Portal Adrenergic Blockade Does Not Inhibit the Gluconeogenic Effects of Circulating Catecholamines on the Liver

Chang An Chu, Dana K. Sindelar, Doss W. Neal, and Alan D. Cherrington

This study was undertaken to determine the impact of portal adrenergic blockade on the gluconeogenic effects of epinephrine (EPI) and norepinephrine (NE). Experiments were performed on 18-hour fasted conscious dogs and consisted of a 100-minute equilibration, a 40-minute basal, and two 90-minute test periods. A pancreatic clamp was used to fix insulin and glucagon levels at basal values. Propranolol (1 μg/kg · min) and phentolamine (2 μg/kg · min) were infused intraportally during both test periods. Portal infusion of α- and β-adrenergic blockers alone (first test period) slightly increased hepatic glucose production from 2.4 ± 0.4 to 2.8 ± 0.5 mg/kg · min (nonsignificant [NS]) NE (500 ng/kg · min) and EPI (180 ng/kg · min) were infused peripherally during the second test period. Arterial NE and EPI increased from 186 ± 63 to 6,725 ± 913 pg/mL and 76 ± 25 to 2,674 ± 344 pg/mL, respectively. Portal NE and EPI increased from 135 ± 32 to 4,082 ± 747 pg/mL and 28 ± 8 to 1,114 ± 174 pg/mL, respectively. Hepatic glucose production, the maximal gluconeogenic rate, and gluconeogenic efficiency increased from 2.8 ± 0.5 to 3.8 ± 0.4 mg/kg · min ($P < .05$), 0.7 ± 0.3 to 2.1 ± 0.6 mg/kg · min ($P < .05$), and 21% ± 8% to 60% ± 13% ($P < .05$), respectively, in response to catecholamine infusion. Net hepatic lactate balance changed from output (1.5 ± 3.3 μmol/kg · min) to uptake (−11.0 ± 3.8 μmol/kg · min, $P < .05$). Net hepatic glycerol uptake increased from −1.5 ± 0.7 to −5.5 ± 2.0 μmol/kg · min ($P < .05$). Net hepatic uptake of gluconeogenic amino acids did not change significantly. Similarly, hepatic glycogenolysis did not increase during catecholamine infusion. In conclusion, portal delivery of adrenergic blockers selectively inhibits the glycogenolytic effects of EPI and NE on the liver, but allows a marked gluconeogenic response to the catecholamines.

IT IS WELL KNOWN that the sympathetic nervous system plays an important role in the regulation of adipose tissue lipolysis, muscle glycogenolysis, and hepatic glucose production. During stressful conditions and pathophysiological states (ie, shock and hypoglycemia), there is an increase in the production of epinephrine (EPI) from the adrenal medulla and norepinephrine (NE) from the sympathetic nerve endings. In turn, the increase in circulating catecholamines generates changes in lipid, protein, and carbohydrate metabolism.[1-4] Early studies[2,5] showed that elevations in plasma levels of either catecholamine stimulated both gluconeogenesis and hepatic glycogenolysis. In a recent study,[6] we demonstrated that a selective increase in portal EPI and NE levels (ie, little or no increase in arterial catecholamines) increased glucose production solely by stimulating hepatic glycogenolysis. Furthermore, we showed that this stimulation could be completely inhibited by portal infusion of α- and β-adrenergic blockers. Thus, the question arises as to whether selective hepatic adrenergic blockade (ie, portal blocker infusion) would inhibit the extrahepatic (gluconeogenic) effects of the catecholamines on the liver.

The aim of the present study therefore was to determine the impact of hepatic adrenergic blockade on the gluconeogenic effects of high levels of circulating catecholamines on the liver. Catecholamines were infused via a peripheral vein during intraportal adrenergic blocker infusion in dogs maintained on a pancreatic clamp to prevent changes in insulin and glucagon from confounding data interpretation.

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MATERIALS AND METHODS

Experiments were performed on five 18-hour fasted conscious mongrel dogs (20 to 26 kg) of either sex that had been fed a standard diet of meat and chow as described elsewhere.[6] The animals were housed in a facility that met American Association for the Accreditation of Laboratory Animal Care guidelines, and the protocols were approved by the Vanderbilt University Medical Center Animal Care Committee.

Sixteen to 18 days before each experiment, a laparotomy was performed to insert catheters and doppler flow probes into or around appropriate blood vessels as described elsewhere.[6] Each experiment consisted of a 100-minute (−140 to −40 minutes) tracer equilibration and hormone adjustment period, a 40-minute basal period (−40 to 0 minutes), and two 90-minute test periods (0 to 90 and 90 to 180 minutes). In all studies, a priming dose of purified (3-^{3}H)glucose (42 μCi) was administered at −140 minutes, followed by a constant infusion of (3-^{3}H)glucose (0.35 μCi/min), (U-^{14}C)alanine (0.35 μCi/min), and indocyanine green (0.1 mg/m^2 · min). An infusion of somatostatin (0.8 μg/kg · min) was started at −130 minutes to inhibit endogenous insulin and glucagon secretion. Concurrently, intraportal replacement infusions of insulin (300 μU/kg · min) and glucagon (0.65 ng/kg · min) were started. The plasma glucose level was monitored every 5 minutes and was kept at a euglycemic value by adjusting the rate of insulin infusion. The final alteration in the insulin infusion rate was made at least 30 minutes before the start of the basal period, and the rate of insulin infusion (mean, 224 μU/kg · min) remained unchanged thereafter. Propranolol (1 μg/kg · min) and phentolamine (2 μg/kg · min) were mixed with ascorbic acid (70 mg/dL) and infused during both test periods via the splenic and jejunal vein catheters. EPI (180 ng/kg · min) and NE (500 ng/kg · min) in a solution of 70 mg/dL ascorbic acid were infused via cephalic vein catheters during the last test period. Blood pressure and heart rate were measured using methods described elsewhere.[6]

