concentration[1] and muscle sympathetic nerve activity.[2,3] Combined systemic α- and β-adrenergic blockade during hypoglycemia prevents glucose recovery when glucagon is also absent, thus indicating that the increased sympathetic activity acts as an alternative mechanism for glucose recovery.[1] Adrenergic counterregulation is particularly important in subjects with type 1 diabetes, in whom the glucagon response to hypoglycemia is nearly uniformly absent.[4]

The adrenergic response promotes glucose recovery in two ways.[5] First, hepatic glucose production increases; and second, peripheral glucose utilization decreases. The former effect has been well studied and appears to be primarily due to the increase in lipolysis and circulating free fatty acids, which stimulates hepatic glucose production.[6] The latter effect is not as well studied. Cellular glucose transport and the rate of glucose delivery determine peripheral glucose uptake.[7,8] The former is determined by the glucose concentration gradient across the cell membrane,[9] the presence or absence of glucose transporters on the cell surface,[10] and the level of free fatty acids in the blood.[6,11,12] Blood flow and capillary recruitment determine the glucose delivery rate.[13]

Increases in adrenergic activity have the potential to affect each of these variables. Epinephrine-induced β-2-adrenergically mediated vasodilation[14,15] may increase the rate of glucose delivery, while increased muscle sympathetic nerve activity and norepinephrine levels should cause α-adrenergically mediated vasoconstriction[16] and thus counterbalance the vasodilation. An increase in lipolysis and free fatty acids due to the systemic effects of increased adrenergic activity[12,17-20] may decrease glucose transport. In addition, changes in adrenergic activity may have other effects on cellular glucose utilization, since nonoxidative glucose metabolism decreases during hypoglycemia.[10,21-23]

This study was designed to determine the local effects of increased α- and β-adrenergic activity on forearm blood flow (FBF) and glucose uptake (FGU). We measured arterial and venous plasma glucose concentrations and FBF during a euglycemic-hyperinsulinemic clamp and a hypoglycemic clamp with concomitant intraarterial infusions of saline, phentolamine, propranolol, and combined phentolamine and propranolol.

SUBJECTS AND METHODS

Subjects

Fourteen healthy control subjects (11 men and three women) who were not on treatment with any medication were studied. The mean age at the start of the study was 24 ± 7 years (mean ± SD) and the mean body mass index was 23 ± 3 kg/m². All subjects provided informed consent, and the University of Iowa Institutional Review Board for Human Investigation approved the protocol.

Protocol

Subjects were admitted to the Clinical Research Center at the University of Iowa at 8:00 AM and were taken to the Human Cardiovascular Physiology Laboratory. Intravenous catheters were placed in each arm. The catheter in the dominant (study) arm was placed in the antecubital fossa with the tip nonpalpable so that blood sampled from this catheter reflected forearm drainage.[24]

Two sphygmomanometric cuffs and a mercury-in-silastic strain gauge were placed on the dominant arm for the measurement of FBF. FBF was measured for 5-minute intervals every 10 minutes throughout the study. During the 5 minutes, the wrist cuff was inflated to 200 mm Hg pressure to occlude hand flow and the upper-arm cuff was cyclically inflated to 40 mm Hg to occlude venous return. The strain gauge was connected to a single-channel EC-4 Hokanson plethysmograph (Seattle, WA).[25] We have previously demonstrated that this method of FBF measurement does not alter the flow, vascular resistance, or sympathoadrenal activity during vehicle infusion.[26,27]

A 27-gauge steel needle attached to a 16-gauge epidural catheter was placed in the brachial artery of the dominant arm. The intraarterial catheter was used for infusions that are described later. This method of intraarterial infusion has been shown not to interfere with blood flow

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measurements or changes.[25] A 20-gauge catheter was inserted into the radial artery of the nondominant arm. This catheter was used for sampling arterial blood and measuring arterial pressure via a pressure transducer. Local anesthesia was used for placement of the steel needle in the brachial artery and the radial artery catheter.

Five minutes of baseline data with intraarterial saline infusion (1 $mL \cdot min^{-1}$) were then recorded. After collection of the baseline data, intraarterial infusions of phentolamine (12 $\mu g \cdot min^{-1}$ per 100 mL forearm tissue), propranolol (25 μg/min), or combined phentolamine and propranolol were started in the study arm at a rate of 1 mL/min. Euglycemic and hypoglycemic control studies (described later) were also performed in which the saline infusion was continued throughout. The dose of intraarterial phentolamine has been shown to decrease forearm vasoconstriction during norepinephrine infusion from 67% to 15% without affecting the systemic blood pressure or heart rate.[28] The dose of propranolol completely blocks isoproterenol-induced vasodilation without systemic effects (unpublished data, March 1993). After a 5-minute equilibration period, 10 minutes of additional baseline measurements were obtained in 5-minute intervals over the next 15 minutes.

An intravenous primed infusion of insulin was started and then maintained at 40 $mU \cdot m^{-2} \cdot min^{-1}$ after the first 10 minutes.[29] For the first 30 minutes, arterial plasma glucose was maintained at euglycemic levels using a 20% dextrose infusion. A stepped hypoglycemic clamp was then initiated with 30-minute steps at arterial plasma glucose concentrations of 70, 60, and 50 mg/dL.

Blood samples (1.5 mL) were taken every 5 minutes from the arterial catheter in the nonstudy arm and the venous catheter in the study arm for the immediate measurement of arterial and venous plasma glucose concentrations and later measurement of plasma insulin. Blood samples were taken immediately before starting the insulin infusion and at the end of each glucose step for measurement of arterial and venous plasma lactate and venous plasma free fatty acid, epinephrine, and norepinephrine concentrations.

