Am J Physiol Endocrinol Metab
279: E463–E473, 2000.

The direct effects of catecholamines on hepatic glucose production occur via α_1- and β_2-receptors in the dog

CHANG AN CHU, DANA K. SINDELAR, KAYANO IGAWA, STEPHANIE SHERCK, DOSS W. NEAL, MAYA EMSHWILLER, AND ALAN D. CHERRINGTON
Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Received 22 October 1999; accepted in final form 13 March 2000

Chu, Chang An, Dana K. Sindelar, Kayano Igawa, Stephanie Sherck, Doss W. Neal, Maya Emshwiller, and Alan D. Cherrington. The direct effects of catecholamines on hepatic glucose production occur via α_1- and β_2-receptors in the dog. *Am J Physiol Endocrinol Metab* 279: E463–E473, 2000.—The role of α- and β-adrenergic receptor subtypes in mediating the actions of catecholamines on hepatic glucose production (HGP) was determined in sixteen 18-h-fasted conscious dogs maintained on a pancreatic clamp with basal insulin and glucagon. The experiment consisted of a 100-min equilibration, a 40-min basal, and two 90-min test periods in *groups 1* and *2*, plus a 60-min third test period in *groups 3* and *4*. In *group 1* [α-blockade with norepinephrine (α-blo+NE)], phentolamine (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused portally during both test periods, and NE (50 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused portally at the start of *test period 2*. In *group 2*, β-blockade with epinephrine (β-blo+EPI), propranolol (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused portally during both test periods, and EPI (8 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused portally during *test period 2*. In *group 3* (α_1-blo+NE), prazosin (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused portally during all test periods, and NE (50 and 100 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused portally during *test periods 2* and *3*, respectively. In *group 4* (β_2-blo+EPI), butoxamine (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused portally during all test periods, and EPI (8 and 40 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused portally during *test periods 2* and *3*, respectively. In the presence of α- or α_1-adrenergic blockade, a selective rise in hepatic sinusoidal NE failed to increase net hepatic glucose output (NHGO). In a previous study, the same rate of portal NE infusion had increased NHGO by 1.6 ± 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$. In the presence of β- or β_2-adrenergic blockade, the selective rise in hepatic sinusoidal EPI caused by EPI infusion at 8 $ng \cdot kg^{-1} \cdot min^{-1}$ also failed to increase NHGO. In a previous study, the same rate of EPI infusion had increased NHGO by 1.6 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$. In conclusion, in the conscious dog, the direct effects of NE and EPI on HGP are predominantly mediated through α_1- and β_2-adrenergic receptors, respectively.

adrenergic receptor; hepatic glucose production; glycogenolytic rate

IN STRESSFUL CONDITIONS and pathophysiological states (e.g., exercise, hypoglycemia, and shock), the rise in circulating catecholamines plays an important role in stimulating liver glucose output (2, 5, 7, 21, 22, 26). The stimulatory effects of the catecholamines on hepatic glucose production arise from their actions on extrahepatic tissues (muscle and adipose tissue) and on the liver. Previous studies in humans (21, 22) and other animals (7, 26) have shown that plasma catecholamines can stimulate glycogenolysis in muscle and lipolysis in adipose tissue and thereby move lactate, alanine, glycerol, and free fatty acids (FFA) to the liver. This in turn increases hepatic gluconeogenesis. Our recent studies (2, 3, 5) have shown that the direct hepatic effects of the catecholamines [norepinephrine (NE) and epinephrine (EPI)] are attributable to their stimulation of glycogenolysis. Taken together, the above studies have shown that the direct and indirect effects of the catecholamines on the liver relate to their glycogenolytic and gluconeogenic actions, respectively. Furthermore, in vitro work (10, 25, 27) has suggested that EPI works on the liver primarily via β-receptors, whereas NE works through α-receptors.

Recent studies in dog hepatocytes (14, 15) showed that the distribution of adrenergic receptors in canine liver is similar to the distribution in human liver (13), that is, predominantly the α_1- and β_2-subtypes. Because the intracellular signaling pathways of α_1- and β_2-adrenergic receptor subtypes are mediated through the G protein isoform Gq as well as Ca^{2+}, and the isoform Gs as well as cAMP, respectively (10, 27), it becomes of interest to determine whether EPI and NE bring about the same hepatic action (glycogenolysis) in the dog through different adrenergic mechanisms. This is all the more important in light of our recent finding (5) that the patterns of the stimulatory effects of the two catecholamines on hepatic glycogenolysis are quite different. The direct effect of EPI is similar to that of glucagon, in that it is quick but wanes with time. The action of NE, although on a molar basis less potent than that of EPI, is sustained over time.

The aim of the present study, therefore, was to determine whether EPI and NE exert their action on glucose production through different hepatic adrenergic receptor subtypes in the conscious dog. To focus on their hepatic actions, the catecholamines were infused

Address for reprint requests and other correspondence: C. A. Chu, Dept. of Molecular Physiology and Biophysics, 702 Light Hall, Vanderbilt Univ. School of Medicine, Nashville, TN 37232-0615.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

portally to avoid their effects on muscle and adipose tissue, and a pancreatic clamp was used to eliminate their effects on the pancreas. Similarly, the adrenergic blockers were infused portally to avoid their effects on the cardiovascular system.

METHODS AND MATERIALS

Experiments were carried out on sixteen 18-h-fasted conscious mongrel dogs (20–30 kg) of either sex that had been fed a standard diet of meat and chow described elsewhere (2, 3). The animals were housed in a facility that met the guidelines of the American Association for the Accreditation of Laboratory Animal Care, and the protocols were approved by the Vanderbilt University Medical Center Animal Care Committee.

A laparotomy was performed 16–18 days before each experiment to implant catheters and ultrasonic (Transonic Systems, Ithaca, NY) flow probes into or around appropriate blood vessels, as described elsewhere (2, 3). Each dog was used for only one experiment. All dogs studied had *1*) a leukocyte count $<18{,}000/mm^3$, *2*) a hematocrit >35%, *3*) a good appetite, and *4*) normal stools.

The experiment consisted of a 100-min tracer equilibration and hormone adjustment period (−140 to −40 min), a 40-min basal period (−40 to 0 min), and two 90-min test periods (0–90 and 90–180 min) in *groups 1* and *2*, plus a 60-min third test period in *groups 3* and *4* (Fig. 1). In all studies, a priming dose of purified [3-^{3}H]glucose (42 μCi) was given at −140 min, 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 $mg \cdot m^{-2} \cdot min^{-1}$). An infusion of somatostatin (0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started at −130 min to inhibit endogenous insulin and glucagon secretion. Concurrently, intraportal replacement infusions of insulin (300 $\mu U \cdot kg^{-1} \cdot min^{-1}$) and glucagon (0.65 $ng \cdot kg^{-1} \cdot min^{-1}$) were started. The plasma glucose level was monitored every 5 min, and euglycemia was maintained by adjusting the rate of insulin infusion. The final alteration in the insulin infusion rate was made ≥30 min before the start of the basal period, and the rate of insulin infusion (mean of 242 $\mu U \cdot kg^{-1} \cdot min^{-1}$) remained unchanged thereafter. The study included four groups. In the first group [α-blockade + NE (α-blo+NE); n = 4], phentolamine (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in a solution of 0.07% ascorbic acid was infused during both test periods via the splenic and jejunal vein catheters. NE (50 $ng \cdot kg^{-1} \cdot min^{-1}$) in 0.07% ascorbic acid was then infused during the second test period via the same catheters. In the second protocol (α_1-blo+NE; n = 4), prazosin (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused into the splenic and jejunal catheters during all test periods, and NE (50 and 100 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused through the same catheters during test *periods 2* and *3*, respectively. In the third protocol (β-blo+EPI; n = 4), propranolol (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and EPI (8 $ng \cdot kg^{-1} \cdot min^{-1}$) were infused in place of phentolamine and NE, respectively. In the fourth protocol (β_2-blo+EPI; n = 4), butoxamine (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused into the splenic and jejunal catheters during all test periods, and EPI (8 and 40 $ng \cdot kg^{-1} \cdot min^{-1}$) was infused through the same catheters during the second and third test periods, respectively. The infusion rates of EPI and NE used in *test period 2* of the present study were the same as those used in our previous studies (2, 5), in which EPI and NE alone had significant stimulatory effects on hepatic glucose production through an effect on glycogenolysis. The infusion rates of EPI and NE used in *test period 3* of the present study were the same as those used in our previous study (3), in which the plasma levels of the catecholamines were increased to the extent seen in extremely stressful situations (i.e., severe hypoglycemia, exhaustive exercise, or hemorrhagic shock). The doses of phentolamine and propranolol infused in the current study were the same as those used in our previous study (3), in which the two together completely blocked the hepatic glycogenolytic effect of high levels of NE and EPI. The doses of