Plasma and blood glucose, plasma [^{3}H]glucose and [^{14}C]glucose, blood lactate, glycerol, alanine, β-hydroxybutyrate (BOHB), glutamine, glutamate, glycine, serine, and threonine, and plasma free fatty acids

(FFA) were determined using methods described elsewhere.[6] Insulin, glucagon, cortisol, EPI, and NE were also determined using previously described methods.[6]

Indocyanine green dye and doppler flow probes were used to estimate total hepatic blood flow.[6-8] Total hepatic blood flow in the basal, blockade, and catecholamine periods measured by doppler probe and indocyanine green dye were 29 ± 5, 31 ± 5, and 31 ± 5 mL/kg · min and 24 ± 3, 26 ± 4, and 26 ± 5 mL/kg · min, respectively. Since in our studies hepatic blood flow measured with the doppler method was more stable than with the indocyanine green dye method, the net hepatic substrate-balance data shown in the figures and tables are those calculated using doppler-determined flow.

The net hepatic balance and fractional extraction of blood glucose, lactate, glycerol, BOHB, alanine, other gluconeogenic amino acids, and plasma FFA were calculated using the arteriovenous-difference method described elsewhere.[6] Hepatic glucose production (rate of appearance [Ra]) and utilization (rate of disappearance [Rd]) were determined using both one- and two-compartment models as previously described.[6] The results were similar regardless of which approach was used, because the deviations from steady-state were minimal. The tracer-determined glucose production data shown in Fig 3 are those calculated using the two-compartment model. Gluconeogenic efficiency was assessed using a double-isotope technique described elsewhere.[6] Maximal and minimal rates of gluconeogenesis from circulating gluconeogenic precursors were calculated using methods previously described.[6]

All statistical comparisons were made using repeated-measures ANOVA and univariate F tests or paired Student's *t* test where appropriate. Statistical significance was accepted at *P* less than .05. Data are reported as the mean ± SE.

RESULTS

Hormone Levels

Arterial and portal levels of insulin and glucagon remained at basal values throughout the study (Fig 1), as did the arterial cortisol level (Table 1). Arterial and portal levels of EPI and NE were stable during the basal and first experimental periods in the group (Fig 2). Peripheral infusion of EPI increased arterial and portal plasma levels of EPI from 76 ± 25 to 2,674 ± 344 pg/mL ($P < .01$) and 28 ± 8 to 1,114 ± 174 pg/mL ($P < .01$), respectively. Peripheral infusion of NE increased arterial and portal plasma levels of NE from 186 ± 63 to 6,725 ± 913 pg/mL ($P < .01$) and 135 ± 32 to 4,082 ± 747 pg/mL ($P < .01$), respectively.

Hepatic Blood Flow, Arterial Blood Pressure, and Heart Rate

Hepatic blood flow, mean arterial blood pressure, and heart rate did not change significantly over the course of the study (Table 2).

Glucose Metabolism

Glucose production (Ra) increased slightly from 2.4 ± 0.4 to 2.8 ± 0.5 mg/kg · min during blocker infusion, and then increased further to 3.8 ± 0.4 mg/kg · min ($P < .05$) during catecholamine + blocker infusion (Fig 3). Changes in net hepatic glucose output paralleled changes in Ra (Fig 3). Arterial blood glucose increased slightly from 77 ± 3 to 86 ± 7 mg/dL during the blockade period, and then further increased to 114 ± 6 mg/dL ($P < .05$) during catecholamine + blocker infusion (Fig 3).

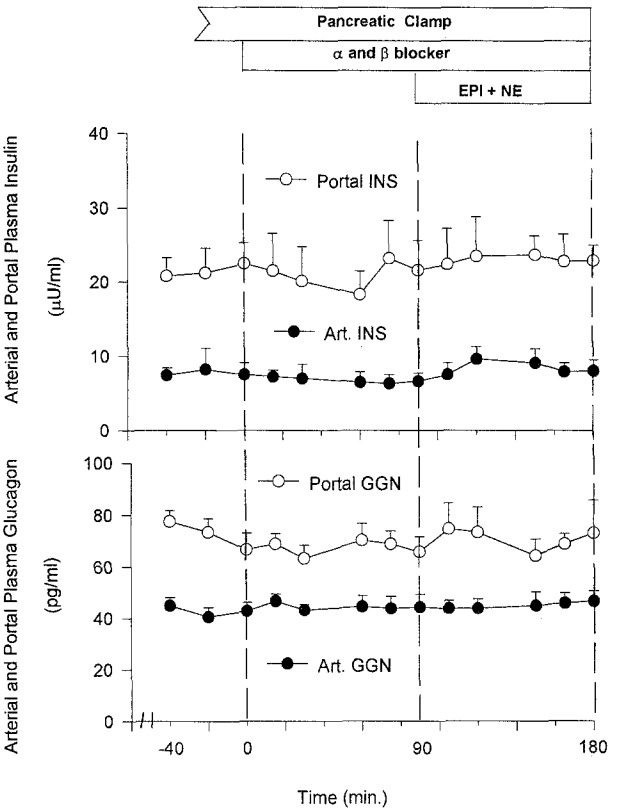

Fig. 1. Arterial (Art.) and portal plasma levels of insulin and glucagon during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE for 5 dogs. GGN, glucagon.