Subjects were asked to participate in all five studies. Seven subjects were studied during a hyperinsulinemic-euglycemic clamp with intraarterial saline and hypoglycemic studies with intraarterial phentolamine or propranolol. Six subjects were studied during hypoglycemia with combined intraarterial phentolamine and propranolol and during hypoglycemia with intraarterial saline. The studies were performed in random order and were separated by at least a 2-week interval. Three subjects completed all five studies, two completed four studies, one each completed three studies and two studies, and seven participated in only one study.

Data Analysis

Data from the Hokanson plethysmograph were recorded on a MacIntosh Quadra 900 computer via MacLab (AD Instruments, Milford, MA). FBF (milliliters per minute per 100 mL forearm) was calculated from the slope of the signal with the upper-arm cuff inflated and was averaged over 5 minutes. Forearm glucose uptake (FGU) was measured using the Fick principle (FGU = FBF [arterial glucose − venous glucose]). The plasma glucose threshold value for increases in epinephrine and FBF was set at the arterial plasma glucose concentration at which they increased to a level greater than 3 SD above the mean hyperinsulinemic-euglycemic level over the first 30 minutes of the study.

Assays

The plasma glucose concentration was measured immediately using one of two YSI 2300 Stat Glucose Analyzers (Yellow Springs Instrument, Yellow Springs, OH). Arterial and venous samples were alternately measured on each machine. Plasma lactate was measured on one of the two analyzers that also had a lactate probe. Plasma norepinephrine and epinephrine concentrations were measured by high-performance liquid chromatography with electrochemical detection. The detection threshold was 30 $pg \cdot mL^{-1}$ for epinephrine and 20 $ng \cdot mL^{-1}$ for norepinephrine. The interassay and intraassay coefficients of variation were 7.7% and 7.1%. Plasma free fatty acids were measured by an enzymatic colorimetric method (Wako NEFA C test kit; Biochemical Diagnostics, Edgewood, NY). The low-, middle-, and high-range coefficients of variation were 2.7%, 1.1%, and 1.1%. Plasma insulin was measured by double-antibody radioimmunoassay with an interassay and intraassay coefficient of variation of 9.4% and 5.3%, respectively.[30]

Statistical Analysis

Changes in the arterial-venous (AV) glucose difference, FBF, and FGU with each intervention were analyzed by repeated-measures ANOVA with study type as a grouping factor. The key changes to be analyzed were from 30 minutes of the insulin clamp (end of euglycemia) to 120 minutes of the clamp (end of the 50-mg/dL step, except in euglycemic study). An ANOVA with study type as a grouping factor was used to assess differences. Post hoc comparisons were made using planned contrasts and the least-square means procedure. Results are presented as the mean ± SE.

RESULTS

Plasma Glucose

Baseline plasma glucose either before or after starting the intraarterial infusions did not differ in any of the groups, nor was there a statistically significant difference during the euglycemic period, 30 minutes after starting insulin. After 60 minutes, arterial plasma glucose levels were significantly higher in the euglycemic study, but did not differ between the hypoglycemic studies. Similar results were found for venous plasma glucose. The glucose infusion rate was higher at the end of the euglycemic versus hypoglycemic studies, but did not differ in any of the hypoglycemic studies (Fig 1).

Heart Rate and Blood Pressure

The mean arterial pressure did not differ in any of the studies or change over time. The heart rate did not differ among studies at baseline or after starting intraarterial infusions, nor did it change during euglycemic hyperinsulinemia. The heart rate increased during hypoglycemia with intraarterial saline ($F = 8.4$, $P = .008$) and phentolamine ($F = 41$, $P < .001$), but did not change during intraarterial propranolol or phentolamine + propranolol. The increase in the heart rate during hypoglycemia + saline was smaller than the increase during hypoglycemia + phentolamine ($F = 4.8$, $P = .04$), but was not statistically different from the lack of change during any of the other hypoglycemic sessions or the euglycemic session (Table 1).

Forearm Glucose Extraction, Blood Flow, and Glucose Transport

The session × time interaction for the AV glucose difference was significant ($F = 2.0$, $P < .001$). Specifically, the AV glucose difference increased during the first 30 minutes of hyperinsulinemic euglycemia during the two studies with intraarterial saline (euglycemia, $F = 13$, $P = .001$; hypoglycemia, $F = 13$, $P = .001$), but did not significantly change during the studies with intraarterial phentolamine, propranolol, or phentolamine + propranolol. It further increased from 30 minutes (7.7 ± 1.5 mg/dL) to 120 minutes (13.4 ± 2.3 mg/dL) during the euglycemic study ($F = 11$, $P = .003$), whereas during the