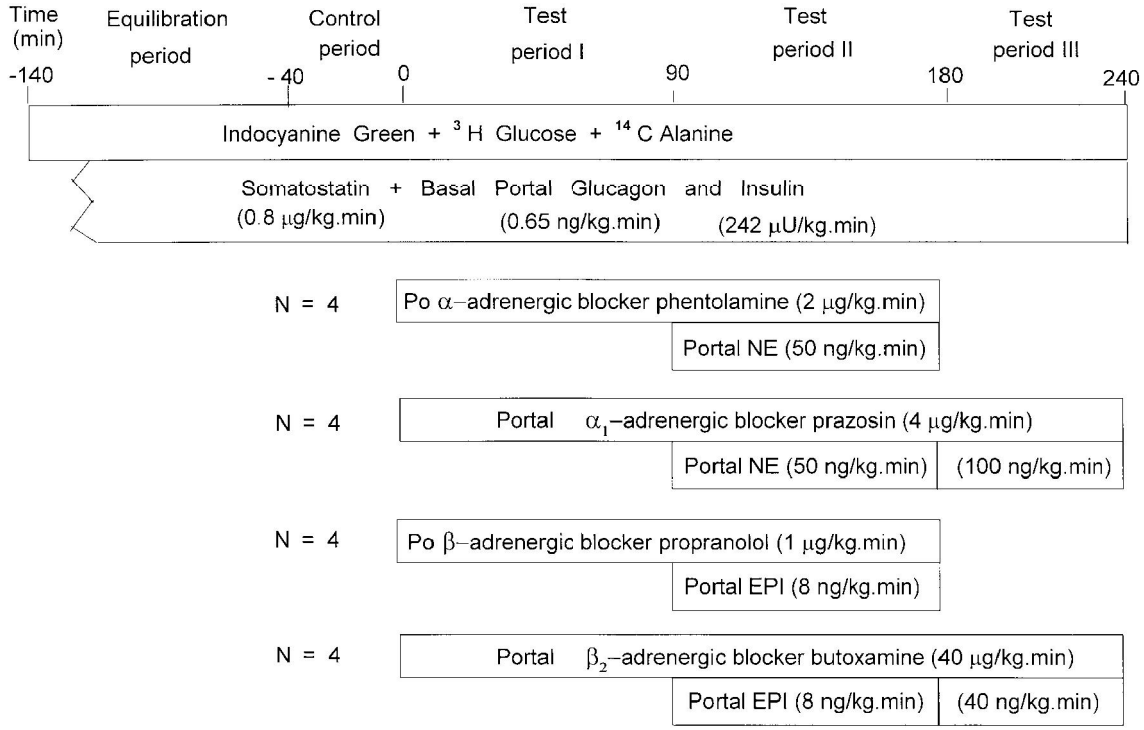

Fig. 1. Protocol. EPI, epinephrine; NE, norepinephrine; Po, portal.

prazosin and butoxamine were chosen from a dose-response study of the effect of the blockers on the actions of NE and EPI, respectively (data not shown). Any direct effects of the adrenergic blockers were presumed not to change between the adrenergic-blockade-alone period and the blockade-plus-catecholamine infusion period.

Blood pressure and heart rate were measured using methods described elsewhere (2, 3). Plasma and blood glucose, plasma [^{3}H]- and [^{14}C]glucose, blood lactate, glycerol, β-hydroxybutyrate (BOHB), alanine, glutamine, glutamate, glycine, serine, threonine, and plasma FFA were determined with previously described methods (2, 3). The levels of insulin, glucagon, cortisol, EPI, and NE were also determined as described elsewhere (2, 3).

Doppler flow probes and indocyanine green dye (ICG) were used to estimate total hepatic blood flow (2, 3). The hepatic blood flow did not change significantly in response to any treatment throughout the study. Because in our studies hepatic blood flows measured by the Doppler method were more stable than those determined by the ICG method, and they did not require an assumption as to the relative contribution of the hepatic artery and portal vein, the data in the figures and tables are those calculated with Doppler-measured flows. The net hepatic balance and fractional extraction of blood glucose, lactate, glycerol, BOHB, alanine, other gluconeogenic amino acids, and plasma FFA were calculated with the use of arteriovenous difference methods described elsewhere (2, 3). Hepatic sinusoidal plasma NE and EPI levels were calculated by means of an equation described previously (2, 5). It should be noted that, to the extent that there was hepatic glucose uptake (HGU), total hepatic glucose release [net hepatic glucose output (NHGO) + HGU] would be slightly higher ($\approx$0.2 mg·kg^{-1}·min^{-1}) than NHGO (2, 19).

Total glucose production (R_a) and utilization (R_d) were determined by use of both one- and two-compartment models, as previously described (2, 3). The results were similar regardless of which approach was employed, because the deviations from steady state were minimal. The R_a and R_d data shown in the figures and tables are those calculated with the two-compartment method. It should also be noted, because the kidneys produce a small amount of glucose, that the rate of endogenous glucose production determined by the tracer method slightly ($\approx$0.3 mg·kg^{-1}·min^{-1}) overestimates total hepatic glucose release (18). This overestimate, however, should be equal in the four groups and would not be expected to change appreciably during the test periods in any group.

Gluconeogenic efficiency was assessed with a double isotope technique described elsewhere (2, 3). Because the conversion of [^{14}C]alanine to [^{14}C]glucose by the kidney is minimal (15), [^{14}C]glucose production in our study was almost exclusively attributable to the liver. Maximal and minimal rates of gluconeogenesis from circulating gluconeogenic precursors were calculated by use of methods described previously (2, 3).

Statistical analysis. All statistical comparisons were made with repeated-measures ANOVA with post hoc analysis by use of univariate *F* tests or the paired Student's *t*-test where appropriate. Statistical significance was accepted at $P < 0.05$. Data are expressed as means ± SE.

RESULTS

Hormone levels. The arterial and portal plasma levels of insulin and glucagon remained at basal values in all groups throughout the study (Fig. 2). Similarly, the arterial plasma cortisol levels did not change significantly (data not shown). The arterial, portal, and hepatic sinusoidal plasma levels of NE and EPI remained unchanged during the basal and first test periods in all protocols (Fig. 3, 4, and Table 1). During the second test period of the α-blo+NE group, the arterial, portal, and hepatic sinusoidal plasma levels of NE increased from 154 ± 63 to 300 ± 51, 137 ± 31 to 3,351 ± 338, and 136 ± 14 to 2,868 ± 275 pg/ml ($P < 0.05$ vs. basal for the portal and sinusoidal levels, Fig. 3), respectively. During the second and third test periods of the α_1-blo+NE group, the plasma levels of NE increased from 227 ± 42 to 320 ± 40 and 404 ± 58 pg/ml in the artery, 218 ± 76 to 3,765 ± 371 and 7,422 ± 926 pg/ml in the portal vein, and 215 ± 57 to 2,875 ± 283 and 5,721 ± 739 pg/ml in the hepatic sinusoid, respectively ($P < 0.05$ vs. basal for the portal and sinusoidal levels, Fig. 3).

During the second test period of the β-blo+EPI group, the arterial, portal, and hepatic sinusoidal plasma levels of EPI increased from 53 ± 9 to 66 ± 11, 29 ± 9 to 746 ± 68, and 32 ± 8 to 668 ± 60 pg/ml ($P < 0.05$ vs. basal for the portal and sinusoidal levels; Fig. 4), respectively. During the second and third test peri-

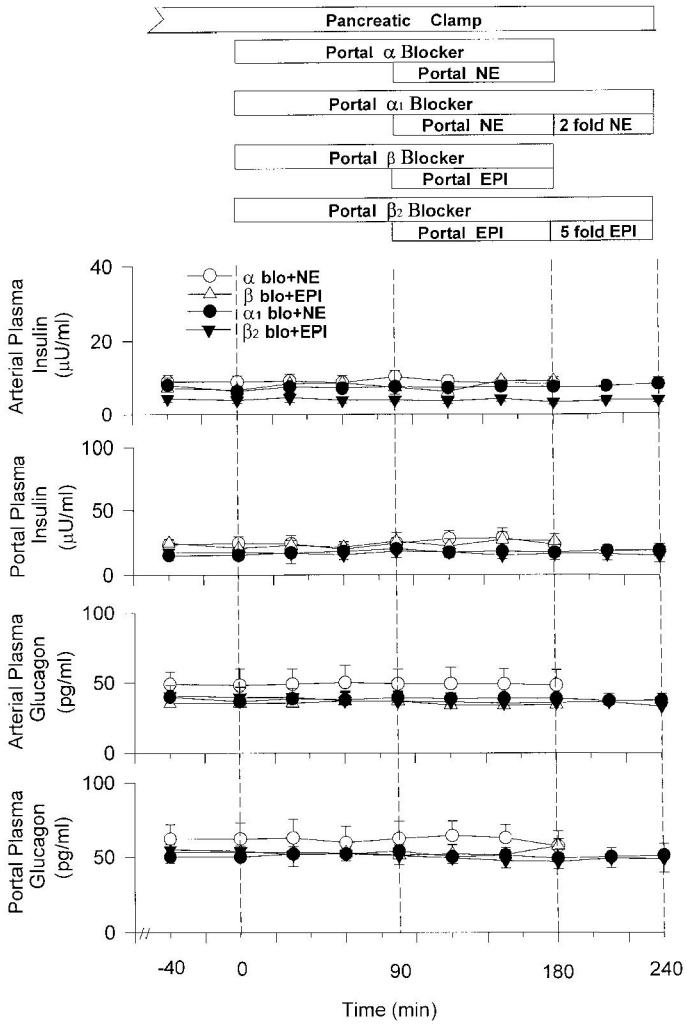

Fig. 2. Arterial and portal plasma levels of insulin and glucagon during control and *test periods 1, 2,* and *3* in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE.

ods of the β_2-blo+EPI group, the plasma levels of EPI increased from 104 ± 36 to 94 ± 23 and 117 ± 50 pg/ml in the artery, 51 ± 10 to 633 ± 110 and 3,221 ± 345 pg/ml in the portal vein, and 68 ± 11 to 508 ± 80 and 2,514 ± 322 pg/ml in the hepatic sinusoid, respectively ($P < 0.05$ vs. basal for the portal and sinusoidal levels; Fig. 4).