The rate of glucose utilization (Rd) remained stable during blocker infusion, and then increased from 2.4 ± 0.2 to 2.9 ± 0.3 mg/kg · min ($P < .05$) during catecholamine + blocker infusion. Glucose clearance did not change significantly (Table 3).

Arterial Blood Level, Net Hepatic Balance, and Fractional Extraction of Alanine

The arterial blood alanine level was stable during the blockade period, but decreased slightly during catecholamine + blocker infusion (Table 4). Net hepatic alanine uptake increased slightly (from 2.8 ± 0.5 to 3.9 ± 0.4 μmol/kg · min) during blockade, but did not increase further during catecholamine +

Table 1. Arterial Plasma Cortisol Levels During the Basal, Portal Blockade, and Peripheral Catecholamine Periods in the Presence of a Pancreatic Clamp in Conscious 18-Hour Fasted Dogs

	Basal Period (min)	Portal Blockade Period (min)					Portal Blockade + Peripheral Catecholamine Period (min)				
	−40-0	15	30	60	75	90	105	120	150	165	180
Arterial cortisol (μg/dL)	1.6 ± 0.3	1.9 ± 0.6	1.7 ± 0.3	1.3 ± 0.2	1.7 ± 0.5	1.8 ± 0.2	1.6 ± 0.3	1.8 ± 0.6	2.0 ± 0.4	1.9 ± 0.3	2.5 ± 0.5

NOTE. Values are the mean ± SE for 5 dogs.

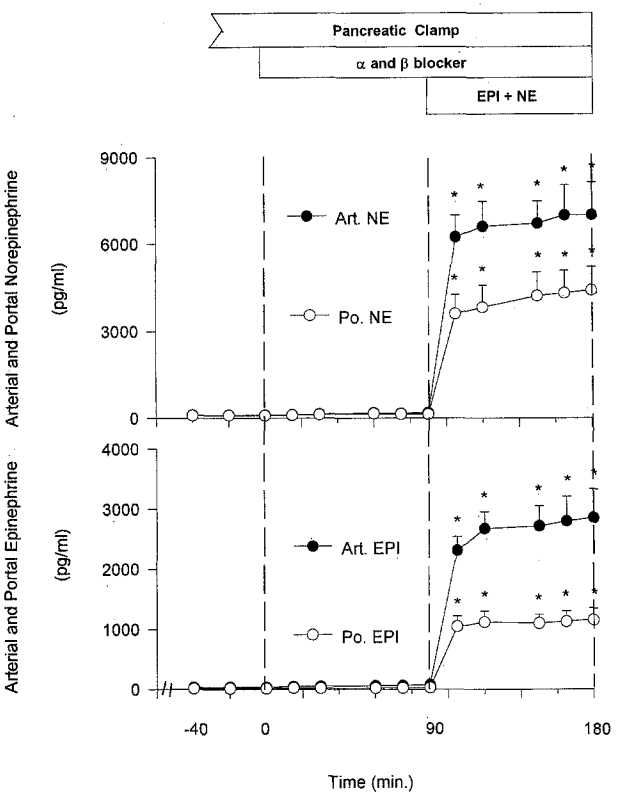

Fig. 2. Arterial (Art.) and portal (Po.) plasma levels of NE and EPI during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE for 5 dogs. *$P < .05$ *v* corresponding basal period.

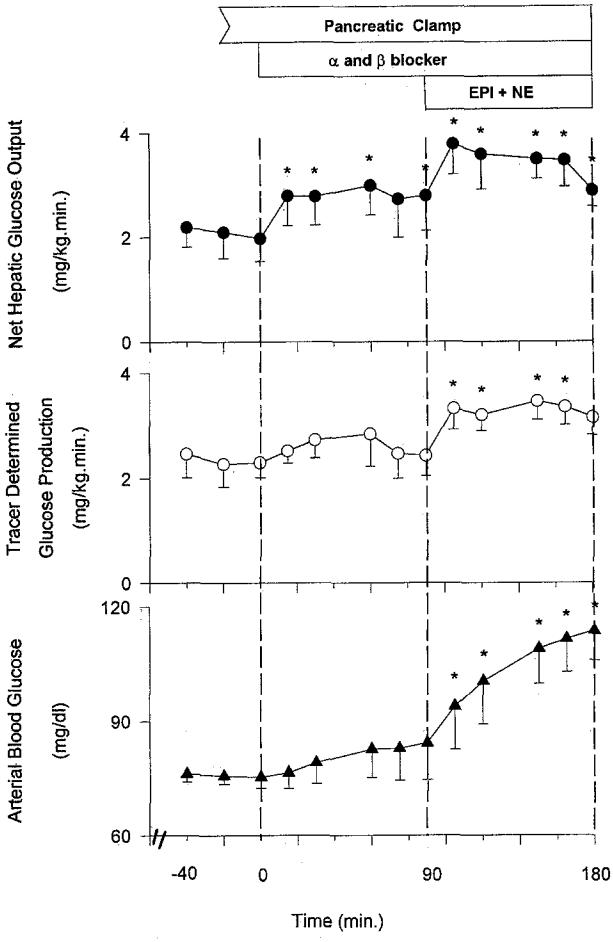

Fig. 3. Net hepatic glucose output, tracer-determined glucose production, and arterial blood glucose during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE. *$P < .05$ *v* corresponding basal period.

blocker infusion (Table 4). Fractional extraction of alanine by the liver increased modestly from 0.27 ± 0.04 to 0.38 ± 0.04 during blockade, but did not increase further during catecholamine + blocker infusion (Table 4).