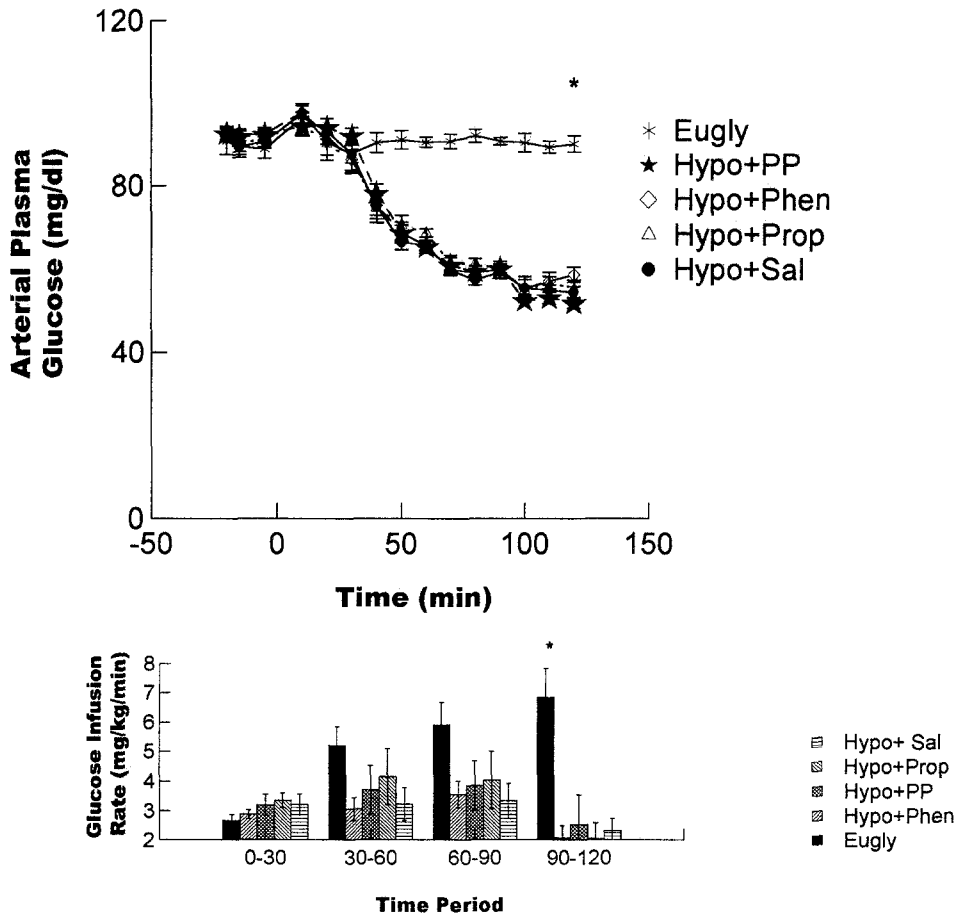

Fig 1. Mean arterial plasma glucose level and glucose infusion rate throughout each study session. *$P < .001$ *v* hypoglycemic studies. Error bars represent the SE. Eugly, euglycemia; Hypo, hypoglycemia; PP, phentolamine + propanolol; Phen, phentolamine; Prop, propanolol; Sal, saline.

hypoglycemic studies no change was found after 30 minutes. The AV glucose difference was significantly higher at the end of the euglycemic study versus any other study (Fig 2).

Changes in the AV difference over the last 90 minutes of the study significantly differed among the treatments ($F = 3.1$, $P = .03$). The increase over the last 90 minutes of euglycemia + intraarterial saline (5.6 ± 2.6 mg/dL) was significantly different from the change during hypoglycemia + intraarterial saline (−1.9 ± 2.3 mg/dL, $F = 6.8$, $P = .02$). The latter did not significantly differ from any of the other studies (Fig 3).

FBF changes varied significantly among sessions (session × time interaction, $F = 14$, $P < .001$). Intraarterial infusion of phentolamine ($F = 8.8$, $P = .006$) and phentolamine + propranolol ($F = 51$, $P < .001$), but not propranolol, increased baseline FBF. The latter increase was greater than the former ($F = 10$, $P = .003$), and both were significantly different versus the lack of change during either propranolol or saline ($P < .05$). FBF did not change during the first 30 minutes of euglycemic hyperinsulinemia with intraarterial infusion of saline or propranolol, but did increase further during both intraarterial phentolamine ($F = 32$, $P < .001$) and phentolamine + propranolol ($F = 6.5$, $P = .02$) infusion. The increase in FBF over the first 30 minutes of euglycemic hyperinsulinemia with intraarterial phentolamine was significantly different ($P = .001$) versus the changes during each of the other studies, except for the increase with intraarterial phentolamine and propranolol (Fig 3).

During the last 90 minutes of the study, FBF did not change during the euglycemic condition. During hypoglycemia + saline, FBF increased from 2.2 ± 0.5 to 4.8 ± 1.0 mL/min/100 mL forearm ($F = 10$, $P = .003$), and during hypoglycemia + phentolamine, it increased from 8.8 ± 1.5 to 22.1 ± 2.3 mL/min/100 mL forearm ($F = 212$, $P < .001$). These increases were eliminated by intraarterial propranolol. FBF did not change during hypoglycemia with intraarterial propranolol (3.2 ± 0.5 and 2.4 ± 0.4 mL/min/100 mL forearm, respectively) and tended to decrease from 12.9 ± 3.4 to 11.1 ± 2.4 mL/min/100 mL forearm ($F = 3.0$, $P = .09$) during hypoglycemia with intraarterial phentolamine + propranolol infusion. The mean arterial plasma glucose threshold for the increases in FBF during hypoglycemia was 55 ± 1 mg/dL during intraarterial saline and 57 ± 2 mg/dL during intraarterial phentolamine (Fig 3).

Changes in FBF over the last 90 minutes of the study significantly differed among sessions ($F = 45$, $P < .001$). The increase in FBF during hypoglycemia + saline was significant versus the lack of change over the last 90 minutes of euglycemia ($F = 5.4$, $P < .027$), hypoglycemia + propranolol ($F = 7.4$, $P < .011$), and phentolamine + propranolol ($F = 11$, $P = .002$). It was significantly less than the change during intraarterial phentolamine ($F = 73$, $P < .001$). The addition of intraarterial propranolol to intraarterial phentolamine blocked the hypoglycemia-induced vasodilation ($F = 124$, $P < .001$) (Table 2).