Hepatic blood flow, arterial blood pressure, and heart rate. Neither hepatic blood flow, mean arterial blood pressure, nor heart rate changed in any protocol (Table 2).

Glucose levels and kinetics. The arterial blood glucose level did not change significantly in the α-blo+NE, α_1-blo+NE, or β_2-blo+EPI groups throughout the study (Fig. 5, *A* and *B*). NHGO did not change in response to either form of α-adrenergic blockade (Fig. 5*A*). Similarly, α-adrenergic blockade prevented the increase in NHGO and tracer-determined glucose production that normally results from NE infusion.

Portal infusion of the β-blocker propranolol increased the arterial blood glucose level from 83 ± 4 to 114 ± 8 by the end of the first test period ($P < 0.05$; Fig. 5*B*). This was the result of an increase in NHGO from 2.0 ± 0.5 to 2.8 ± 0.7 $mg \cdot kg^{-1} \cdot min^{-1}$, which occurred within 30 min of blocker infusion. In the presence of β-blockade, portal EPI failed to increase the arterial glucose level or NHGO (Fig. 5*B*). Portal infusion of the β_2-blocker butoxamine did not change the arterial blood glucose level or NHGO (Fig. 5*B*). In the presence of the β_2-blocker, neither portal EPI infusion failed to increase the arterial glucose level or NHGO significantly (Fig. 5*B*). The glucose production data obtained by the tracer method confirmed a small stimulatory effect of propranolol (Fig. 5, *A* and *B*).

Tracer-determined R_d did not change significantly during α- or α_1-blockade ($P < 0.05$) and was not affected by portal NE infusion (Table 3). R_d did not change significantly during β-blockade but increased slightly during the portal EPI infusion in the presence of propranolol (Table 3; $P < 0.05$). R_d did not change significantly in the β_2-blo+EPI group (Table 3). Glu-

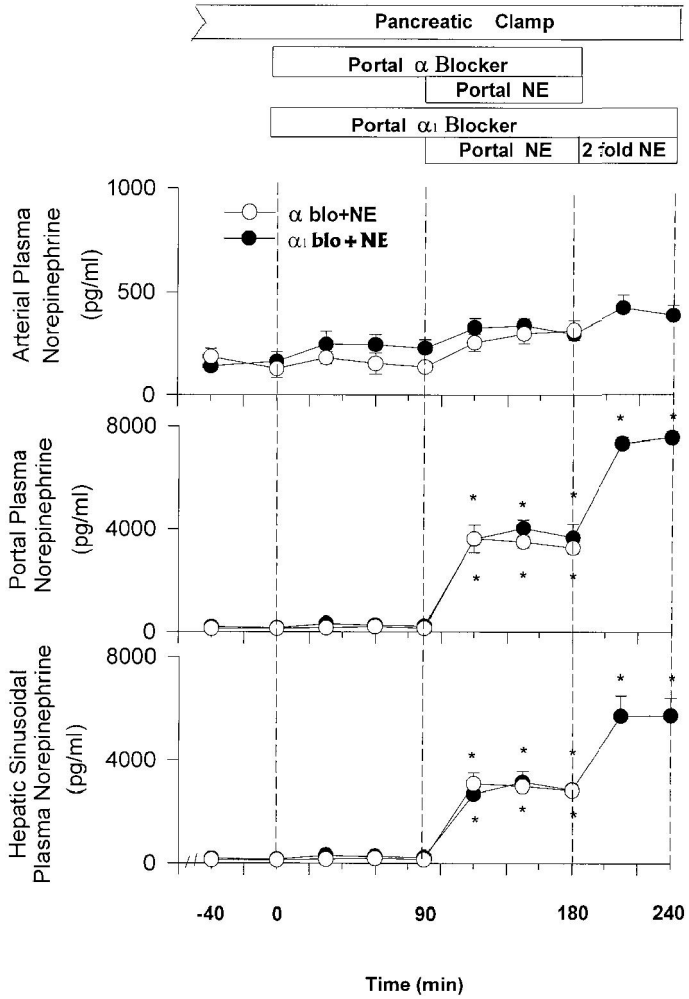

Fig. 3. Arterial, portal, and hepatic sinusoidal plasma levels of NE during control and *test periods 1, 2,* and *3* in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE. *$P <$ 0.05 vs. corresponding basal period.

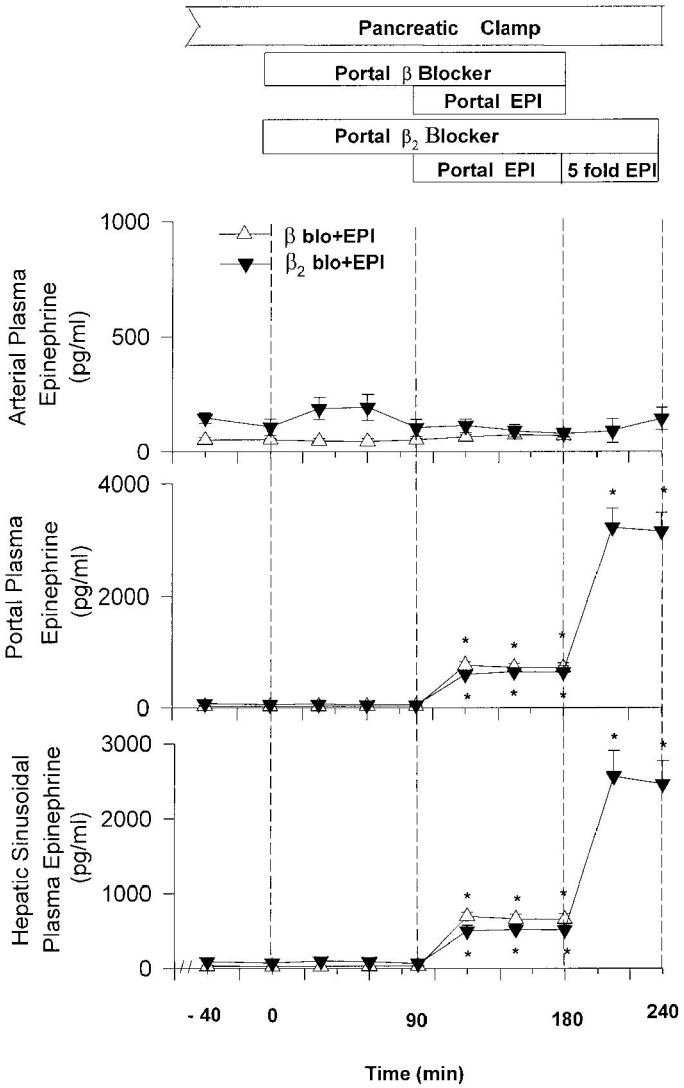

Fig. 4. Arterial, portal, and hepatic sinusoidal plasma levels of EPI during control and *test periods 1, 2,* and *3* in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE. *$P <$ 0.05 vs. corresponding basal period.

Table 1. *Arterial plasma levels of norepinephrine and epinephrine during the basal, portal blockade, portal blockade + catecholamine, and portal blockade + high catecholamine periods of four groups in the presence of a pancreatic clamp in conscious 18-h-fasted dogs*

	Basal Period	Portal Ad Blo			Portal Ad Blo + CATS			Portal Ad Blo + High CATS	
Time, min	−40–0	30	60	90	120	150	180	210	240
Epinephrine, pg/ml									
β-blo + EPI	135 ± 28	164 ± 38	164 ± 45	160 ± 26	148 ± 26	152 ± 17	165 ± 41		
β_2-blo + EPI	118 ± 17	121 ± 16	121 ± 16	110 ± 14	98 ± 12	96 ± 16	93 ± 13	94 ± 16	136 ± 15
Norepinephrine, pg/ml									
α-blo + NE	67 ± 23	52 ± 26	38 ± 25	68 ± 30	73 ± 35	77 ± 30	91 ± 31		
α_1-blo + NE	103 ± 42	65 ± 20	141 ± 80	116 ± 23	96 ± 59	77 ± 30	72 ± 46	79 ± 50	95 ± 45

Data are means ± SE. EPI, epinephrine; NE, norepinephrine; ad blo, adrenergic blockade; CATS, catecholamines. The data in basal period were calculated based on the samples taken at −40 and 0 min. *$P < 0.05$ vs. corresponding basal period.

cose clearance did not change significantly during α- or α_1-blockade but decreased slightly in response to high-dose portal NE infusion (Table 3). Glucose clearance did not change significantly in the β-blo+EPI and β_2-blo+EPI groups (Table 3).