Arterial Blood Level and Net Hepatic Balance of Lactate

The arterial blood lactate level changed minimally (746 ± 107 to 830 ± 129 μmol/L, nonsignificant [NS]) during blocker infusion, and then increased to 989 ± 160 μmol/L ($P < .05$) during catecholamine + blocker infusion (Fig 4). Net hepatic lactate output decreased slightly from 4.6 ± 3.1 to 1.5 ± 3.2 μmol/kg · min (NS) during blockade, and switched to net uptake (−11.5 ± 4.0 μmol/kg · min, $P < .05$) during catecholamine + blocker infusion (Fig 4).

Arterial Blood Level, Net Hepatic Balance, and Fractional Extraction of Glycerol

Arterial blood glycerol was stable during blockade, and then increased from 60 ± 14 to 248 ± 50 μmol/L ($P < .05$) during catecholamine + blocker infusion (Fig 5). Net hepatic glycerol uptake increased slightly (−0.7 ± 0.2 to −1.5 ± 0.7 μmol/kg · min, NS) during blocker infusion, but then increased to −5.6 ± 1.9 μmol/kg · min ($P < .05$) during catecholamine + blocker infusion (Fig 5). Hepatic fractional extraction of glycerol was not significantly different in the three periods (Fig 5).

Table 2. Mean Arterial Blood Pressure, Heart Rate, and Hepatic Blood Flow During the Basal, Portal Blockade, and Peripheral Catecholamine Periods in the Presence of a Pancreatic Clamp in Conscious 18-Hour Fasted Dogs

Parameter	Basal Period (min)	Portal Blockade Period (min)					Portal Blockade + Peripheral Catecholamine Period (min)				
	−40-0	15	30	60	75	90	105	120	150	165	180
Mean arterial blood pressure (mm Hg)	105 ± 4	100 ± 2	95 ± 2	101 ± 3	96 ± 3	96 ± 4	112 ± 7	108 ± 13	105 ± 7	103 ± 9	105 ± 6
Heart rate (beats/min)	80 ± 4	87 ± 4	81 ± 5	83 ± 4	91 ± 5	92 ± 3	93 ± 9	90 ± 9	90 ± 10	88 ± 5	84 ± 6
Hepatic blood flow (mL/kg · min)	30 ± 4	30 ± 5	31 ± 5	32 ± 5	32 ± 5	31 ± 5	29 ± 5	30 ± 5	31 ± 4	32 ± 5	34 ± 5

NOTE. Values are the mean ± SE for 5 dogs.

Table 3. Tracer-Determined Glucose Utilization and Clearance During the Basal, Portal Blockade, and Peripheral Catecholamine Periods in the Presence of a Pancreatic Clamp in Conscious 18-Hour Fasted Dogs

Parameter	Basal Period (min)	Portal Blockade Period (min)					Portal Blockade + Peripheral Catecholamine Period (min)				
	−40-0	15	30	60	75	90	105	120	150	165	180
Glucose utilization (mg/kg · min)	2.4 ± 0.2	2.3 ± 0.2	2.4 ± 0.2	2.6 ± 0.3	2.4 ± 0.3	2.4 ± 0.2	2.4 ± 0.3	2.7 ± 0.3	2.9 ± 0.3*	2.8 ± 0.2*	2.9 ± 0.2*
Glucose clearance (mL/kg · min)	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.3 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	2.0 ± 0.3	2.1 ± 0.2	1.9 ± 0.1	1.9 ± 0.2

NOTE. Values are the mean ± SE for 5 dogs.
*$P < .05$ *v* corresponding basal period.

Arterial Plasma Level, Net Hepatic Balance, and Fractional Extraction of FFA

The arterial plasma FFA level increased minimally (646 ± 73 to 740 ± 181 μmol/L, NS) during blocker infusion, but then increased to 2,107 ± 309 μmol/L ($P < .05$) during catecholamine + blocker infusion (Fig 6). Net hepatic FFA uptake increased from −2.9 ± 0.8 to −4.3 ± 2.9 μmol/kg · min (NS) during blocker infusion, and then increased further to −11.3 ± 3.8 μmol/kg · min ($P < .05$) during catecholamine + blocker infusion (Fig 6). Hepatic fractional extraction of FFA remained unchanged throughout the study (Fig 6).

Arterial Blood Level and Net Hepatic Balance of BOHB

The arterial BOHB level remained unchanged during blocker infusion, and then increased from 18 ± 5 to 50 ± 14 μmol/L ($P < .05$) during catecholamine + blocker infusion (Fig 7). Net hepatic BOHB output was stable during blocker infusion, and then increased from 0.9 ± 0.3 to 2.6 ± 0.9 μmol/kg · min ($P < .05$) during catecholamine + blocker infusion (Fig 7). The ratio of hepatic BOHB production to FFA uptake was 0.26 ± 0.02, 0.23 ± 0.03, and 0.26 ± 0.05, respectively, during the basal, blockade, and catecholamine + blocker periods (Table 4).

Gluconeogenic Amino Acids

Arterial blood levels and net hepatic balance of glutamate, glutamine, glycine, serine, and threonine did not change significantly over the course of the study (Table 5).

Gluconeogenic Parameters

Gluconeogenic efficiency did not change significantly during blocker infusion, but increased from 21% ± 8% to 60% ± 13% ($P < .05$) during catecholamine + blocker infusion (Fig 8). The maximal gluconeogenic rate (0.5 ± 0.3 to 0.7 ± 0.3 mg/kg · min) did not change during blocker infusion, but increased markedly to 2.1 ± 0.6 mg/kg · min ($P < .05$) during catecholamine + blocker infusion (Fig 8). The minimal gluconeogenic rate did not change during blocker infusion, but increased from 0.2 ± 0.1 to 1.3 ± 0.2 mg/kg · min ($P < .05$) during catecholamine + blocker infusion (Fig 8).

