Differential Effects of Physiological Versus Pathophysiological Plasma Concentrations of Epinephrine and Norepinephrine on Ketone Body Metabolism and Hepatic Portal Blood Flow in Man

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Few studies that have examined the effects of catecholamines on ketogenesis have considered the effects of catecholamines on hepatic portal blood flow. Since hepatic blood flow is a major determinant of hepatic ketogenesis (via modification of free fatty acid availability), interpretation of these studies is difficult. To better define the relative contributions of these variables, we studied the effects of physiological and pathophysiological plasma concentrations of epinephrine and norepinephrine on plasma ketone body concentrations and hepatic portal blood flow in controlled paired studies in young healthy male volunteers. To assess the effects of physiological catecholamine concentrations, each of eight subjects received 60-minute sequential infusions of epinephrine (10 ng/kg/min) and norepinephrine (32.5 ng/kg/min) together with a control infusion of heparin (0.4 U/kg/min) separated by 60-minute washout periods. Similar increments in plasma nonesterified fatty acid ([NEFA] to ~1 mmol/L) were observed during each infusion. The ketotic ratios, calculated as the ratio of plasma ketone bodies to fatty acids integrated above baseline for 90 and 120 minutes, respectively, for epinephrine and norepinephrine infusions were both significantly greater ($P < .005$ for each) than for the heparin control infusion. To assess the effects of pathophysiological plasma catecholamine concentrations, each of eight subjects also received sequential 60-minute infusions of epinephrine 60 ng/kg/min, norepinephrine 80 ng/kg/min (plus heparin 0.1 U/kg/min), and a separate control infusion of heparin with or without Intralipid (KabiVitrum, Alameda, CA). Whereas integrated plasma fatty acid levels were approximately twofold greater than those observed in the physiological protocol, the absolute integrated ketone body response to the pathophysiological concentration of epinephrine was significantly lower than that observed for the physiological dose of the hormone ($P < .05$). In contrast, the ketotic ratio for norepinephrine was significantly greater ($P < .005$) than for both epinephrine and the control infusion of heparin with or without Intralipid. Significant ($P < .01$) increases above baseline fasting levels were observed in plasma glucose and immunoreactive insulin concentrations during infusion of pathophysiological concentrations of epinephrine. Because of the technical difficulties of simultaneously measuring portal blood and sampling blood frequently, studies were repeated in six additional subjects using noninvasive image-guided flowmetry to measure percentage changes in hepatic portal blood flow during catecholamine infusion. Norepinephrine reduced hepatic portal blood flow significantly at the low-physiological concentration by 12% ($P < .05$) and at the pathophysiological concentration by 18% ($P < .05$). In summary, (1) both epinephrine and norepinephrine were associated with significant ketotic effects at physiological plasma concentrations; and (2) when infused at pathophysiological concentrations, only norepinephrine exerted a significant additional ketotic effect. Since norepinephrine has a significant simultaneous effect of reducing hepatic portal blood flow, we conclude that previous studies may have underestimated the effect of norepinephrine on hepatic ketogenesis.
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THE PHYSIOLOGICAL importance of epinephrine and norepinephrine as regulators of ketone body metabolism is well established.[1-2] Substantial data support a ketogenic effect of norepinephrine in animals,[3,4] as well as in normal[5] and diabetic[6] man. Experimental evidence indicates that the ketogenic action of norepinephrine is mediated via increased availability of nonesterified fatty acid (NEFA) substrate arising from stimulation of adipocyte lipolysis, and via modulation of the metabolic fate of NEFAs following hepatic extraction from the portal circulation. Within the hepatocyte, norepinephrine promotes β-oxidation of NEFAs to ketone bodies (3-hydroxybutyrate and acetoacetate) while simultaneously reducing their reesterification to triglycerides.[7] The lipolytic[8,9] and ketogenic[10,11] effects of norepinephrine are mediated mainly via β-adrenergic tissue receptors.