Blood levels and net hepatic balance of lactate. Neither the arterial level of lactate nor the net hepatic lactate balance changed significantly in the α-blo+NE and α_1-blo+NE groups (Fig. 6*A*). The arterial lactate level increased from 515 ± 108 to 677 ± 189 and to 846 ± 262 μmol/l ($P < 0.05$) during the first and second test periods, respectively, in the β-blo+EPI protocol (Fig. 6*B*). Net hepatic lactate balance switched from net uptake to net output (−1.4 ± 1.5 to 4.5 ± 1.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, $P < 0.05$) in response to β-blockade and remained in output during EPI infusion. Neither the arterial level of lactate nor the net hepatic lactate balance changed significantly in the β_2 blo+EPI group (Fig. 6*B*).

Glycerol, FFA, BOHB, and alanine. Neither the arterial levels nor the net hepatic balances of glycerol changed significantly in the α-blo+NE, α_1-blo+NE, and β-blo+EPI groups. The arterial level and net hepatic balance of glycerol decreased slightly in the β_2-blo+EPI group during high-dose portal EPI infusion. Neither the arterial plasma levels nor the net hepatic balances of FFA changed significantly in the α-blo+NE, α_1-blo+NE, and β-blo+EPI groups throughout the study. The arterial plasma level of FFA decreased gradually from 749 ± 93 to 440 ± 90, and to 320 ± 68 μmol/l (both $P < 0.05$), and net hepatic uptake decreased from 2.3 ± 0.8 to 0.8 ± 0.5, and to 0.9 ± 0.4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (both $P < 0.05$), respectively, during the second and third test periods in the β_2-blo+EPI group. Neither the arterial levels nor the net hepatic balances of BOHB changed significantly in the α-blo+NE, α_1-blo+NE, and β-blo+EPI groups throughout the study. The arterial level and net hepatic output of BOHB decreased gradually from 25 ± 4 to 17 ± 3 and to 16 ± 2 μmol/l (both $P < 0.05$), as well as from 0.7 ± 0.1 to 0.4 ± 0.1 and to 0.4 ± 0.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (both $P < 0.05$), respectively, during the second and third test periods in the β_2-blo+EPI group.

The blood level and net hepatic balance of alanine did not change significantly in the α-blo+NE and α_1-blo+NE groups (Table 4). The blood level (283 ± 21 to 399 ± 62 μmol/l, $P < 0.05$) and net hepatic balance

Table 2. *Hepatic blood flow, mean arterial blood pressure, and heart rate during the basal, portal blockade, portal blockade + catecholamine, and portal blockade + high catecholamine periods of four groups in the presence of a pancreatic clamp in conscious 18-h-fasted dogs*

	Basal Period	Portal Ad Blo			Portal Ad Blo + CATS			Portal Ad Blo + High CATS	
Time, min	−40–0	30	60	90	120	150	180	210	240
Hepatic flow, ml· kg^{-1}· min^{-1}									
α-blo + NE	30 ± 5	31 ± 4	30 ± 5	30 ± 5	30 ± 6	29 ± 6	31 ± 6		
α_1-blo + NE	23 ± 6	25 ± 6	22 ± 5	22 ± 6	23 ± 6	22 ± 5	22 ± 5	21 ± 5	22 ± 5
β-blo + EPI	26 ± 6	29 ± 8	28 ± 7	29 ± 8	28 ± 7	29 ± 7	28 ± 7		
β_2-blo + EPI	24 ± 4	25 ± 4	26 ± 4	25 ± 3	25 ± 4	24 ± 4	23 ± 5	23 ± 4	23 ± 4
Blood pressure, mmHg									
α-blo + NE	122 ± 5	116 ± 5	113 ± 3	113 ± 2	112 ± 8	112 ± 9	108 ± 7		
α_1-blo + NE	120 ± 14	111 ± 15	110 ± 8	105 ± 6	97 ± 11	90 ± 11	89 ± 11	90 ± 12	91 ± 13
β-blo + EPI	122 ± 4	119 ± 3	117 ± 4	112 ± 5	113 ± 6	114 ± 7	117 ± 2		
β_2-blo + EPI	150 ± 7	148 ± 14	159 ± 6	153 ± 7	153 ± 8	146 ± 9	141 ± 6	135 ± 12	147 ± 6
Heart rate, beats/min									
α-blo + NE	91 ± 10	83 ± 12	83 ± 15	93 ± 21	95 ± 22	107 ± 28	103 ± 30		
α_1-blo + NE	116 ± 16	113 ± 15	119 ± 13	130 ± 7	125 ± 21	112 ± 12	99 ± 15	102 ± 17	98 ± 15
β-blo + EPI	83 ± 10	86 ± 11	80 ± 8	75 ± 8	82 ± 16	94 ± 18	91 ± 15		
β_2-blo + EPI	99 ± 18	88 ± 20	91 ± 19	87 ± 11	84 ± 11	79 ± 13	68 ± 6	68 ± 7	67 ± 7

Data are means ± SE. The data in basal period were calculated based on the samples taken at −40 and 0 min.

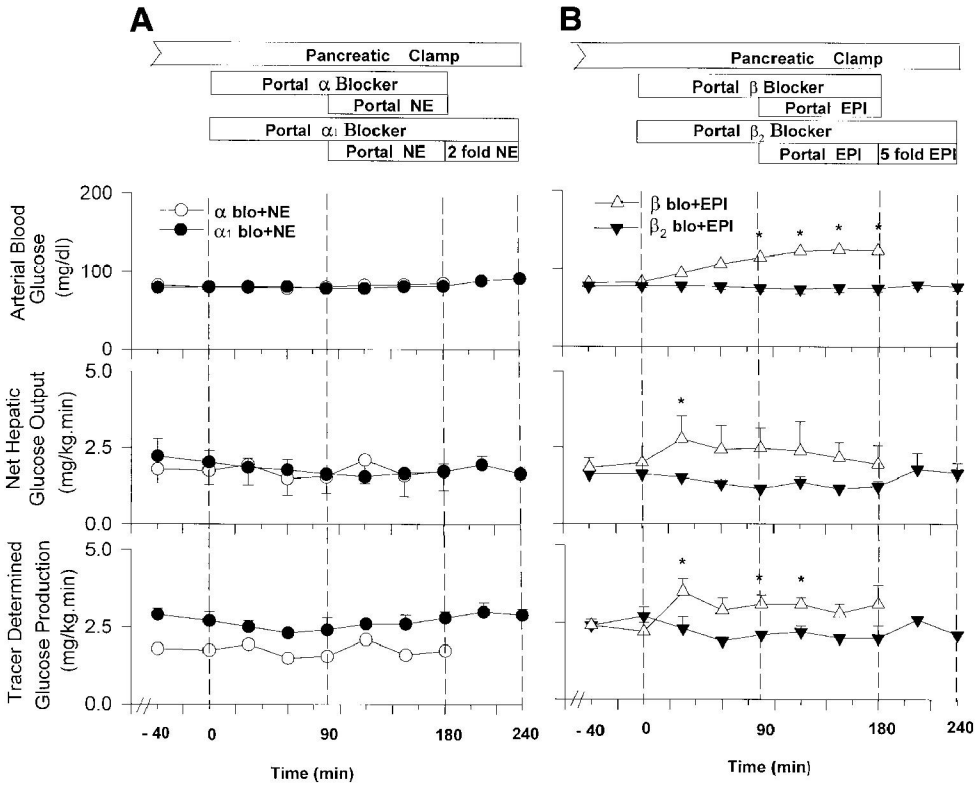

Fig. 5. Arterial blood glucose, net hepatic glucose output, and tracer-determined glucose production during control and *test periods 1*, *2*, and *3* in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE. $^*P < 0.05$ vs. corresponding basal period.

(-1.6 ± 0.4 to -2.6 ± 0.8 μmol·kg^{-1}·min^{-1}, $P < 0.05$) of alanine increased slightly in the β blo+EPI group during the portal EPI infusion. The blood level did not change significantly, and the net hepatic balance of alanine increased slightly in the β_2-blo+EPI group from -2.0 ± 0.2 to -3.8 ± 1.0 μmol·kg^{-1}·min^{-1} during the high dose portal EPI infusion.