DISCUSSION

The primary aim of the present study was to examine the impact of portal adrenergic blockade on the gluconeogenic effects of circulating catecholamines while plasma insulin and glucagon levels were clamped at basal values. It is well known that catecholamines increase hepatic glucose production as a result of an increase in both hepatic glycogenolysis and gluconeogenesis. The gluconeogenic effects of catecholamines are thought to result primarily from their actions on extrahepatic tissues (indirect). In muscle they stimulate glycogenolysis, whereas in adipose tissue they stimulate lipolysis, thus in turn increasing the gluconeogenic substrate supply to the liver. In a recent study,[6] we showed that the effect of portally delivered catecholamines on hepatic glucose production is solely attributable to a stimulation of glycogenolysis. This is explained by the fact that the efficient removal of EPI and NE by the liver resulted in a very small increase in their arterial levels and the fact that they have no direct gluconeogenic effects on the liver. We also showed that the stimulation of glycogenolysis could be completely blocked by portally infused α- and β-adrenergic blockers. The question thus arises as to whether selective hepatic adrenergic blockade (portal blocker infusion) would alter the gluconeogenic effects of peripherally delivered catecholamines.

Table 4. Arterial Level, Net Hepatic Uptake and Fractional Extraction of Alanine, and Ratio of Net Hepatic BOHB Output to Net Hepatic FFA Uptake During the Basal, Portal Blockade, and Peripheral Catecholamine Periods in the Presence of a Pancreatic Clamp in Conscious 18-Hour Fasted Dogs

Parameter	Basal Period (min)	Portal Blockade Period (min)					Portal Blockade + Peripheral Catecholamine Period (min)				
	−40-0	15	30	60	75	90	105	120	150	165	180
Arterial blood alanine (μmol/L)	343 ± 46	350 ± 50	341 ± 57	321 ± 53	322 ± 49	310 ± 40	309 ± 47	282 ± 41	262 ± 40	258 ± 35	244 ± 20
Net hepatic alanine uptake (μmol/kg · min)	2.8 ± 0.5	3.1 ± 0.2	3.7 ± 0.6	3.9 ± 0.4	3.9 ± 0.7	3.8 ± 0.7	4.3 ± 0.9	3.7 ± 0.4	3.3 ± 0.4	3.8 ± 0.7	3.5 ± 0.4
Hepatic alanine fractional extraction	0.27 ± 0.04	0.29 ± 0.05	0.34 ± 0.02	0.37 ± 0.06	0.38 ± 0.04	0.38 ± 0.03	0.45 ± 0.04	0.40 ± 0.03	0.37 ± 0.03	0.41 ± 0.04	0.39 ± 0.01
BOHB output/FFA uptake	0.26 ± 0.02	0.36 ± 0.04	0.21 ± 0.03	0.20 ± 0.02	0.26 ± 0.04	0.21 ± 0.02	0.24 ± 0.03	0.20 ± 0.03	0.27 ± 0.04	0.26 ± 0.05	0.26 ± 0.05

NOTE. Values are the mean ± SE for 5 dogs.

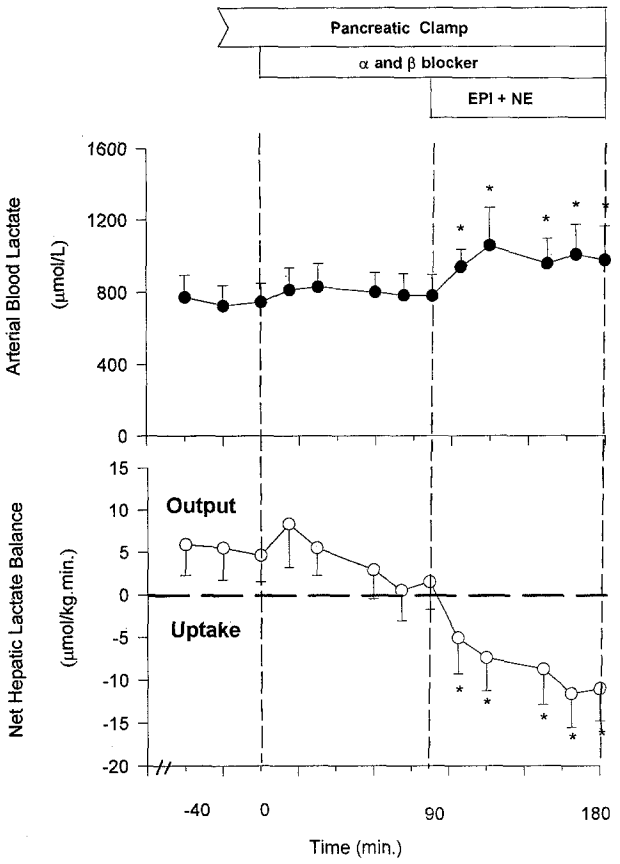

Fig. 4. Arterial blood lactate and net hepatic lactate balance during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE. *$P < .05$ *v* corresponding basal period.