By contrast, the actions of epinephrine on ketone body metabolism are less well defined. Studies of perfused rat livers and isolated hepatocytes have provided evidence for both ketogenic and antiketogenic effects of epinephrine.[3] In some instances, these discrepancies may reflect the variations in hepatic α- and β-adrenoceptor concentration with age and sex in the rat.[3] In vivo studies in rats indicate that epinephrine has an antiketogenic effect.[12] Furthermore, there is experimental evidence supporting a relatively antiketogenic action of epinephrine in humans.[13]

In addition to their effects on lipolysis and ketogenesis, catecholamines exert physiological effects that may independently influence ketone body metabolism. Epinephrine increases circulating concentrations of antiketogenic metabolites, including glucose,[14] while modulating the endogenous secretion of insulin[15] and glucagon.[16] Catecholamines also modify hepatic portal blood flow and hence the delivery rate of NEFAs to the hepatocyte.[4]

To date, no direct comparisons of the ketotic effects of

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epinephrine and norepinephrine have been reported in man. This is important because these two adrenergic hormones are structurally different and are released from anatomically separate sites. Therefore, we have compared the ketotic effects of epinephrine and norepinephrine in a series of studies in normal volunteers. The effects of both physiological and pathophysiological plasma concentrations of each catecholamine were examined in separate paired-infusion studies in each subject. Since the rate of hepatic ketogenesis is proportional to NEFA availability, the protocols were designed to produce physiological elevations in plasma NEFA concentrations in concert with Doppler flowmetry measurement of changes in hepatic portal blood flow (which may significantly alter NEFA availability for ketogenesis). Thus, these studies provide data on the ketotic effect of epinephrine and norepinephrine in man with consideration of the effects of these hormones on altered NEFA availability produced by concomitant changes in hepatic portal blood flow.

SUBJECTS AND METHODS

Subjects

Fourteen healthy male volunteers aged 20 to 33 years with normal fasting triglyceride concentrations (<2.0 mmol/L) provided informed written consent to participate in the studies, which were approved by the Human Research Review Committee of the University of New Mexico School of Medicine. All subjects were within 20% of their ideal body weight,[17] with no family history of diabetes mellitus. Hepatic and renal disease were excluded by routine biochemical tests. None of the subjects were receiving medication that would influence the investigations.

For each protocol, subjects were studied on two separate occasions separated by a period of at least 4 weeks. On one occasion, subjects received infusions of epinephrine and norepinephrine calculated to produce circulating catecholamine concentrations within the range encountered during mild to moderate exercise.[18] These catecholamine concentrations have previously been shown to exert effects on both lipolysis and ketone body metabolism.[13,19] On the second occasion, each catecholamine was infused at a rate designed to produce elevations in plasma to levels associated with pathological states such as diabetic ketoacidosis and myocardial infarction.[11,18,20] On each occasion, a separate control infusion of heparin with or without neutral fat emulsion as required was administered to provide a comparable increase in plasma NEFA substrate. Each infusion was followed by a 60-minute washout period, and the sequence of the three infusions (epinephrine, norepinephrine, and heparin control) was varied randomly for each subject. However, for each individual, the sequence of infusions was similar for both the physiological and pathophysiological protocols.

For each investigation, subjects were admitted on the night before the study to the Clinical Research Center of the University of New Mexico Hospital. A 1,200-kcal low-carbohydrate evening meal was provided at 6:00 PM containing approximately 15% carbohydrate, 20% protein, and 65% fat. The purpose of the low-carbohydrate diet was to deplete hepatic glycogen stores and thereby enhance the ketogenic effect of the catecholamines. Subjects were then fasted overnight, but water was permitted ad libitum.

Studies commenced at 6:30 AM the following morning with placement of venous cannulae (Deseret Medical, Becton Dickinson, Sandy, UT) in a wrist vein and in an antecubital vein of the contralateral arm, respectively. The wrist line was kept patent by a slow infusion (~1 mL/min) of 0.45% saline. This cannula was used exclusively for blood sampling. The subject's hand and wrist were placed in a warming device maintained at 37°C throughout the study to produce arterialized blood samples. The antecubital venous cannula was used for infusions of hormones and substrates and was kept patent by a slow saline infusion (75 mL/h) delivered by an electromechanical displacement pump (IMED, San Diego, CA). Subjects remained in a semisupine position throughout the investigations. Basal blood samples were withdrawn, and a 60-minute baseline observation period was commenced. At 60 minutes, the first of three sequential 60-minute infusions of epinephrine, norepinephrine, or heparin with or without fatty acid control was commenced, each followed by a 60-minute washout period (Fig 1).