Gluconeogenic amino acids. The arterial levels and net hepatic balances of glutamate, glutamine, glycine, serine, and threonine did not change significantly in response to any treatment (Table 5).

Hepatic gluconeogenic and glycogenolytic rates. The gluconeogenic rate did not change significantly in response to any treatment (Fig. 7, *A* and *B*). Because no significant change was seen in gluconeogenic rate, the increase in NHGO observed in response to β-blocker infusion alone must have resulted from an increase in hepatic glycogenolysis (1.8 ± 0.3 to 2.8 ± 0.3 mg·kg^{-1}·min^{-1}; $P < 0.05$; Fig. 7*B*). Because neither NHGO nor gluconeogenesis changed significantly in response to NE infusion, it is clear that in the presence of α- or α_1-blockade, NE was unable to increase hepatic glycogenolysis significantly (Fig. 7, *A* and *B* and Fig. 8). Likewise, in the presence of β- or β_2-blockade, EPI was unable to increase hepatic glycogenolysis significantly (Fig. 7, *A* and *B* and Fig. 8).

Table 3. *TDGU and TDCL during the basal, portal blockade, portal blockade + catecholamine, and portal blockade + high catecholamine periods of four groups in the presence of a pancreatic clamp in conscious 18-h-fasted dogs*

	Basal Period	Portal Ad Blo			Portal Ad Blo + CATS			Portal Ad Blo + High CATS	
Time, min	−40–0	30	60	90	120	150	180	210	240
TDGU (R_d), mg·kg^{-1}·min^{-1}									
α-blo+NE	2.4±0.2	2.1±0.1	2.0±0.2	2.0±0.1	2.1±0.2	2.3±0.1	2.3±0.2		
α_1-blo+NE	2.7±0.2	2.7±0.2	2.4±0.1	2.4±0.1	2.5±0.2	2.6±0.3	2.6±0.1	2.5±0.3	2.5±0.2
β-blo+EPI	2.3±0.2	2.5±0.2	2.4±0.3	2.3±0.2	2.8±0.2	2.8±0.1*	3.1±0.3*		
β_2-blo+EPI	2.6±0.3	2.3±0.4	2.1±0.3	2.3±0.2	2.3±0.2	2.2±0.3	2.3±0.3	2.4±0.2	2.2±0.2
TDCL, ml·kg^{-1}·min^{-1}									
α-blo+NE	2.2±0.2	1.9±0.1	1.9±0.2	1.9±0.1	1.9±0.2	2.1±0.1	2.0±0.1		
α_1-blo+NE	2.6±0.2	2.7±0.3	2.2±0.1	2.2±0.2	2.3±0.1	2.3±0.1	2.3±0.2	2.0±0.1*	1.9±0.1*
β-blo+EPI	2.1±0.2	1.9±0.1	1.7±0.2	1.6±0.2	1.8±0.2	1.7±0.1	1.9±0.1		
β_2-blo+EPI	2.5±0.2	2.2±0.3	2.0±0.2	2.3±0.3	2.3±0.2	2.2±0.3	2.3±0.3	2.3±0.2	2.1±0.2

Data are means ± SE. TDGU, tracer-determined glucose utilization; TDCL, tracer-determined glucose clearance. The data in basal period were calculated based on the samples taken at −40 and 0 min. $^*P < 0.05$ vs. corresponding basal period.

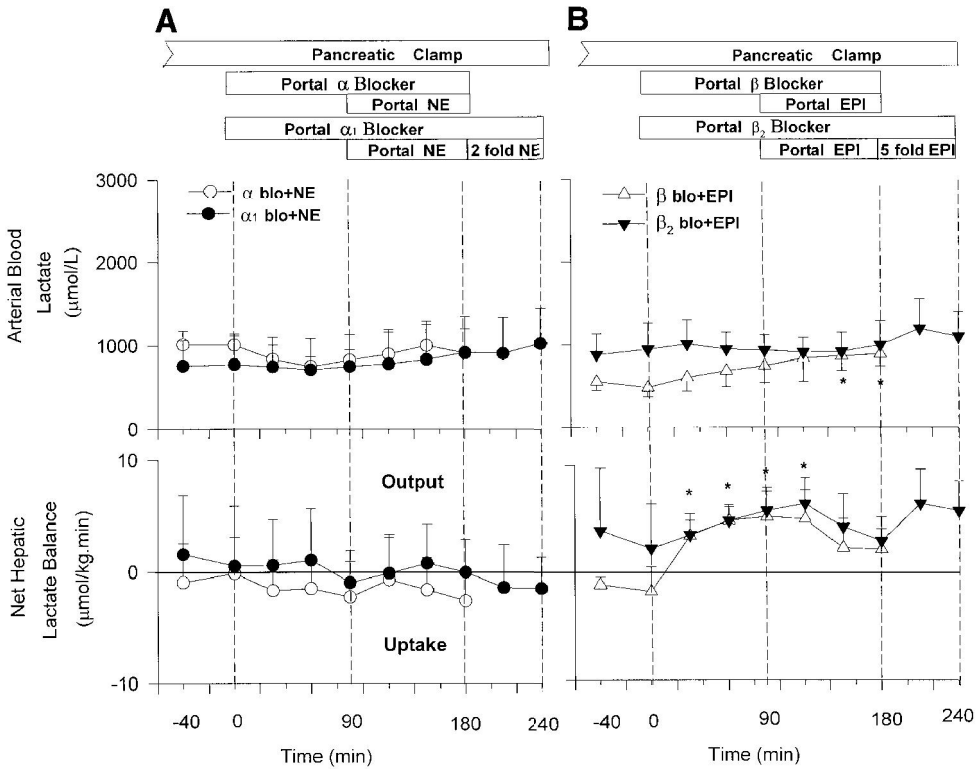

Fig. 6. Arterial blood levels and net hepatic balances of lactate during control and *test periods 1*, *2*, and *3* in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE. $^*P < 0.05$ vs. corresponding basal period.

DISCUSSION

The aim of the present study was to determine whether epinephrine and norepinephrine exert their actions on hepatic glucose production in the conscious dog through different adrenergic receptor subtypes. The arterial and portal levels of insulin and glucagon were clamped at basal values in all groups (Fig. 2), thereby eliminating any effect of the catecholamines on the pancreas. By bringing about a selective increase in hepatic sinusoidal norepinephrine or epinephrine, we

Table 4. *Arterial blood or plasma levels and net hepatic balance of glycerol, FFA, BOHB, and alanine during the basal, portal blockade, and portal blockade + catecholamine periods of four groups in the presence of a pancreatic clamp in conscious 18-h-fasted dogs*

	Arterial Blood or Plasma Level, μmol/l				Net Hepatic Balance, $\mu mol \cdot kg^{-1} \cdot min^{-1}$			
	Basal	P a- or b-blo	P blo+CATS	P blo+Hi-CATS	Basal	P a- or b-blo	P blo+CATS	P blo+Hi-CATS
Time, min	−40–0	0–90	90–180	180–240	−40–0	0–90	90–180	180–240
Glycerol								
α-blo+NE	72±18	69±20	94±17		−1.3±0.3	−1.3±0.2	−1.9±0.6	
α_1-blo+NE	74±15	72±13	76±10	71±13	−1.7±0.3	−1.8±0.4	−2.0±0.3	−1.9±0.5
β-blo+EPI	70±10	66±16	55±10		−1.3±0.3	−1.3±0.4	−1.0±0.3	
β_2-blo+EPI	80±11	80±17	63±10	55±9*	−1.5±0.4	−1.4±0.5	−1.1±0.4	−1.0±0.4*
Plasma FFA								
α-blo+NE	646±110	663±126	762±190		−2.6±0.8	−1.6±1.2	−2.4±0.8	
α_1-blo+NE	583±194	596±158	540±137	546±134	−3.7±1.2	−4.3±1.5	−3.4±1.0	−2.9±1.3
β-blo+EPI	831±117	796±190	639±158		−2.8±0.3	−3.3±1.1	−2.7±1.3	
β_2-blo+EPI	749±93	626±137	440±90*	320±68*	−2.3±0.8	−1.4±0.4	−0.8±0.5*	−0.9±0.4*
BOHB								
α-blo+NE	17±5	19±6	22±9		0.7±0.2	0.7±0.2	0.9±0.2	
α_1-blo+NE	24±5	26±6	26±6	23±5	0.9±0.2	0.9±0.3	0.9±0.2	0.9±0.2
β-blo+EPI	23±4	32±14	23±6		1.1±0.4	1.4±0.8	0.9±0.3	
β_2-blo+EPI	25±4	18±2	17±3*	16±2*	0.7±0.1	0.6±0.2	0.4±0.1*	0.4±0.1*
Alanine								
α-blo+NE	416±48	354±53	346±44		−2.8±0.7	−3.0±1.0	−3.6±1.0	
α_1-blo+NE	373±86	368±99	381±115	373±104	−3.0±0.5	−3.5±0.5	−3.6±0.9	−4.0±1.1
β-blo+EPI	283±21	269±38	399±62*		−1.6±0.4	−2.6±1.0	−2.6±0.8*	
β_2-blo+EPI	473±84	491±72	514±63	560±103	−2.0±0.2	−2.7±0.6	−2.5±0.6	−3.8±1.0*