In the current study, arterial plasma levels of EPI and NE were increased to 2,674 ± 344 and 6,725 ± 913 pg/mL, respectively. In turn, portal plasma levels of EPI and NE increased to 1,114 ± 174 and 4,082 ± 747 pg/mL, respectively. In the presence of portal adrenergic blockade and elevated catecholamines, glucose production increased from 2.8 ± 0.5 to 3.8 ± 0.4 mg/kg · min ($P < .05$). Direct measurement of the gluconeogenic rate showed that it increased by 1.1 to 1.4 mg/kg · min depending on whether the minimal or maximal estimates of the process are considered. It is thus evident that in the presence of adrenergic blockade the entire increase in glucose production was attributable to an increase in gluconeogenesis. Hepatic glycogenolysis, on the other hand, did not increase, and may in fact have decreased. The latter would not be surprising and could have resulted from the inhibitory effect of hyperglycemia per se on glycogenolysis.[4,9] The present data confirm our previous observation that the hepatic glycogenolytic effect of the catecholamines could be completely blocked by portal infusion of α- and β-adrenergic blockers.[6] Since gluconeogenic efficiency increased from 21% ± 8% to 60% ± 13% ($P < .05$) and net hepatic uptake of lactate and glycerol increased markedly, the present data further indicate that hepatic adrenergic blockade did not inhibit the gluconeogenic effects of the catecholamines.

Since catecholamines, unlike glucagon, are not thought to directly affect hepatic gluconeogenic efficiency,[6] the question arises as to what caused the increase in efficiency observed during catecholamine infusion. Hepatic adrenergic blockade per se did not alter gluconeogenic efficiency (Fig 8), nor does increasing the gluconeogenic precursor load reaching the liver, as shown in a previous study.[10] On the other hand, Clore et al[11] found that increasing FFA availability increased both gluconeogenesis and glucose production. In agreement with this, Puhakainen and Yki-Jarvinen[12] showed that decreasing FFA availability reduced gluconeogenesis and glucose production. In the present study, the increase in catecholamines caused a marked increase in FFA availability and, as a result, net hepatic FFA uptake. Taken together, these studies suggest that the increase in FFA caused by catecholamines in the present study may play a role in the increased gluconeogenic efficiency. Interestingly, in the present study hepatic ketoneogenesis increased threefold during catecholamine infusion, indicating that more FFA underwent β-oxidation. An increase in FFA oxidation within the liver could stimulate gluconeogenic efficiency by producing additional adenosine triphosphate for the support of gluconeogenesis, by increasing the availability of reduced nicotinamide adeninedinucleotide needed for the glyceraldehyde-3-phosphate dehydrogenase reaction, or by activating pyruvate carboxylase via an increase in acetyl coenzyme A and other thioesters.[13]

Since no significant changes were found in hepatic blood

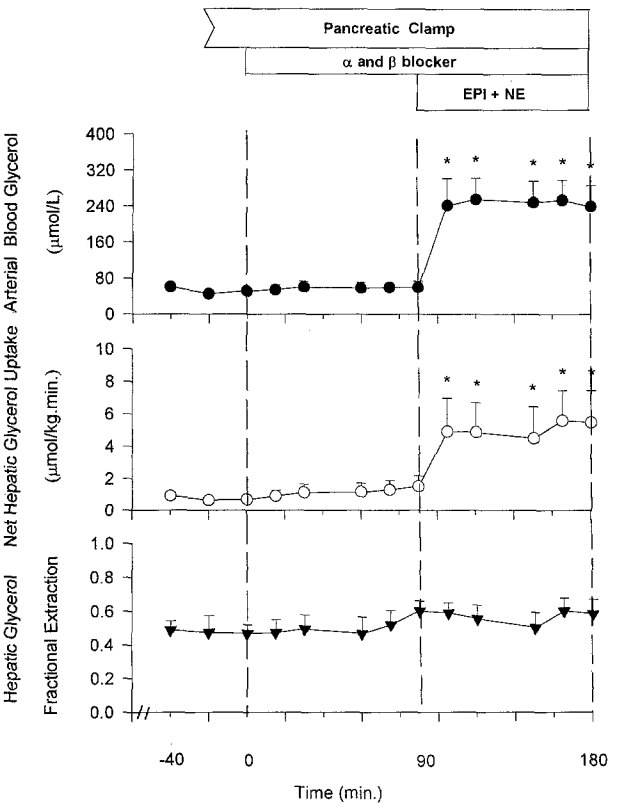

Fig. 5. Arterial blood glycerol, net hepatic glycerol uptake, and hepatic glycerol fractional extraction during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE. *$P < .05$ *v* corresponding basal period.

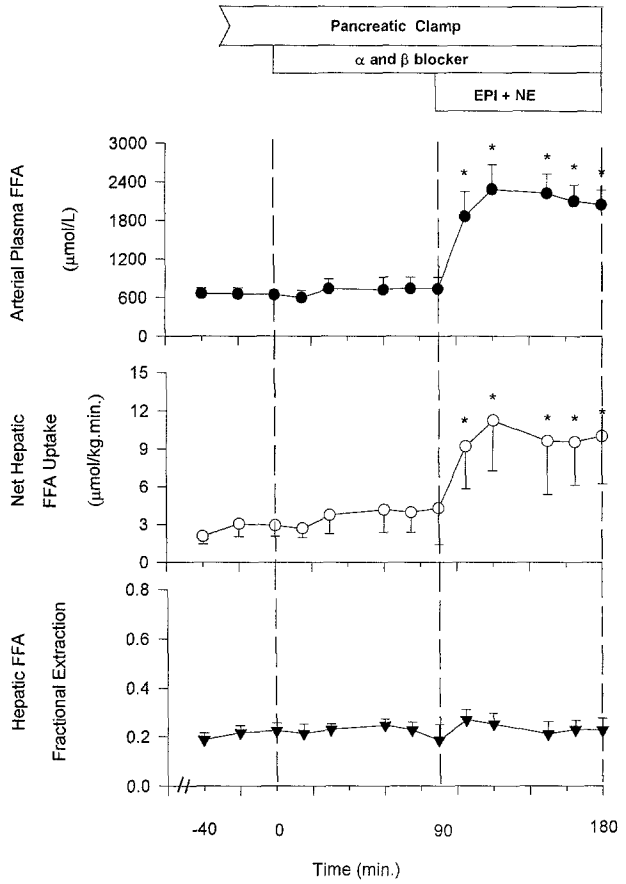

Fig. 6. Arterial plasma FFA, net hepatic FFA uptake, and hepatic FFA fractional extraction during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE. *$P < .05$ *v* corresponding basal period.