Catecholamines were infused in 0.9% saline diluent containing ascorbic acid (2.8 mmol/L) as an antioxidant.[13] Infusions were protected from light during administration, and were administered using a computerized Harvard syringe pump (Harvard Apparatus, South Natick, MA). Potassium chloride was administered at a mean rate of approximately 4 mmol/h to avoid β-adrenoceptor–mediated hypokalemia during epinephrine infusions. Blood pressure and heart rate were measured every 15 minutes using an automated sphygmomanometer (Dinamap; Critikon, Tampa, FL) with continuous electrocardiographic monitoring in each subject (data not shown).

Low-Dose (physiological) Catecholamine Concentrations

The subjects (n = 8) received sequential infusions of epinephrine (Abbott Laboratories, N. Chicago, IL) 10 ng/kg/min and norepinephrine (Winthrop Pharmaceuticals, Division of Sterling Health, New York, NY) 32.5 ng/kg/min, together with a heparin control infusion (Eklins-Sinn, Cherry Hill, NJ) at a rate of 0.4 U/kg/min to activate lipolysis of circulating endogenous triglyceride by endothelial lipoprotein lipase.[6]

High-Dose (pathophysiological) Catecholamine Concentrations

In these studies, the subjects (n = 8) received sequential infusions of epinephrine 60 ng/kg/min and norepinephrine 80 ng/kg/min. The control infusion contained heparin (200 U as a bolus followed by 0.4 U/kg/min) plus a neutral fat emulsion (20% Intralipid; KabiVitrum, Alameda, CA) 0.06 mL/kg/min. Additionally, heparin 0.1 U/kg/min was infused simultaneously with norepinephrine to produce similar integrated increases in NEFA substrate during each infusion. This dose of heparin was selected from pilot studies that demonstrated a smaller increment in plasma NEFAs during infusion of norepinephrine compared with epinephrine. This difference was anticipated in view of the relatively greater β-adrenergic–mediated lipolytic effect of epinephrine compared with norepinephrine.[8,18]

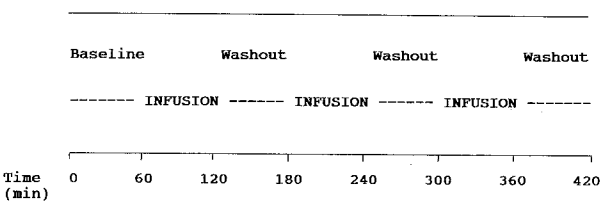

Fig 1. Outline of the experimental protocols.

Blood Samples

Basal blood samples were withdrawn at −20, −10, and 0 minutes. Thereafter, blood was withdrawn at 15-minute intervals until the end of each study (at 420 minutes) for measurement of epinephrine, norepinephrine, glucose, NEFA, acetoacetate, 3-hydroxybutyrate, immunoreactive insulin, and glucagon levels.

Analytical Methods

Plasma glucose level was measured using a glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma NEFA levels were measured using automated enzymatic spectrophotometric methods. Plasma acetoacetate and 3-hydroxybutyrate were immediately frozen at −20°C and then determined within 36 hours of each study using automated enzymatic spectrophotometric methods (Wako Chemicals, Dallas, TX). Plasma immunoreactive insulin and glucagon were assayed in duplicate by radioimmunoassay (Diagnostic Products, Los Angeles, CA, and ICN, Costa Mesa, CA, respectively). Plasma epinephrine and norepinephrine levels were measured using established radioenzymatic methods.[21]

Hepatic Portal Blood Flow

Because of the technical difficulty of performing simultaneous hormonal infusions, blood pressure monitoring, timed blood sampling, and measurements of portal blood flow, paired infusion studies were repeated in the remaining six subjects. In these studies, changes in hepatic portal blood flow were measured by noninvasive ultrasonic Doppler flowmetry.[22-24] An image-guided 3-Hz abdominal probe (model 600; ATL, Bothell, WA) was used to measure portal vein temporal mean diameters and blood flow velocities that were used to calculate percent changes in portal flows. This method has been extensively evaluated in vitro and in vivo. In our hands, the 95% confidence levels by a blinded observer for percent changes due to pharmacological intervention is ±7%. Portal blood flow data are presented as the mean changes in flow from baseline levels during each 60-minute infusion.

Calculations

Baseline (fasting) concentrations of catecholamines, glucose, immunoreactive insulin, and glucagon were calculated as the mean of values between −20 and 0 minutes. Plasma catecholamine concentrations attained during infusions of epinephrine and norepinephrine were calculated as the mean of the 15-, 30-, 45-, and 60-minute measurements of the appropriate infusion period.