Data are means ± SE. Negative and positive numbers in the table mean net hepatic uptake and output, respectively. P, portal; FFA, free fatty acids; BOHB, β-hydroxybutyrate. Samples were taken at −40, 0, 30, 60, 90, 105, 120, 150, and 180 min, respectively, during the study. $^*P < 0.05$ vs. 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 portal catecholamine + blockade periods of the α-adrenergic blocker + norepinephrine and β-adrenergic blocker + epinephrine groups in the presence of a pancreatic clamp in conscious 18-h-fasted dogs*

	Arterial Blood Level, μmol/l			Net Hepatic Balance, $\mu mol \cdot kg^{-1} \cdot min^{-1}$		
	Basal	Portal α- or β-blockade	Portal catecholamine + blockade	Basal	Portal α- or β-blockade	Portal catecholamine + blockade
Time, min	−40–0	0–90	90–180	−40–0	0–90	90–180
Glutamate						
α-blo + NE	91 ± 6	85 ± 10	77 ± 7	0.0 ± 0.2	0.0 ± 0.2	0.2 ± 0.5
α_1-blo + NE	104 ± 19	95 ± 20	85 ± 16	−0.2 ± 0.3	0.0 ± 0.1	0.0 ± 0.1
β-blo + EPI	79 ± 6	76 ± 6	70 ± 4	−0.1 ± 0.2	0.1 ± 0.1	−0.1 ± 0.1
β_2-blo + EPI	99 ± 6	91 ± 9	81 ± 6	−0.1 ± 0.2	−0.1 ± 0.2	0.0 ± 0.1
Glutamine						
α-blo + NE	913 ± 62	905 ± 63	900 ± 42	0.5 ± 0.7	−1.4 ± 2.2	0.3 ± 1.6
α_1-blo + NE	1041 ± 108	1039 ± 104	1050 ± 103	1.7 ± 1.0	0.4 ± 0.6	−0.6 ± 0.7
β-blo + EPI	830 ± 74	881 ± 67	780 ± 74	1.7 ± 0.5	1.1 ± 0.6	0.3 ± 1.3
β_2-blo + EPI	982 ± 105	1028 ± 86	998 ± 83	0.4 ± 0.8	0.7 ± 0.7	0.7 ± 0.7
Glycine						
α-blo + NE	216 ± 38	191 ± 33	171 ± 36	−1.4 ± 0.9	−1.4 ± 0.9	−1.1 ± 0.6
α_1-blo + NE	234 ± 33	216 ± 25	192 ± 17	−1.1 ± 0.6	−0.9 ± 0.5	−0.7 ± 0.4
β-blo + EPI	228 ± 28	207 ± 20	180 ± 12	−1.1 ± 0.4	−1.0 ± 0.6	−1.0 ± 0.3
β_2-blo + EPI	282 ± 38	266 ± 37	232 ± 36	−1.0 ± 0.4	−1.2 ± 0.4	−0.7 ± 0.4
Serine						
α-blo + NE	146 ± 20	133 ± 23	126 ± 30	−1.1 ± 0.6	−0.9 ± 0.6	−0.7 ± 0.6
α_1-blo + NE	142 ± 17	131 ± 13	114 ± 8	−0.7 ± 0.3	−0.5 ± 0.2	−0.5 ± 0.2
β-blo + EPI	148 ± 10	136 ± 5	119 ± 6	−0.5 ± 0.2	−0.3 ± 0.3	−0.5 ± 0.1
β_2-blo + EPI	165 ± 18	157 ± 15	142 ± 20	−0.5 ± 0.2	−0.9 ± 0.5	−0.5 ± 0.2
Threonine						
α-blo + NE	245 ± 65	210 ± 47	205 ± 53	−1.6 ± 1.2	−0.9 ± 0.8	−0.6 ± 0.4
α_1-blo + NE	238 ± 48	224 ± 42	220 ± 45	−0.2 ± 0.4	0.0 ± 0.3	−0.2 ± 0.2
β-blo + EPI	217 ± 39	198 ± 36	190 ± 34	−0.1 ± 0.4	−0.2 ± 0.9	−0.1 ± 0.2
β_2-blo + EPI	242 ± 23	245 ± 22	231 ± 30	0.1 ± 0.2	0.2 ± 0.4	−0.2 ± 0.3

Data are means ± SE. Negative and positive numbers in the table mean net hepatic uptake and output, respectively. Samples were taken at −40, 0, 30, 60, 150, and 180 min, respectively, during the study.

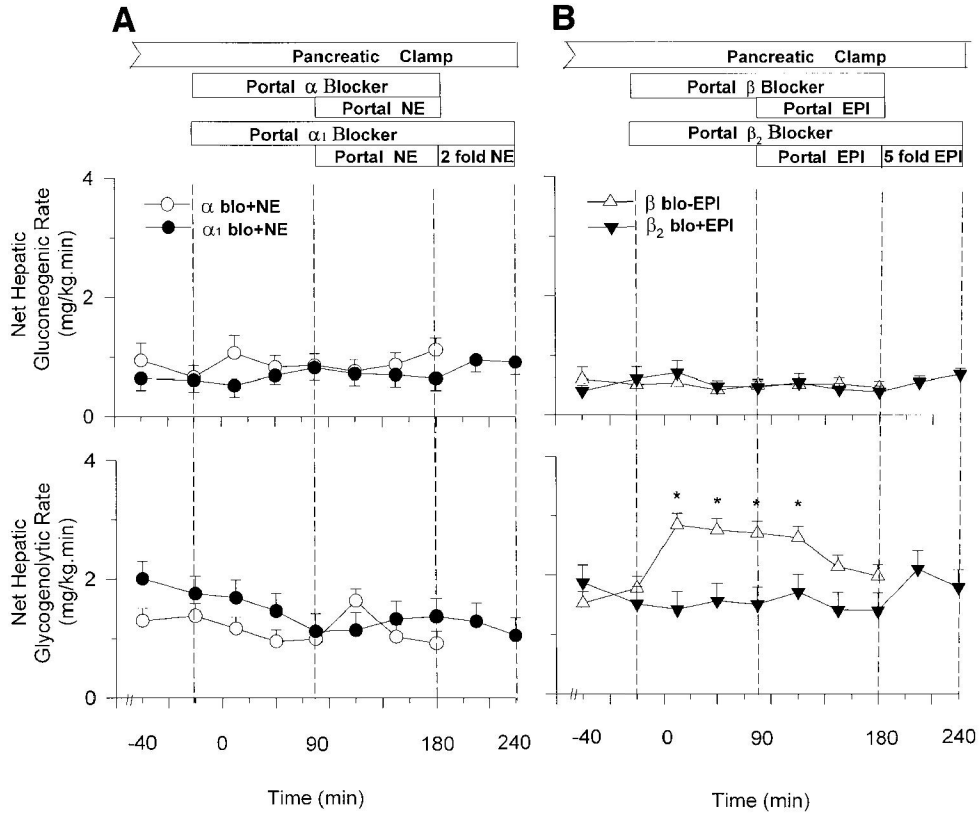

Fig. 7. Net hepatic gluconeogenic and glycogenolytic rates during control and *test periods 1*, *2*, and *3* in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE. $^*P < 0.05$ vs. corresponding basal period.

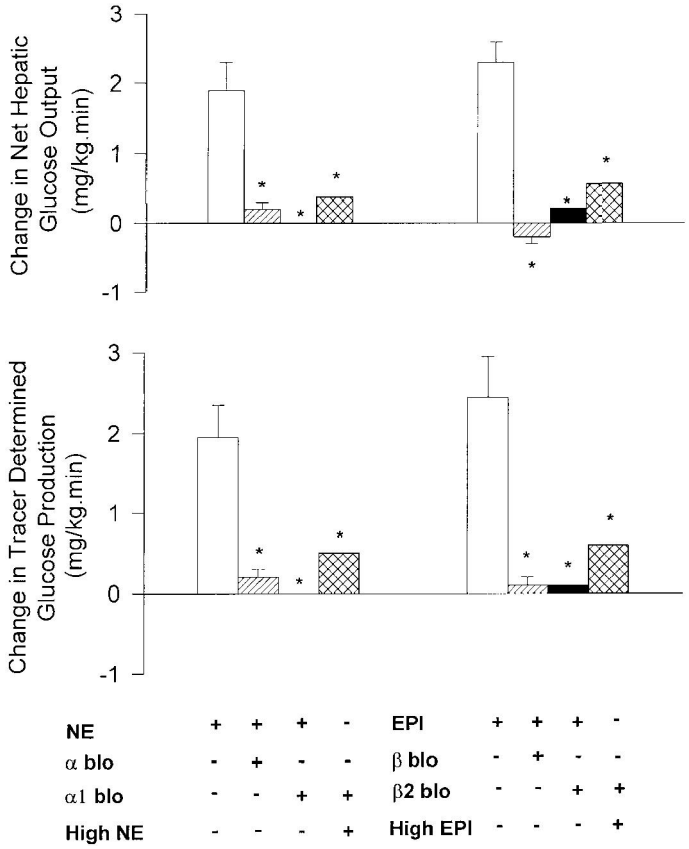

Fig. 8. Summary of the change in net hepatic glucose output and tracer-determined endogenous glucose production over the first 30 min of each test period in presence of a pancreatic clamp in conscious 18-h-fasted dogs. Values are means ± SE. $*P < 0.05$ vs. corresponding NE or EPI treatment alone.