FGU changes also varied significantly among sessions

Table 1. Mean Arterial Glucose Concentration, Heart Rate, and Arterial Pressure at the End of Each Period for Each Study Session

Condition	Baseline (−20 min)	Arterial Infusion (0 min)	Insulin Clamp 30 min	Insulin Clamp 120 min
Euglycemia				
ART	91 ± 3	89 ± 2	88 ± 2	90 ± 2
HR	55 ± 2	55 ± 2	58 ± 2	58 ± 3
MAP	88 ± 3	90 ± 3	92 ± 2	90 ± 3
Hypo + Sal				
ART	93 ± 1	91 ± 2	88 ± 4	54 ± 1*
HR	58 ± 5	58 ± 5	60 ± 5	67 ± 5*
MAP	87 ± 2	87 ± 2	88 ± 2	90 ± 4
Hypo + Prop				
ART	92 ± 1	92 ± 2	86 ± 3	55 ± 2*
HR	60 ± 2	57 ± 2	55 ± 1	57 ± 4
MAP	84 ± 5	85 ± 4	86 ± 5	90 ± 3
Hypo + Phen				
ART	93 ± 2	93 ± 1	86 ± 2	59 ± 2*
HR	56 ± 4	56 ± 3	59 ± 2	74 ± 2*
MAP	85 ± 3	87 ± 3	90 ± 3	96 ± 5
Hypo + PP				
ART	93 ± 2	92 ± 2	92 ± 2	52 ± 1*
HR	58 ± 3	58 ± 3	57 ± 3	58 ± 3
MAP	77 ± 3	81 ± 2	82 ± 2	78 ± 2

Abbreviations: Hypo, hypoglycemic; Phen, phentolamine; PP, phentolamine + propranolol; Prop, propranolol; Sal, saline; ART, arterial glucose (mg/dL); HR, heart rate (bpm); MAP, mean arterial pressure (mm Hg).

*$P < .01$ *v* euglycemia.

(session × time interaction, F = 2.2, $P < .001$). Intraarterial infusion of phentolamine (F = 3.4, $P = .02$) and phentolamine + propranolol (F = 11, $P = .003$), but not propranolol alone, increased baseline FGU. Both increases were significantly different versus the lack of change during intraarterial propranolol ($P < .05$) but did not differ from each other. The increase during intraarterial phentolamine + propranolol ($P = .009$) was significant versus the lack of change during saline, whereas differences between the effects of intraarterial phentolamine alone and saline did not reach statistical significance. During the first 30 minutes of insulin infusion, while blood glucose was kept constant, FGU increased during both studies with saline infusion (combined F = 5.1, $P = .03$) and increased significantly during infusion with phentolamine (F = 5.0, $P = .03$) and phentolamine + propranolol (F = 13, $P = .001$), but did not change with propranolol alone (Fig 4).

FGU did not differ at 120 minutes versus 30 minutes of euglycemia. During hypoglycemia + intraarterial saline, FGU tended to increase from 0.20 ± 0.05 to 0.38 ± 0.10 mg/min/100 mL forearm ($P = .08$), and during hypoglycemia + phentolamine, it increased from 0.46 ± 0.12 to 0.82 ± 0.10 mg/min/100 mL forearm (F = 11, $P = .002$). During hypoglycemia + propranolol, FGU did not change, whereas during hypoglycemia with phentolamine + propranolol, it decreased significantly from 0.66 ± 0.17 to 0.43 ± 0.14 mg/min/100 mL forearm (F = 4.2, $P = .05$) (Fig 4).

The change in FGU over the last 90 minutes of the study also differed among the conditions (F = 4.1, $P = .009$; Table 2). The decrease in FGU over the last 90 minutes of hypoglycemia + intraarterial phentolamine + propranolol was less than the increase that occurred during hypoglycemia + phentolamine (F = 14, $P < .001$) or the lack of change during hypoglycemia + intraarterial saline.

Catecholamines

The epinephrine response differed significantly among studies (time × study interaction, F = 19, $P < .001$). There was no change between baseline and hyperinsulinemic euglycemia for any of the studies, nor was any significant change found over the last 90 minutes of the euglycemic clamp. During the four hypoglycemic clamps, plasma epinephrine was significantly increased at the end of the first hypoglycemic step and increased further with each step. The increase was significantly greater