The response of plasma glucose, immunoreactive insulin, and glucagon concentrations to each 60-minute infusion, either catecholamine or control, was calculated as the mean of the plasma concentrations of the metabolite or hormone for the 60 minutes during the infusion and 30 minutes during the observation period immediately following termination of the infusion, ie, 90 minutes total.

For each infusion period, the integrated increase in plasma NEFAs was calculated as the increment above baseline (fasting) concentrations for 90 minutes. Similarly, the integrated increase in total ketone bodies (acetoacetate plus 3-hydroxybutyrate) was calculated for the 120-minute period from the start of the infusion, ie, incorporating data during the 60-minute hormone/substrate infusion period and the subsequent 60-minute washout period. These periods were selected to encompass the expected increase and subsequent decline in plasma NEFAs in response to infusion of catecholamine or heparin with or without Intralipid. Data for total ketone bodies were integrated for 120 minutes to allow for the inherent delay in intrahepatic synthesis of ketone bodies and their subsequent release into the circulation. Previous observations in man suggest that this delay is on the order of approximately 30 minutes.[6]

The ratio of integrated plasma (total ketone bodies/NEFAs) was calculated for each individual hormone/substrate infusion. This arbitrary ratio provides an overall index of the increase in ketone body concentrations relative to available NEFA substrate, and is referred to as the ketotic ratio.[25]

Statistical Analysis

For each protocol (ie, physiological *v* pathophysiological plasma concentrations of each catecholamine), differences in the integrated changes in plasma NEFAs and total ketone bodies between epinephrine, norepinephrine, and heparin with or without Intralipid were compared using one-way ANOVA.[26] The mean ketotic ratios for the three infusions were also compared by ANOVA. Where ANOVA demonstrated a significant overall difference between infusions, differences between pairs of infusions were sought using a post hoc analysis allowing for multiple comparisons (Fisher's least-significant difference test).[26] Differences in hormone or metabolite responses between the physiological and pathophysiological studies were examined using two-tailed paired *t* tests, as were changes from baseline within each study in mean plasma hormone and metabolite levels. In the studies of hepatic portal blood flow, differences between the heparin control and catecholamine infusions in the percentage change from baseline levels were examined using repeated-measures ANOVA.[26] Data are presented as the mean ± SEM.

RESULTS

Low-Dose (physiological) Catecholamine Concentration Protocol

Catecholamines. During low-dose infusions, the plasma concentration of epinephrine increased significantly from a baseline level of 32 ± 5 ng/L to 224 ± 31 ng/L ($P < .001$). Plasma norepinephrine concentration increased from a baseline of 198 ± 10 ng/L to 993 ± 107 ng/L ($P < .001$).

NEFAs. For each of the infusions (epinephrine, norepinephrine, and heparin), similar significant increments were observed in plasma NEFA above baseline fasting levels ($P < .01$; Table 1). By design, plasma NEFA concentrations—integrated above the baseline value over a period of 90 minutes—were not significantly different between heparin, epinephrine, and norepinephrine infusions ($F = 1.5$, $P > .1$), implying similar hepatic substrate availability during each of the 3 infusions (Fig 2A).

Total ketone bodies (acetoacetate + 3-hydroxybutyrate). Increases in plasma total ketone body concentrations were observed in response to each of the three substrate/hormone infusions (Table 1). A significant overall difference ($F = 13.4$, $P < .001$) was demonstrated by ANOVA between the three infusions in total ketone body concentrations integrated above baseline (Fig 2B). The integrated increments in total ketone bodies in response to both epinephrine ($P < .005$) and norepinephrine ($P < .005$) were each significantly greater than observed for the heparin control infusion (Fig 2B).