were also able to eliminate the peripheral (muscle and fat) effects of the catecholamines. As a result, there were no significant changes in the blood metabolite levels or any cardiovascular parameters throughout the study (Figs. 6 and 7, Tables 2 and 4). Similarly, by infusing all adrenergic blockers intraportally, we were able to eliminate the effects of these blockers on the cardiovascular system, because most of them were metabolized by the liver through a first pass effect (Table 2). We were thus able to address directly the effect of the catecholamines on the liver per se. Our results showed that the direct effect of norepinephrine on hepatic glucose production was almost completely abolished by α- (phentolamine) or α_1- (prazosin) blockers. Likewise, the direct effect of epinephrine on hepatic glucose production was markedly inhibited by β- (propranolol) or β_2- (butoxamine) blockers.

In one of our previous studies using the pancreatic clamp to fix insulin and glucagon at basal levels (5), the same rate of portal norepinephrine infusion as the one used in the present study increased NHGO from 1.9 ± 0.2 to 3.5 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$ (Fig. 8). It also increased the arterial blood glucose level from 79 ± 5 to 89 ± 6 mg/dl within 30 min. In a control study (5), that degree of hyperglycemia alone decreased NHGO from 2.1 ± 0.2 to 1.8 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$, so the net effect of norepinephrine on hepatic glucose production was a rise of 1.9 $mg \cdot kg^{-1} \cdot min^{-1}$. In the current study, in the presence of α- or α_1-adrenergic blockers, a physiological rise in hepatic sinusoidal norepinephrine had no significant effect on NHGO (1.6 ± 0.5 to 1.9 ± 0.7 or 1.6 ± 0.1 to 1.6 ± 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ over the first 30 min; Fig. 8). Furthermore, in the presence of an α_1-adrenergic blocker, even high sinusoidal plasma norepinephrine levels corresponding to those seen in the synaptic clefts in extremely stressful conditions (≈5,700 pg/ml) failed to increase NHGO significantly (1.7 ± 0.3 to 2.0 ± 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$; Fig. 8). The results obtained with tracer-determined glucose production paralleled those seen with NHGO. Because our earlier study (5) was performed recently using the same methodology, similar insulin (mean of 245 $\mu U \cdot kg^{-1} \cdot min^{-1}$), and the same glucagon infusion rates, the usual caveats regarding the use of historical data for comparison should not apply. Taken together, the data from our current and earlier studies (5) indicate that the direct effect of norepinephrine on hepatic glucose production is markedly inhibited by α-adrenergic blockade and, furthermore, that the effects of the catecholamine are predominantly attributable to α_1-receptors. In our previous study (5), the direct effect of norepinephrine on hepatic glucose production was attributable to its effect on hepatic glycogenolysis. Because no significant changes were seen in any gluconeogenic parameter or in NHGO in the current study, one can conclude that the effect of norepinephrine on glycogenolysis was predominantly mediated by α_1-adrenergic receptors.

Garceau et al. (11) reported that, in the anesthetized dog, the increase in hepatic venous glucose concentration caused by hepatic arterial norepinephrine injection was partially inhibited by either phentolamine or propranolol delivered peripherally. In a human study, Meguid et al. (17) showed that in the absence of a pancreatic clamp, the norepinephrine-induced rise in blood glucose concentration was blocked by 60% when phentolamine was infused. Interpretation of the data from those studies is complicated by the fact that effects of norepinephrine on the pancreas and/or muscle and adipose tissues, as well as on the cardiovascular system and liver, were all present. It has been shown in vitro (6, 12) that norepinephrine has very low affinity for β_2-receptors (7% that of epinephrine) and that it is this β-subtype that predominates in canine liver (14, 17). This is consistent with our data in which, in the presence of the α_1-blocker, a slight glycemic (15–20%) effect (Fig. 8) was seen only in response to extremely high norepinephrine infusion (*test period 3*). This may also explain the failure of others to completely block the effects of norepinephrine. Likewise, in vitro work has shown that norepinephrine has a high affinity for α_1-receptors, and it is this α-adrenergic receptor subtype that is found in the canine liver (6, 12, 14). Thus these in vitro data are in line with our findings and suggest that, in the dog, norepinephrine stimulates hepatic glucose production predominantly by interaction with α_1-receptors.

In another of our previous studies using the pancreatic clamp (2), portal epinephrine infusion at the same rate as in the present study increased NHGO from 2.1 ± 0.3 to 3.7 ± 0.5 mg·kg^{-1}·min^{-1} (Fig. 8) and arterial blood glucose level from 76 ± 2 to 92 ± 3 mg/dl within 30 min. In the control protocol (2), that degree of hyperglycemia alone decreased NHGO from 2.1 ± 0.2 to 1.4 ± 0.3 mg·kg^{-1}·min^{-1}, so the net effect of epinephrine on hepatic glucose production was an increase of 2.3 mg·kg^{-1}·min^{-1}. In the present study, the effect of the same rise in hepatic sinusoidal epinephrine on NHGO was completely inhibited by portal β- or β_2-adrenergic blockers (2.4 ± 0.9 to 2.2 ± 0.9 or 1.2 ± 0.1 to 1.4 ± 0.2 mg·kg^{-1}·min^{-1} over the first 30 min; Fig. 8). Once again, the similarity of our earlier study (2) to the current one and its recent date should allow direct comparison between the two groups. In that study, the direct effect of epinephrine on hepatic glucose production was solely attributable to its effect on hepatic glycogenolysis. Because no significant changes were seen in any gluconeogenic parameter or in NHGO in the current study, one can conclude that the effects of epinephrine on glycogenolysis must be inhibited by β-adrenergic blockade.

It should be noted that, in the presence of the β_2-adrenergic blocker butoxamine, a sinusoidal plasma epinephrine level seen only during extreme stress (≈2,500 pg/ml) increased both NHGO and tracer-determined glucose production by only 0.6 mg·kg^{-1}·min^{-1} over the first 30 min [≈75% inhibition of the response expected based on our earlier data (3)]. There are two possible explanations for the incomplete blockade. First, because the effect of this high level of plasma epinephrine on glucose production was inhibited only 15% by a low-dose butoxamine infusion (4 μg·kg^{-1}·min^{-1}; data not shown), it is possible that the dose of butoxamine (40 μg·kg^{-1}·min^{-1}) used in the present study was not high enough to completely abolish the effect of the high level of epinephrine on β_2-adrenergic receptors. Second, it could be that the effect was attributable to a small α-adrenergic action of the catecholamine on hepatic glucose production.

In an earlier study, Steiner et al. (25) showed that preincubation of canine hepatocytes with propranolol (200 nmol/l) caused a 77% inhibition of the glucose output caused by epinephrine. Phentolamine (200 nmol/l), on the other hand, caused a 27% inhibition of the glucose output caused by epinephrine. This suggested that the glycogenolytic effect of epinephrine on the canine hepatocyte is mediated primarily by a β-adrenergic mechanism but with a small α-component. Rizza et al. (20) reported that, in the absence of a pancreatic hormone clamp, epinephrine can stimulate glucose production in humans via both α- and β-adrenergic mechanisms. Because both insulin and glucagon increased in their study, it was not possible to determine which adrenergic mechanism was involved in the direct effect of epinephrine on hepatic glucose production.

As noted above, our results suggest that epinephrine exerts little of its effects through α-stimulation. In agreement with our data, Deibert and DeFronzo (9) reported that, in the presence of a euglycemic-hyperinsulinemic clamp, all of the effects of epinephrine on glucose production in the human could be accounted for by a β-adrenergic mechanism. Similarly, Best et al. (1), in another human study, showed a lack of a direct α-adrenergic effect of epinephrine on glucose production in the presence of a pancreatic clamp. Likewise, Rizza et al. (20) reported that, in the presence of pancreatic hormone clamp in the human, peripherally delivered phentolamine failed to alter the effects of peripherally delivered epinephrine on glucose production. On the other hand, peripherally delivered propranolol (β-adrenergic blocker) inhibited the effects of epinephrine by 80%. As in our study, the failure to completely inhibit the effect of epinephrine on hepatic glucose production may have resulted from incomplete blockade or a small α-component (20). Taking all of the findings together, one can conclude that the effect of epinephrine on NHGO in the conscious dog is predominantly mediated by β_2-adrenergic receptors.