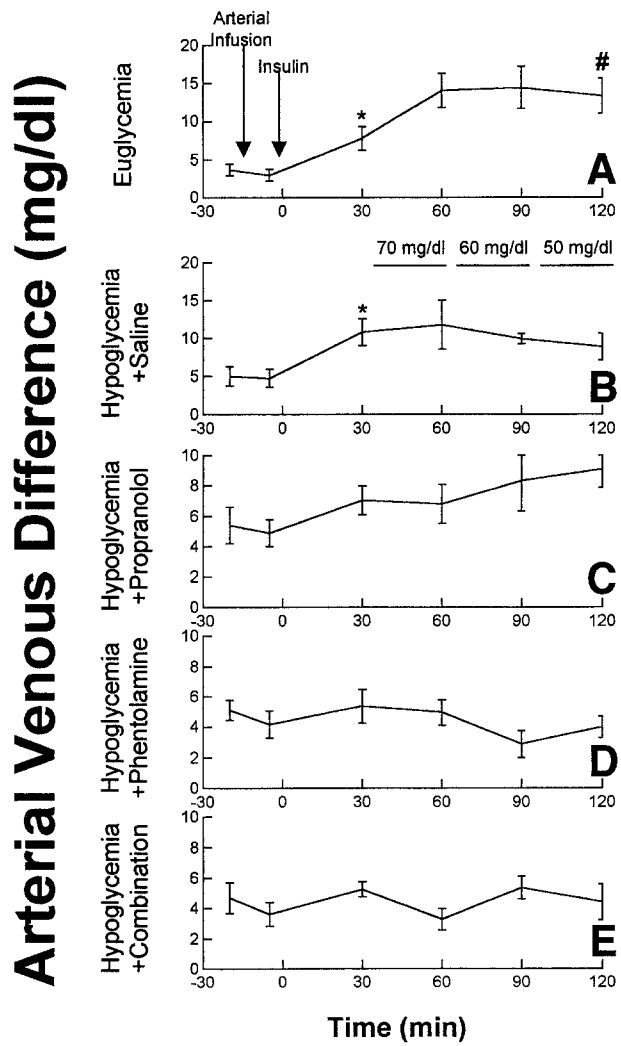

Fig 2. Mean AV plasma glucose difference during hyperinsulinemic clamp. Insulin infusion started at 0 min for all conditions. (A) Euglycemia with intraarterial saline infusion throughout. Stepped hypoglycemia began at 30 min for other panels. (B) Intraarterial saline infusion throughout. (C-E) Intraarterial infusion of propranolol, phentolamine, or phentolamine + propranolol beginning at −20 min. *$P < .001$ *v* −5 min (preinsulin) for same session. #$P < .05$ *v* 30 min (euglycemia) for same session. Error bars represent the SE.

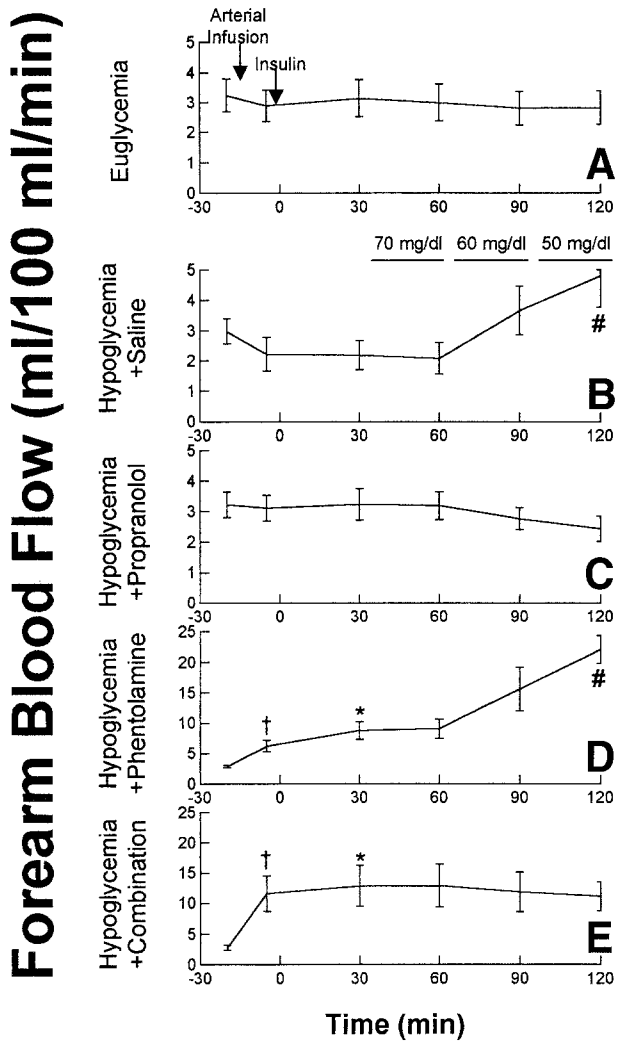

Fig 3. Mean FBF during hyperinsulinemic clamp. Insulin infusion started at 0 min for all conditions. (A) Euglycemia with intraarterial saline infusion throughout. Stepped hypoglycemia began at 30 min for other panels. (B) Intraarterial saline infusion throughout. (C-E) Intraarterial infusion of propranolol, phentolamine, or phentolamine + propranolol beginning at −20 min. *$P < .02$ *v* −5 min (preinsulin) for same session. #$P < .01$ *v* 30 min (euglycemia) for same session. †$P < .01$ *v* −25 min (prearterial infusion) for same session. Error bars represent the SE.

during hypoglycemia + propranolol versus hypoglycemia + saline (F = 7.4, $P = .01$), tended to be greater versus hypoglycemia + phentolamine ($P = .09$), and was smaller versus hypoglycemia with phentolamine + propranolol (F = 24, $P < .001$). The mean arterial plasma glucose threshold for the increase in epinephrine was 61 ± 2 mg/dL, which is significantly higher versus the threshold for the increase in FBF (Fig 5).

Baseline venous plasma norepinephrine levels were significantly higher with intraarterial phentolamine or phentolamine + propranolol compared with intraarterial saline infusion ($P < .03$). The former two did not differ. No changes were observed for plasma norepinephrine during the euglycemic study. Norepinephrine was significantly increased after 30 minutes of insulin during the combined infusion of phentolamine + propranolol only. Venous plasma norepinephrine during hypoglycemia was increased at the end of the 60-mg/dL step (F = 6.7, $P = .02$) and further increased at the end of the 50-mg/dL step (F = 8.5, $P = .008$) of the hypoglycemia + intraarterial phentolamine study. Venous plasma norepinephrine levels were also increased at the end of the 50-mg/dL step with intraarterial phentolamine + propranolol. No changes were found during the other studies. The change during phentolamine was significantly different versus the other studies ($P < .04$).