Ketotic ratio. The ketotic ratios were significantly different ($F = 16.0$, $P < .001$) between the three infusions by ANOVA (Fig 2C). Post hoc analysis demonstrated that this difference was accounted for by significantly greater ketotic ratios for epinephrine ($P < .005$) and norepinephrine

Table 1. Metabolite and Hormone Concentrations (mean ± SEM) at Baseline (−20 to 0 minutes) and Responses to Heparin With or Without Intralipid Control, Epinephrine, and Norepinephrine (with or without heparin) Infusions

Parameter	Baseline	Infusion			F	P
		Heparin	Epinephrine	Norepinephrine		
Physiological catecholamines						
NEFA (mmol/L)	0.71 ± 0.05	1.03 ± 0.08	1.24 ± 0.09	1.10 ± 0.07	1.8	>.1
TKB (mmol/L)	0.27 ± 0.05	0.56 ± 0.11	0.78 ± 0.09	0.77 ± 0.16	13.4	<.005
Glucose (mg/dL)	83 ± 2	81 ± 2	85 ± 4	85 ± 4	1.2	>.1
Insulin (μU/mL)	5.7 ± 0.3	5.1 ± 0.2	5.6 ± 0.4	5.7 ± 0.6	0.5	>.1
Glucagon (ng/L)	63 ± 6	56 ± 7	56 ± 6	64 ± 4	0.6	>.1
Pathophysiological catecholamines						
NEFA (mmol/L)	0.62 ± 0.05	1.40 ± 0.14	1.54 ± 0.07	1.55 ± 0.19	1.8	>.1
TKB (mmol/L)	0.21 ± 0.04	0.42 ± 0.10	0.57 ± 0.08	0.73 ± 0.11	10.1	<.001
Glucose (mg/dL)	85 ± 2	83 ± 2	121 ± 7*†	92 ± 2	25.4	<.001
Insulin (μU/mL)	5.7 ± 0.3	4.9 ± 0.5	10.5 ± 1.7*†	6.3 ± 1.1	5.6	<.02
Glucagon (ng/L)	65 ± 6	51 ± 6	64 ± 6	60 ± 5	1.3	>.1

NOTE. F and *P* values refer to differences between the 3 infusions by ANOVA.
Abbreviation: TKB, total ketone bodies.
*$P < .01$ *v* heparin control.
†$P < .01$ *v* norepinephrine.

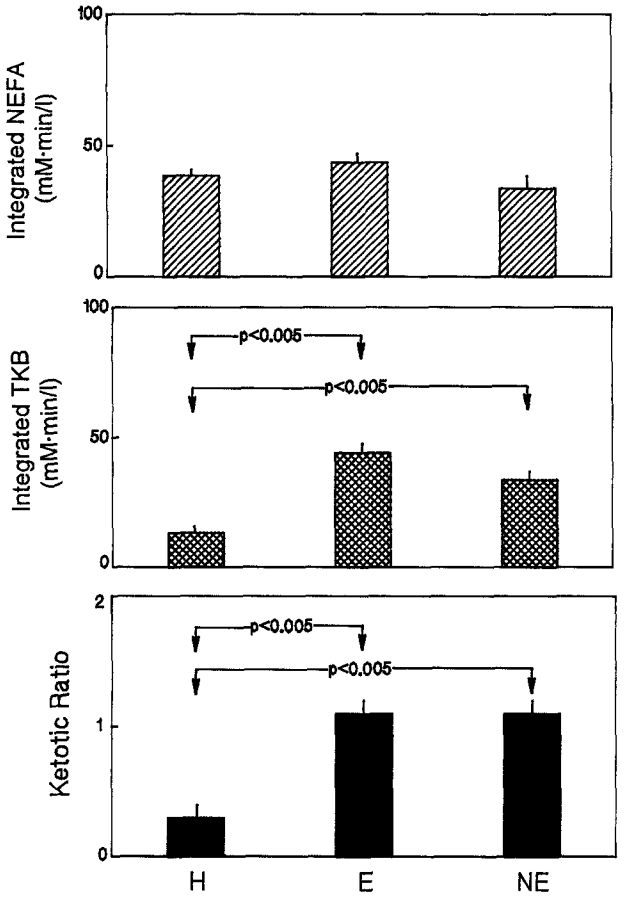

Fig 2. Mean (±SEM) plasma concentrations of NEFAs and total ketone bodies (TKB) integrated above baseline over 90 and 120 minutes, respectively, and plasma ketotic ratio (integrated TKB/integrated NEFAs) in response to 60-minute infusions of heparin control (0.4 U/kg/min), epinephrine (10 ng/kg/min), and norepinephrine (32.5 ng/kg/min) in 8 healthy volunteers. *P* values indicate significant differences between groups by paired *t* test.

($P < .005$) infusions compared with the heparin control infusion (Fig 2C).

Glucose. Plasma glucose concentrations did not change significantly from baseline in response to any of the three substrate/hormone infusions (Table 1).