Our previous studies (3, 4) showed that combined α- + β-adrenergic blockade per se increased arterial glucose (77 ± 3 to 92 ± 7 mg/dl), NHGO (2.0 ± 0.2 to 3.3 ± 0.3 mg·kg^{-1}·min^{-1}), and net hepatic lactate output (2.8 ± 2.7 to 9.1 ± 4.8 μmol·kg^{-1}·min^{-1}). In the current study, β-adrenergic blockade with propranolol alone increased arterial glucose (86 ± 4 to 114 ± 12 mg/dl), as well as NHGO (1.7 ± 0.5 to 2.5 ± 1.0 mg·kg^{-1}·min^{-1}), and switched the liver from net lactate uptake to output (−2.4 ± 2.6 to 3.7 ± 2.2 μmol·kg^{-1}·min^{-1}). No such change was seen during the portal infusion of the α-adrenergic blockers or the β_2-blocker. The present data thus indicate that the effects of the combined α- + β-adrenergic blockade seen in our previous study (3, 4) were attributable to the β-adrenergic blocker propranolol. Also, because no such change was seen during the portal infusion of the β_2-adrenergic blocker butoxamine in the present study, the effect must be attributable to propranolol itself or to β_1-stimulation and not to β_2-adrenergic receptor stimulation. In agreement with our data, Shaw and Wolfe (24) reported that propranolol alone increased glucose production either in the presence or in the absence of a pancreatic hormone clamp in conscious dogs. The explanation for the effect of propranolol on hepatic glucose production is not clear. One possibility is that propranolol may have an intrinsic (partial agonist) effect on β-adrenergic receptors and thereby increase glucose production. Another is that propranolol may inhibit glucose oxidation and energy expenditure (7, 23, 24) and thus indirectly increase hepatic glucose release. Regardless, the explanation for this interesting finding remains to be elucidated.

In conclusion, *1*) the direct effect of norepinephrine on hepatic glucose production (glycogenolysis) is predominantly mediated through α_1-adrenergic receptors; *2*) the direct effect of epinephrine on hepatic glucose production (glycogenolysis) is predominantly mediated through β_2-adrenergic receptors.

We are grateful to Dr. Mary Courtney Moore for valuable comments and careful review of this manuscript. We specially appreciate assistance from Margaret Salvino, Jon Hastings, Eric J. Allen, Pam Venson, Wanda Snead, Paul Flakoll, E. Patrick Donahue, and Yang Ying.

This research was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases Grants 2RO1 DK-18243 and 5P60 DK-20593 (Diabetes Research and Training Center).

REFERENCES

1. **Best JD, Ward WK, Pfeifer MA, and Halter JB.** Lack of a direct α-adrenergic effect of epinephrine on glucose production in human subjects. *Am J Physiol Endocrinol Metab* 246: E271–E276, 1984.
2. **Chu CA, Sindelar DK, Neal DW, Allen EJ, Donahue EP, and Cherrington AD.** Comparison of the direct and indirect effects of epinephrine on hepatic glucose production. *J Clin Invest* 99: 1044–1056, 1997.
3. **Chu CA, Sindelar DK, Neal DW, and Cherrington AD.** Direct effects of catecholamines on hepatic glucose production in conscious dogs are due to glycogenolysis. *Am J Physiol Endocrinol Metab* 271: E127–E137, 1996.
4. **Chu CA, Sindelar DK, Neal DW, and Cherrington AD.** Portal adrenergic blockade does not inhibit the gluconeogenic effects of circulating catecholamines on the liver. *Metabolism* 46: 458–465, 1997.
5. **Chu CA, Sindelar DK, Neal DW, and Cherrington AD.** The direct effect of norepinephrine on HGP in the conscious dog. *Am J Physiol Endocrinol Metab* 274: E162–E171, 1998.
6. **Clutter WE, Rizza RA, and JE, Gerich.** Regulation of glucose metabolism by sympathochromaffin catecholamines. *Diabetes Metab Rev* 4: 1–15, 1988.
7. **Connolly CC, Steiner KE, Stevenson RW, Neal DW, Williams PE, Alberti KGMM, and Cherrington AD.** Regulation of glucose metabolism by norepinephrine in conscious dogs. *Am J Physiol Endocrinol Metab* 261: E764–E772, 1991.
8. **DeFronzo RA, Thorin D, Felber JP, Simonson DC, Thiebaud D, Jequier E, and Golay A.** Effect of beta and alpha adrenergic blockade on glucose-induced thermogenesis in man. *J Clin Invest* 73: 633–639, 1984.
9. **Deibert DC and DeFronzo RA.** Epinephrine-induced insulin resistance in man. *J Clin Invest* 65: 717–721, 1980.
10. **Exton JH.** Mechanisms of hormonal regulation of hepatic glucose metabolism. *Diabetes Metab Rev* 3: 163–183, 1987.
11. **Garceau D, Yamaguchi N, and Goyer R.** Hepatic adrenoceptors involved in the glycogenolytic response to exogenous (-)-norepinephrine in the dog liver in vivo. *Life Sci* 37: 1963–1970, 1985.
12. **Hieble JP, Bondinell WE, and Ruffolo RR.** α- and β-Adrenoceptors: from the gene to the clinic. 1. Molecular biology and adrenoceptor subclassification. *J Med Chem* 38: 3415–3444, 1995.
13. **Kawai Y, Powell A, and Arinze IJ.** Adrenergic receptors in human liver plasma membranes: predominance of β_2- and α_1-receptor subtypes. *J Clin Endocrinol Metab* 62: 827–832, 1986.
14. **Lefkowitz RJ.** Heterogeneity of adenylate cyclase-coupled β-adrenergic receptors. *Biochem Pharmacol* 24: 583–590, 1975.
15. **Liu MS and Ghosh S.** Changes in β-adrenergic receptors in dog livers during endotoxic shock. *Am J Physiol Regulatory Integrative Comp Physiol* 244: R718–R723, 1983.
16. **McGuinness OP, Fujiwara T, Murrell S, Bracy D, Neal DW, O'Connor D, and Cherrington AD.** Impact of chronic stress hormone infusion on hepatic carbohydrate metabolism in the conscious dog. *Am J Physiol Endocrinol Metab* 265: E314–E322, 1993.
17. **Meguid MM, Moore MC, Fitzpatrick G, and Moore FD.** Norepinephrine-induced insulin and substrate changes in normal man: incomplete reversal by phentolamine. *J Surg Res* 18: 365–369, 1975.
18. **Meyer C, Stumvoll M, Chintalapudl U, Gutierrez O, Kreider M, Perriello G, Welle S, and Gerich J.** Alanine and glutamine: selective markers for hepatic and renal gluconeogenesis in humans. *Diabetes* 45, *Suppl* 1: 945, 1996.
19. **Pagliassotti MJ, Holste LC, Moore MC, Neal DW, and Cherrington AD.** Comparison of the time courses of insulin and the portal signal on hepatic glucose and glycogen metabolism in the conscious dog. *J Clin Invest* 97: 81–91, 1996.
20. **Rizza RA, Cryer PE, Haymond MW, and Gerich JE.** Adrenergic mechanisms for the effect of epinephrine on glucose production and clearance in man. *J Clin Invest* 65: 682–689, 1980.
21. **Rizza RA, Haymond MW, Cryer PE, and Gerich JE.** Differential effects of epinephrine on glucose production and disposal in man. *Am J Physiol Endocrinol Metab Gastrointest Physiol* 237: E356–E362, 1979.
22. **Sacca L, Morrone G, Cicala M, Corso G, Ungaro B.** Influence of epinephrine, norepinephrine, and isoproterenol on glucose homeostasis in normal man. *J Clin Endocrinol Metab* 50: 680–684, 1980.
23. **Schimmel RJ.** Roles of alpha and beta adrenergic receptors in control of glucose oxidation in hamster epididymal adipocytes. *Biochem Biophys Acta* 428: 379–387, 1976.
24. **Shaw JH and Wolfe RR.** The integrated effect of adrenergic blockade on glucose, fatty acid, and glycerol kinetics: responses in the basal state and during hormone control with somatostatin-hormonal infusion. *J Surg Res* 42: 257–272, 1987.
25. **Steiner KE, Stevenson RW, Green DR, and Cherrington AD.** Mechanism of epinephrine's glycogenolytic effect in isolated canine hepatocytes. *Metabolism* 34: 1020–1023, 1985.
26. **Stevenson RW, Steiner KE, Connolly CC, Fuchs H, George K, Alberti MM, Williams PE, and Cherrington AD.** Dose-related effects of epinephrine on glucose production in conscious dogs. *Am J Physiol Endocrinol Metab* 260: E363–E370, 1991.
27. **Summers RJ and McMartin LR.** Adrenoceptors and their second messenger systems. *J Neurochem* 60:10–23, 1993.