Insulin, Lactate, and Free Fatty Acids

Mean basal plasma insulin levels were similar in all studies. After starting insulin infusion, plasma insulin increased and again was similar in all studies. Arterial plasma lactate increased throughout the study (time effect, F = 8.4, $P < .001$), but the responses were similar in all studies. Specifically, arterial lactate increased after 30 minutes of insulin infusion (F = 17, $P < .001$) and remained elevated throughout. Forearm lactate output (FLO) increased during hypoglycemia with intraarterial phentolamine (F = 17, $P < .001$), but did not change during hypoglycemia with any of the other studies. Venous free fatty acid levels were suppressed by insulin infusion ($P < .005$) but did not differ among the sessions either for euglycemia or for hypoglycemia (Table 3).

DISCUSSION

These results demonstrate that FBF and glucose delivery increase and glucose extraction decreases during hyperinsulinemic hypoglycemia. These changes have opposing effects on FGU such that FGU is not different during hyperinsulinemic hypoglycemia versus hyperinsulinemic euglycemia of similar duration. The increase in FBF occurs at a lower plasma glucose concentration than does the increase in plasma epinephrine, is blocked by local propranolol infusion, and is thus β-adrenergically mediated. During hypoglycemia with local α-adrenergic blockade, FBF and FGU increase markedly, which suggests that increased α-adrenergic activity during hypoglycemia may counter the β-mediated vasodilation.

Hickner et al[31] reported results similar to ours in the rat.

Table 2. Difference Between 120-Minute and 30-Minute Values for AV Glucose Difference, FBF, and FGU During Hyperinsulinemic Clamp With Euglycemia, and Stepped Hypoglycemia Beginning After 30 Minutes With Intraarterial Saline, Phentolamine, Phentolamine + Propranolol, and Propranolol Alone

Condition	AV Difference (mg/dL)	FBF (mL/min/100 mL)	FGU (mg/min/100 mL)
Euglycemia	5.6 ± 2.6	−0.31 ± 0.11	0.11 ± 0.07
Hypo + Sal	−1.9 ± 2.2*	2.6 ± 0.7*	0.17 ± 0.09
Hypo + Prop	2.0 ± 1.0*	−0.81 ± 0.4†	−0.020 ± 0.039
Hypo + Phen	−1.3 ± 1.1*	13 ± 1.2†	0.35 ± 0.14
Hypo + PP	−0.8 ± 0.98*	−1.7 ± 1.6‡	−0.23 ± 0.15*‡

NOTE. See Table 1 for abbreviations.
*$P < .05$ *v* euglycemia.
†$P < .05$ *v* Hypo + Sal.
‡$P < .05$ *v* Hypo + Phen.

However, they found normal vasodilation during hypoglycemia with combined local α- and β-adrenergic blockade, whereas we found mild vasoconstriction during hypoglycemia with combined blockade. Because of the normal vasodilation during hypoglycemia with combined blockade, they concluded that adrenergic stimulation was not essential for hypoglycemic vasodilation. Our results show that this is not the case in the human. The differences may be due to differences in the relative degree of alpha and beta blockade or may be species-specific.[31]

In the human, Hilsted et al[32] and Capaldo et al[33] have also studied peripheral hemodynamic changes during hypoglycemia using techniques similar to ours. Like the present study, both studies found marked peripheral vasodilation. Hilsted et al also found increased cardiac output and no change in splanchnic resistance. Capaldo et al found that systemic propranolol blocked forearm vasodilation during hypoglycemia. In contrast to these results and ours, Moberg et al,[34] using the microdialysis and ethanol perfusion technique, found no increase in skeletal muscle blood flow during insulin-induced hypoglycemia, but did find an increase in adipose blood flow. Since FBF is primarily skeletal muscle flow, especially during β-adrenergic stimulation,[35] the reason for the conflicting results is not clear.