Immunoreactive insulin. Neither of the catecholamine infusions nor the heparin control infusion produced a significant change from baseline in plasma immunoreactive insulin levels (Table 1).

Hepatic portal blood flow. In the separate group of six subjects, there was no significant decrease ($P > .1$) in hepatic portal blood flow during the low-dose infusion of

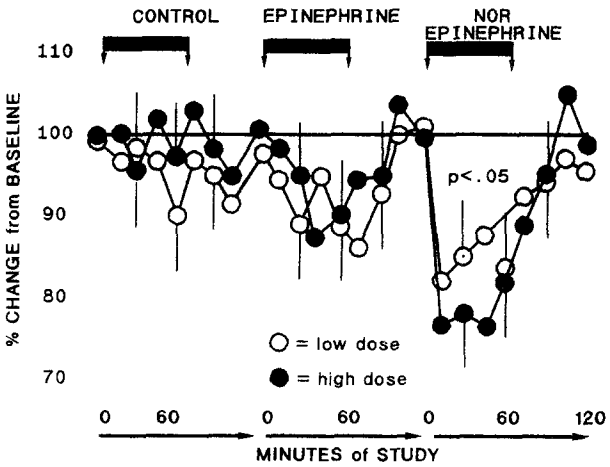

Fig 3. Changes in hepatic portal blood flow (mL/min) expressed as percentage change from fasting baseline levels in response to heparin with or without Intralipid control, epinephrine (10 and 60 ng/kg/min), and norepinephrine (32.5 and 80 ng/kg/min), respectively, in paired studies performed on separate occasions in 6 healthy volunteers. *P* values indicate significant differences between physiological and pathophysiological norepinephrine infusions *v* heparin with or without Intralipid control infusion by repeated-measures ANOVA.

epinephrine (Fig 3). Low-dose norepinephrine reduced blood flow significantly ($P < .05$) by 12% ± 2% (Fig 3).

High-Dose (pathophysiological) Catecholamine Concentration Protocol

Catecholamines. During high-dose infusions, the plasma concentration of epinephrine increased significantly from a fasting baseline level of 32 ± 5 ng/L to 902 ± 49 ng/L ($P < .001$). Plasma norepinephrine concentration increased from a baseline of 171 ± 20 ng/L to 2,549 ± 188 ng/L ($P < .001$).

NEFAs. Plasma NEFA concentrations significantly increased from basal levels in response to each of the three substrate/hormone infusions ($P < .01$; Table 1). Plasma NEFA concentrations (Table 1) and NEFA concentrations integrated above baseline (Fig 4A) did not differ ($F = 0.3$, $P > .1$) between the three infusions. Mean integrated NEFA levels for each of the infusions during this protocol were significantly higher ($P < .01$) than those observed for the respective infusions in the low-dose protocol.