flow, mean arterial blood pressure, or heart rate in response to catecholamine infusion, it is possible that a small amount of the adrenergic blockers passed through the liver and entered the peripheral circulation. However, infusion of catecholamines in the absence of blockers in another study showed that changes in the cardiovascular system were not significantly different from those in the present study (in the presence of blockers). It is not possible to estimate with any accuracy the extent to which blockers overflowed from the liver to peripheral tissues. It has been shown in a human study[14] that hepatic extraction of propranolol is 75% and greater than 90% of circulating propranolol and phentolamine are bound to plasma proteins. It is thus likely that only modest amounts of adrenergic blockers were available to muscle and adipose tissue. Furthermore, the high doses of catecholamines used would create a ratio of arterial blockers to arterial catecholamines that was markedly in favor of the catecholamines.

The question thus arises as to whether extrahepatic blockade might have inhibited the effects of catecholamines on muscle (glycogenolysis) and adipose tissue (lipolysis), thus limiting the magnitude of their gluconeogenic effects on the liver. In the current study, catecholamine infusion increased the arterial lactate level only moderately (830 ± 129 to 989 ± 160 μmol/L), but net hepatic lactate uptake increased dramatically (1.5 ± 3.2 to −11.5 ± 4.0 μmol/kg · min). This indicates that the increases in the arterial lactate level and net hepatic lactate uptake must be solely attributable to an increase in extrahepatic lactate production (muscle). An early study by Stevenson et al[4] showed that in the presence of a pancreatic clamp, an arterial EPI level of 2,495 ± 427 pg/mL could increase the arterial lactate level to a greater degree than it did in the present study. Since EPI is also a potent glycogenolytic stimulator in the liver, the increase in the arterial lactate level in the study by Stevenson et al[4] was presumably due to both hepatic and muscle glycogenolysis. The fact that the liver acted as a sink for lactate in the present study probably explains the smaller increase in blood lactate that we observed. When one considers the magnitude of the estimated change in muscle lactate production, it becomes evident that the overflow of adrenergic blockers probably had little impact on the ability of these large doses of catecholamines to alter muscle glucose metabolism. Infusion of catecholamines at the rates used in the present study in the absence of blockers in an early study shed little light on this issue, because the pronounced glycogenolytic effect of catecholamines on the liver led to hyperglycemia, which in turn caused a breakthrough of the somatostatin blockade and resulted in changes in insulin and glucagon levels (data not shown).

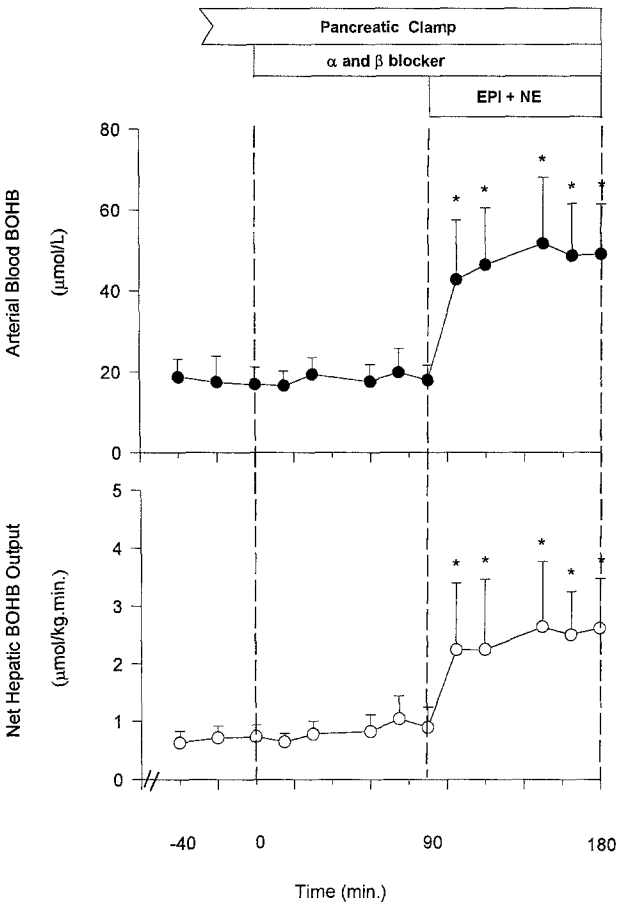

Fig. 7. Arterial blood BOHB and net hepatic BOHB output during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE. *$P < .05$ *v* corresponding basal period.