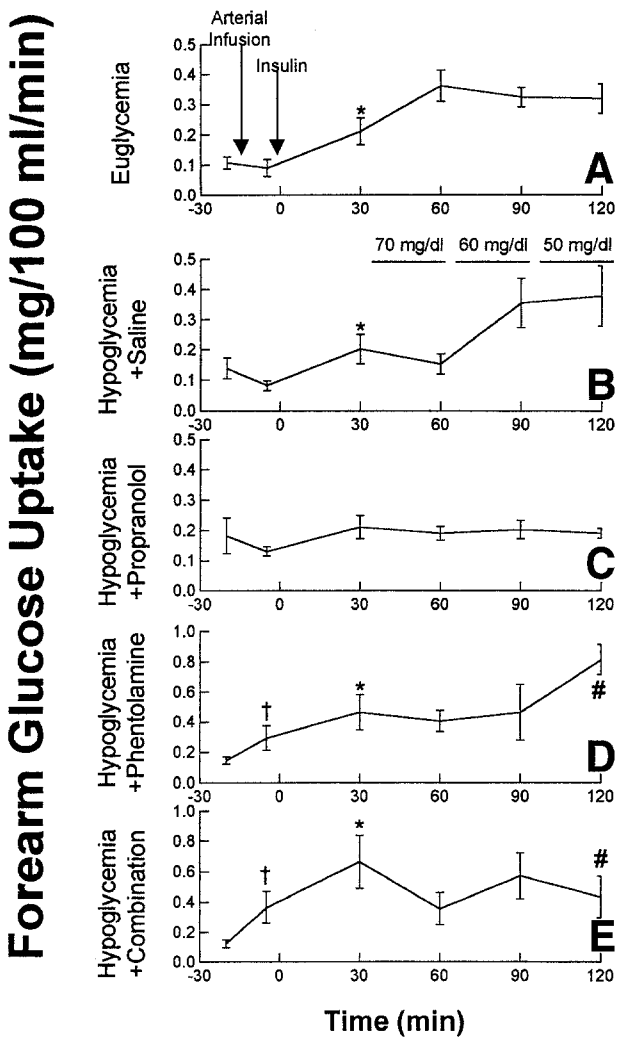

Fig 4. Mean FGU during hyperinsulinemic clamp. Insulin infusion started at 0 min for all conditions. (A) Euglycemia with intraarterial saline infusion throughout. Stepped hypoglycemia began at 30 min for other panels. (B) Intraarterial saline infusion throughout. (C-E) Intraarterial infusion of propranolol, phentolamine, or phentolamine + propranolol beginning at −20 min. *$P < .05$ *v* −5 min (preinsulin) for same session. #$P < .05$ *v* 30 min (euglycemia) for same session. †$P < .02$ *v* −25 min (prearterial infusion) for same session. Error bars represent the SE.

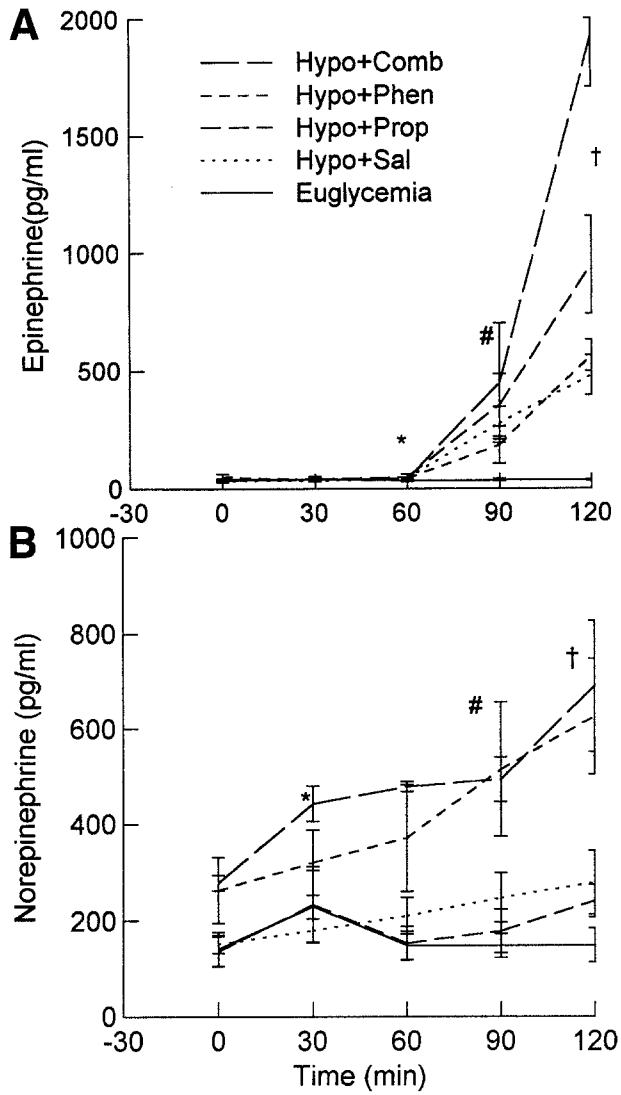

Fig 5. Mean (A) epinephrine and (B) norepinephrine levels during hyperinsulinemic clamp. Insulin infusion started at 0 min for all conditions. The study sessions were euglycemia with intraarterial saline infusion throughout and stepped hypoglycemia beginning at 30 min with intraarterial saline infusion throughout (Hypo + Sal) and intraarterial infusion of propranolol (Hypo + Prop), phentolamine (Hypo + Phen), or phentolamine + propranolol (Hypo + PP) beginning at −20 min. (A) *$P < .05$ *v* 30 min Hypo + Sal only; #$P < .05$ *v* 30 min for all sessions except Hypo + Phen and euglycemia; †$P < .05$ *v* 30 min for all sessions except euglycemia. (B) *$P < .05$ *v* 0 min Hypo + Comb only; #$P < .05$ *v* 30 min for Hypo + Phen; †$P < .05$ *v* 30 min for all Hypo + Phen and Hypo + Comb. Error bars represent the SE.

Table 3. Mean Arterial Plasma Insulin (μU/mL), Venous Free Fatty Acids (mmol/L), FLO (mg/100 mL/min) at the End of Each Period for Euglycemia and Hypoglycemia Plus Intraarterial Phentolamine, Phentolamine + Propranolol, Propranolol, and Saline

Condition	Baseline (−20 min)	Arterial Infusion Alone (0 min)	Insulin Clamp 30 min	Insulin Clamp 120 min
Euglycemia				
Insulin	10 ± 5	11 ± 5	99 ± 28	99 ± 18
FFA		0.57 ± 0.14	0.14 ± 0.06*	0.07 ± 0.05*
FLO		0.13 ± 0.03	0.13 ± 0.03	0.06 ± 0.06
Hypo + Sal				
Insulin	10 ± 3	10 ± 3	91 ± 13	94 ± 22
FFA		0.60 ± 0.09	0.25 ± 0.05*	0.26 ± 0.05*
FLO		0.10 ± 0.02	0.04 ± 0.03	0.12 ± 0.08
Hypo + Prop				
Insulin	7 ± 5	7 ± 3	139 ± 28	93 ± 16
FFA		0.54 ± 0.08	0.17 ± 0.06*	0.11 ± 0.05*
FLO		0.06 ± 0.25	0.02 ± 0.05	0.16 ± 0.04
Hypo + Phen				
Insulin	10 ± 3	10 ± 2	85 ± 11	71 ± 14
FFA		0.50 ± 0.09	0.17 ± 0.05*	0.24 ± 0.06*
FLO		0.22 ± 0.07	0.29 ± 0.06	0.79 ± 0.24†
Hypo + PP				
Insulin	12 ± 6	11 ± 5	108 ± 22	115 ± 18
FFA		0.56 ± 0.12	0.26 ± 0.04*	0.16 ± 0.03*
FLO		0.22 ± 0.06	0.36 ± 0.17	0.41 ± 0.10

NOTE. See Table 1 for abbreviations.
*$P < .005$ *v* baseline.
†$P < .05$ *v* 30 min.