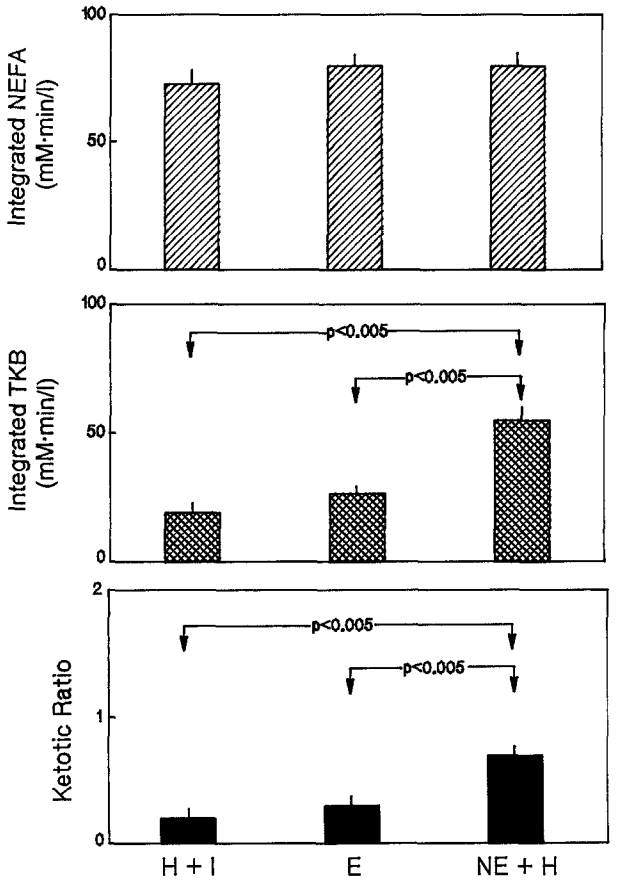

Fig 4. Mean (±SEM) plasma concentrations of NEFAs and total ketone bodies (TKB) integrated above baseline over 90 and 120 minutes, respectively, and plasma ketotic ratio (integrated TKB/integrated NEFAs) in response to 60-minute infusions of heparin control (0.4 U/kg/min + 20% Intralipid 0.06 mL/kg/min), epinephrine (60 ng/kg/min), and norepinephrine + heparin (80 ng/kg/min) in 8 healthy volunteers. *P* values indicate significant differences between groups by paired *t* test.

Total ketone bodies (acetoacetate + 3-hydroxybutyrate). Despite the approximately twofold greater integrated NEFA concentrations attained with the high-dose protocol, plasma total ketone body concentrations during the heparin + Intralipid control, epinephrine, and norepinephrine infusions were not significantly different from those observed during the low-dose (physiological) protocol (Table 1). However, total ketone body levels integrated over time were significantly different ($F = 10.1$, $P < .001$) between the three substrate/hormone infusions. Integrated total ketone body concentrations for norepinephrine (Fig 4B) were significantly greater than for either the heparin with Intralipid control infusion ($P < .005$) or the epinephrine infusion ($P < .005$). By contrast, the integrated total ketone body response to epinephrine was not significantly different from that of the heparin + Intralipid control (Fig 4B). Furthermore, integrated plasma total ketone body levels were lower than those observed for the low-dose epinephrine infusion (26.6 ± 4.2 *v* 44.3 ± 5.3 mmol/L · min, respectively, $P < .05$).

Ketotic ratio. As in the case of the integrated total ketone body levels, the ketotic ratio observed in response to the pathophysiological plasma concentration of epinephrine was not significantly different from that in response to the heparin + Intralipid control infusion (Fig 4C). Furthermore, the ketotic ratio was significantly lower than that observed during the low-dose physiological infusion of this hormone ($P < .01$). The ketotic ratio for epinephrine was significantly lower ($P < .005$) than that observed in response to the pathophysiological concentration of norepinephrine (Fig 4C).

Glucose. The pathophysiological plasma concentration of epinephrine was associated with a significant increase ($P < .01$) in plasma glucose above baseline fasting levels (Table 1). No significant changes ($P > .1$) were observed in glucose concentrations in response to either the heparin + Intralipid control or norepinephrine infusions (Table 1).

Immunoreactive insulin. The high-dose infusion of epinephrine was associated with a significant increase ($P < .01$) in plasma immunoreactive insulin concentration above baseline (Table 1). In each subject, the increase in plasma insulin concentration was observed during the 30-minute observation period immediately following termination of the epinephrine infusion.

Hepatic portal blood flow. In the separate group of six subjects, there was no significant decrease ($P > .1$) in hepatic portal blood flow during the low-dose infusion of epinephrine (Fig 3). High-dose norepinephrine reduced blood flow significantly ($P < .05$) by 18% ± 3% (Fig 3).

DISCUSSION

These results indicate differences in the dose-response characteristics of epinephrine and norepinephrine on ketone body metabolism and hepatic portal blood flow in normal young men. At low-physiological plasma concentrations, epinephrine and norepinephrine exerted similar ketotic effects, as judged by the observed increases in plasma ketone body concentrations. These effects were significantly greater than that accounted for by the provi-

sion of NEFA substrate alone. In contrast, at pathophysiological plasma concentrations associated with diabetic ketoacidosis and myocardial infarction, the ketotic effect of norepinephrine was even greater, whereas epinephrine was associated with a relatively antiketotic effect. Furthermore, ketotic actions of norepinephrine were evident despite a concomitant significant reduction of 12% to 18% in portal blood flow. Our results appear to be at variance with the study reported by Beylot et al,[13] which suggested an antiketogenic effect of low-physiological concentrations of epinephrine in man. In that study, exogenous infusion of epinephrine at a rate of 10 ng · kg/min in normal volunteers was associated with a decrease in the proportion of NEFAs converted to ketone bodies by the liver above basal rates. We used the same epinephrine infusion rate in our physiological protocol. However, in contrast to the results reported by Beylot et al., we found that plasma ketone body concentrations were significantly greater than those observed in response to a heparin–fatty acid control infusion, implying a stimulatory effect of epinephrine on hepatic ketogenesis or a decrease in ketone utilization. Differences in study design and methodology, relating in particular to the supraphysiological plasma NEFA concentrations ($\sim$3 mmol/L) attained in the study by Beylot et al, may in part account for these apparent discrepancies. Instead, we found evidence for a relatively antiketotic effect of epinephrine at pathophysiological plasma concentrations.