Table 5. Arterial Blood Levels and Net Hepatic Balances of Glutamate, Glutamine, Glycine, Serine, and Threonine During the Basal, Portal Blockade, and Peripheral Catecholamine Periods in the Presence of a Pancreatic Clamp in Conscious 18-Hour Fasted Dogs

Amino Acid	Arterial Blood Substrate Level (μmol/L)			Net Hepatic Balance (μmol/kg · min)		
	Basal −40-0 min	Blockade 0-90 min	Catecholamines 90-180 min	Basal −40-0 min	Blockade 0-90 min	Catecholamines 90-180 min
Glutamate	114 ± 42	112 ± 43	119 ± 36	−0.2 ± 0.2	−0.2 ± 0.2	0.0 ± 0.2
Glutamine	673 ± 155	645 ± 144	680 ± 155	0.4 ± 0.4	0.0 ± 0.6	0.8 ± 1.0
Glycine	189 ± 22	148 ± 12	162 ± 17	−1.1 ± 0.3	−1.2 ± 0.3	−1.2 ± 0.3
Serine	146 ± 19	115 ± 7	127 ± 17	−0.8 ± 0.3	−0.6 ± 0.1	−0.5 ± 0.2
Threonine	169 ± 17	141 ± 13	160 ± 9	0.0 ± 0.3	−0.4 ± 0.3	−0.1 ± 0.2

NOTE. Negative and positive values in the table indicate net hepatic uptake and output, respectively. Values are the mean ± SE for 5 dogs. Samples were taken at −40, 0, 60, 90, 150, and 180 minutes, respectively, during the experimental periods.

Increases in the arterial blood level and net hepatic uptake of glycerol were 188 μmol/L and 4.1 μmol/kg · min, respectively, during catecholamine infusion. Increases in the arterial plasma level and net hepatic uptake of FFA were 1,367 μmol/L and 7.0 μmol/kg · min, respectively. Since glycerol and FFA levels increased in the presence of increases in glycerol and FFA uptake by the liver, it is clear that the catecholamines must have stimulated lipolysis in adipose tissue. A previous study by Connolly et al[3] showed that in the presence of a pancreatic clamp, an arterial NE level of 3,244 pg/mL could increase arterial blood glycerol by 244 μmol/L, arterial plasma FFA by 1,604 μmol/L, and net hepatic FFA uptake by 8.4 μmol/kg · min, respectively. Therefore, it seems likely that the lipolytic effect of catecholamines in the present study was almost maximal.

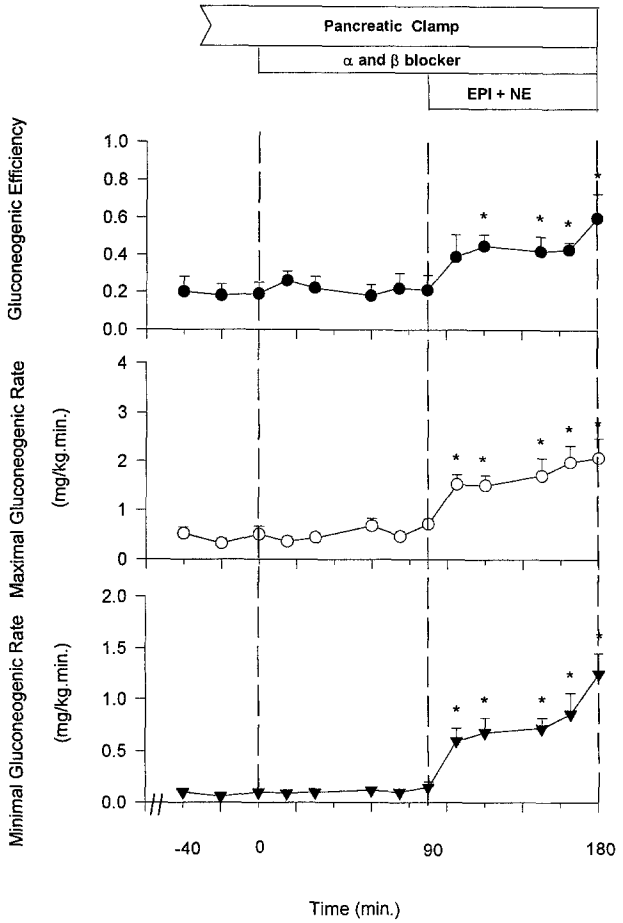

Fig. 8. Gluconeogenic efficiency and maximal and minimal gluconeogenic rates during the basal, portal blockade, and peripheral catecholamine periods in the presence of a pancreatic clamp in conscious 18-hour fasted dogs. Values are the mean ± SE. *$P < .05$ *v* corresponding basal period.

In our recent study,[6] portal infusion of α- and β-adrenergic blockers increased the arterial blood glucose level and hepatic glucose production by 20 mg/dL and 0.7 mg/kg · min, respectively. In the current study, portal infusion of α- and β-adrenergic blockers (same dose) increased the arterial blood glucose level and hepatic glucose production by 9 mg/dL and 0.4 mg/kg · min, respectively. Wolfe and Shaw[15] have also reported that peripheral infusion of α- and β-adrenergic blockers increases glucose production. However, the mechanism by which portal adrenergic blockade increases glucose production is not clear. A possible explanation is that phentolamine and/or propranolol have intrinsic (partial agonist) effects on α- and β-receptors. In this way, they themselves would then stimulate hepatic glucose production (primarily glycogenolysis) and thus increase the arterial blood glucose level and net hepatic lactate output. Clearly, this interesting observation remains to be studied further.

In summary, in the presence of portal adrenergic blockade with a pancreatic clamp, high levels of circulating catecholamines caused (1) an increase in glucose production of 1.0 mg/kg · min (2.8 ± 0.5 to 3.8 ± 0.4); (2) an increase in nonhepatic lactate production and an increase in net hepatic lactate uptake; (3) an increase in lipolysis and net hepatic uptake of glycerol and FFA; and (4) an increase in gluconeogenic efficiency (21% to 60%) and increases in the minimal and maximal gluconeogenic rates (1.1 and 1.4 mg/kg · min, respectively). Thus, it can be concluded that portal delivery of adrenergic blockers selectively inhibits the hepatic glycogenolytic effects of EPI and NE, but has little or no effect on their gluconeogenic actions resulting from their effects on muscle and adipose tissue.

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