Capaldo et al[33] found a decrease in FGU during hypoglycemia alone compared with hyperinsulinemia, while we found FGU to be similar at the end of the euglycemic and hypoglycemic studies with intraarterial saline infusion. We did find a compensatory decrease in forearm glucose extraction that counterbalanced the increase in the glucose delivery rate. More interestingly, Capaldo et al found that systemic propranolol infusion increased FGU during hypoglycemia, and Atvall et al[36,37] found that systemic propranolol infusion increased total-body glucose uptake during hypoglycemia. On the other hand, we found that FGU was lower during hypoglycemia with intraarterial propranolol versus hypoglycemia with intraarterial saline, although the two were not statistically different. When local propranolol was administered along with local phentolamine, FGU decreased during hypoglycemia and was clearly lower in comparison to hypoglycemia with phentolamine alone, when FGU increased. In contrast, systemic phentolamine and propranolol infusions during hypoglycemia have additive effects to increase peripheral glucose uptake.[1]

The difference between these results and ours is likely due to the mode of administration of propranolol and has important physiologic implications. Systemic propranolol blocks the lipolytic response to hypoglycemia and leads to lower free fatty acid levels and less competitive inhibition of glucose uptake.[38] In our study, venous plasma free fatty acid levels were the same during hypoglycemia with intraarterial propranolol and saline. Thus, the differing effects of the local propranolol infusion in our study and the systemic propranolol infusion used by Calpaldo et al[33] indicate that the major mechanism by which an increase in β-adrenergic activity during hypoglycemia decreases peripheral insulin sensitivity is systemically not locally mediated. Studies using local infusion of epinephrine during euglycemia have yielded conflicting results regarding this point.[39,40]

Traditionally, α-adrenergic stimulation was believed to have little impact on glucose metabolism.[33] Recently, this idea has been challenged. Sympathetic activation due to lower-limb venous occlusion decreases FGU by 20% without a change in epinephrine levels.[16] The effect is partially due to vasoconstriction, since local norepinephrine infusion that produces similar vasoconstriction only decreases glucose uptake by 14%. Our results suggest that α-adrenergic stimulation during hypoglycemia may protect against excess β-adrenergic-mediated vasodilation, since FBF increased dramatically during hypoglycemia with intraarterial phentolamine. The increase in glucose delivery was also associated with a marked increase in FGU and FLO, as well. Increased α-adrenergic activity appears to have little effect on FGU apart from counteracting vasodilation, since the responses did not differ for hypoglycemia with intraarterial phentolamine + propranolol versus hypoglycemia with intraarterial propranolol alone.

Our study was designed specifically to examine the local effects of phentolamine and propranolol on FBF and FGU. It is therefore important that the doses used herein have no systemic effects, particularly on lipolysis, and that marked differences in catecholamine responses are not present. To ascertain that this was the case, we monitored heart rate, blood pressure, and free fatty acids throughout the study. The dose of intraarterial phentolamine clearly had no systemic effects, since the mean blood pressure and heart rate were the same during the hypoglycemia + phentolamine sessions and the hypoglycemia + saline sessions. The higher norepinephrine levels in the venous drainage from the study arm are likely due to increased local α-adrenergic activity in the body's attempt to overcome the block. The hypoglycemic increase in heart rate was diminished during intraarterial propranolol, suggesting that the dose used had some systemic effect. The slightly higher epinephrine levels in this session also suggest this. However, the effect was small, since intraarterial propranolol infusion did not alter the baseline heart rate or mean arterial pressure. Furthermore, there was no evidence of a significant metabolic effect, since plasma free fatty acid levels and glucose infusion rates did not differ during any of the hypoglycemic sessions. Any systemic beta-blockade present would minimize rather than enhance differences between our study and that of Capaldo et al.[33]

Differences in plasma volume between euglycemia and hypoglycemia or between hypoglycemic sessions could also affect our calculation of FGU. Hilsted et al[32] found that plasma volume decreased during hypoglycemia. A lower plasma volume would mean a lower rate of glucose delivery during hypoglycemia compared with euglycemia. This difference could account for the lack of difference in FGU between euglycemia and hypoglycemia with intraarterial saline. However, the effect is likely minimal, since plasma volume only decreases by about 7%.[32] Differences in volume should not be present between hypoglycemic sessions.

One other potential confounder in our investigation is that we studied both male and female subjects. Female rats have been found to have a lower epinephrine response to hypoglycemia,[41] which may decrease the peripheral vasodilatory response to hypoglycemia. We had an insufficient number of women in our study to analyze them separately, but an analysis of the results from the men only does not alter our conclusions.

In conclusion, this study demonstrates that during hypoglycemia, β-adrenergically mediated vasodilation increases forearm glucose delivery. To compensate for the increase in glucose delivery, there is a proportional decrease in forearm glucose extraction which is likely mediated by systemic adrenergic effects, since it was not altered by local β- or combined α- and β-adrenergic blockade.

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