Alternative explanations for the relative antiketotic effect of pathophysiological plasma concentrations of epinephrine merit consideration. First, the high infusion rate of epinephrine was associated with a significant increase in plasma glucose concentration. Antiketogenic effects of glucose have been demonstrated in both animals and man.[7,27] The ketotic effect of epinephrine may therefore have been attenuated by the concomitant hyperglycemia. Second, plasma immunoreactive insulin concentrations increased significantly during the period following termination of the high-dose epinephrine infusion. This finding suggests liberation of islet β cells from adrenergic suppression of insulin secretion,[15] resulting in hyperinsulinemia in response to epinephrine-induced hyperglycemia. Due to hepatic extraction of insulin, intraportal insulin concentrations are likely to have been higher than those measured in the systemic circulation. Hyperinsulinemia may exert antiketotic effects by reducing the rate of hepatic ketogenesis[28] and by enhancing ketone body disposal by peripheral tissues.[29] In contrast to other studies in man,[16,20] we did not observe a significant increase in plasma glucagon concentration during any of the catecholamine infusions.

Our experimental protocols were designed to produce similar increases in plasma NEFA concentrations during each infusion, which were within the physiological range in man.[8] For both the physiological and pathophysiological catecholamine infusion protocols, the effects attributable to each catecholamine were compared with the effect of increasing the provision of circulating NEFAs alone. By randomizing the sequence of infusions and incorporating washout periods between the infusions, we sought to minimize the potential for sequence effects. Since hepatic uptake of NEFAs is proportional to the plasma concentration,[30] the resulting plasma ketone body concentrations reflect differences in the intrahepatic metabolic fate of NEFAs or, alternatively, differences in the disposal of ketone bodies by peripheral tissues. Ketone body turnover studies including collection and measurement of ketone body concentrations will be necessary to clarify the relative contributions of these mechanisms to the observed increases in ketone body concentrations. These techniques were not used in these studies because of technical constraints imposed by the procedures we used.

Statistically significant decreases in hepatic blood flow were observed during both the physiological and pathophysiological concentrations of norepinephrine. These results appear to be consistent with reports in man of a decrease in splanchnic blood flow in response to administration of norepinephrine.[31] Smaller nonsignificant decrements in hepatic portal blood flow were also observed during infusion of epinephrine, but the latter changes were not significantly different from those observed during the control infusion. Since a reduction in hepatic portal blood flow would be expected to reduce delivery of NEFAs to the liver, our data suggest that the direct stimulatory effects of norepinephrine on hepatic ketogenesis may be even greater than previously suggested by infusion studies in man.[5,6,32]

It is acknowledged that exogenous infusion of catecholamines may not accurately represent the summation of metabolic effects of endogenously secreted catecholamines in man. Under physiological conditions, release of catecholamines into the circulation is accompanied by increased activity of the sympathetic nervous system, which may induce additional metabolic effects in target tissues.[33] Moreover, indirect effects mediated via changes in local vasculature may modulate tissue actions of catecholamines.[33] This caveat notwithstanding, the design of our study allows comparisons of the dose-response effects of epinephrine and norepinephrine at plasma concentrations known to be of relevance to physiological and pathophysiological states in man.[18]

In summary, our results indicate comparable ketotic effects of epinephrine and norepinephrine at physiological circulating concentrations in normal man. By contrast, at pathophysiological plasma concentrations, norepinephrine exerted additional ketotic effects that were not observed for epinephrine. Concomitant increases in plasma glucose and insulin concentrations may have contributed to the attenuated ketogenic effect observed with the pathophysiological dose of epinephrine. The reduction in hepatic NEFA supply resulting from decreased hepatic portal blood flow implies that norepinephrine may have even greater ketotic activity in the liver than previously reported.

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