Epinephrine Plasma Metabolic Clearance Rates and Physiologic Thresholds for Metabolic and Hemodynamic Actions in Man

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ABSTRACT To determine the plasma epinephrine thresholds for its metabolic and hemodynamic actions and plasma epinephrine metabolic clearance rates, 60-min intravenous epinephrine infusions at nominal rates of 0.1, 0.5, 1.0, 2.5, and 5.0 μg/min were performed in each of six normal human subjects. These 30 infusions resulted in steady-state plasma epinephrine concentrations ranging from 24 to 1,020 pg/ml. Plasma epinephrine thresholds were 50–100 pg/ml for increments in heart rate, 75–125 pg/ml for increments in blood glycerol and systolic blood pressure, 150–200 pg/ml for increments in plasma glucose (the resultant of increments in glucose production and decrements in glucose clearance), blood lactate, blood β-hydroxybutyrate, and diastolic blood pressure, and >400 pg/ml for early decrements in plasma insulin. Changes in blood alanine, plasma glucagon, plasma growth hormone, and plasma cortisol were not detected. At steady-state plasma epinephrine concentrations of 24–74 pg/ml, values overlapping the basal normal range, the mean (±SE) plasma metabolic clearance rate of epinephrine was 52±4 $ml \cdot min^{-1} \cdot kg^{-1}$; this value rose to 89±6 $ml \cdot min^{-1} \cdot kg^{-1}$ ($P < 0.01$) at steady-state epinephrine concentrations of 90–1,020 pg/ml. We conclude that in human subjects: (*a*) the plasma epinephrine thresholds for its hemodynamic and metabolic actions lie within the physiologic range, (*b*) epinephrine and norepinephrine accelerate their own metabolic clearance, and (*c*) epinephrine is 10 times more potent than norepinephrine.

INTRODUCTION

Sensitive isotope derivative methods (1) have made it possible to measure the plasma concentrations of norepinephrine and epinephrine in the basal state and in diverse physiologic and pathophysiologic states in humans (2). Although the multiple metabolic and hemodynamic actions of the catecholamines are well known (3, 4), the plasma catecholamine concentrations required to produce these effects have not been fully defined. The finding that, in order to produce measurable effects, plasma norepinephrine concentrations must be raised to levels considerably higher than those occurring under most physiologic conditions (5) indicates that the biologic actions of norepinephrine are primarily attributable to its sympathetic postganglionic neurotransmitter function. In some physiologic states, such as vigorous exercise, and in a variety of pathophysiologic states, plasma norepinephrine concentrations are high enough to produce biologic actions. Thus, norepinephrine may also subserve a hormonal function under these conditions (5).

The plasma concentrations of the adrenomedullary hormone epinephrine required to produce its biologic actions have not been established. Clearly, this information is critical to rational interpretation of measurements of plasma epinephrine levels. To determine these threshold levels, we have infused epinephrine at five nominal rates into each of six normal human subjects to produce steady-state plasma epinephrine concentrations that span the physiologic range. These studies demonstrate that the threshold plasma epinephrine concentrations lie within the physiologic range.

METHODS

Six normal subjects (five men and one woman), whose characteristics are listed in Table I, each consented to five 60-min epinephrine infusions at nominal rates of 0.1, 0.5, 1.0, 2.5, and 5.0 μg/min. All infusions were performed after an overnight fast, including abstinence from caffeine and tobacco; subjects were supine throughout each infusion. In a given subject, infusions were separated by intervals of at least 1 wk. The dose sequence was varied and not known to the subject. No untoward effects occurred, although the highest infusion rate commonly produced palpitations.

Intravenous catheters, two for infusion (one arm) and one

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TABLE I
Characteristics of the Subjects

Number	Sex	Age	Weight	Height
		yr	*kg*	*cm*
1	M	38	89.7	183
2	M	27	72.7	175
3	F	26	61.4	168
4	M	26	91.3	180
5	M	25	70.9	187
6	M	27	86.4	183

for sampling (the opposite arm), were inserted into antecubital veins 90 min before the infusion of epinephrine. Appropriate amounts of (−)epinephrine (adrenaline chloride, Parke, Davis & Co., Detroit, Mich.) were diluted in 45 ml of saline containing ascorbic acid (0.5 mg/ml) and infused with a Harvard infusion apparatus (Harvard Apparatus Co., Inc., S. Natick, Mass.). Preliminary studies showed that such infusate epinephrine concentrations were stable at room temperature for 120 min; stability was confirmed by measurements of infusate epinephrine concentrations before and after each infusion.

Blood samples (11.0 ml) were drawn (and heart rate and blood pressure recorded) at 5–10-min intervals before and during each infusion and at 15-min intervals for 30 min after each infusion. Blood was promptly distributed into iced tubes containing heparin, heparin plus reduced glutathione, or EDTA plus aprotinin (Trasylol; SDA Pharmaceuticals, New York.); 2.0-ml aliquots of heparinized blood were then transferred to an iced tube containing an equal volume of 3 M perchloric acid. All tubes were promptly centrifuged in a refrigerated centrifuge and the supernates frozen for subsequent analysis.

Plasma norepinephrine and epinephrine concentrations were measured by a single isotope derivative method (6, 7). Plasma glucose concentrations were measured with a glucose oxidase technique. Plasma levels of insulin (8), glucagon (9), and growth hormone (10) were determined by radioimmunoassay; cortisol was measured with a competitive protein binding technique (11). Microfluorometric enzymatic techniques were used to measure blood levels of lactate (12), alanine (13), β-hydroxybutyrate (14), and glycerol (15).

Glucose kinetics were determined by means of a primed, continuous infusion of [6,6-$^2H_2$]glucose (16, 17). Isotopic enrichment of plasma glucose was determined in the 6-0-acetyl-1,2:3,5 di-0-(*n*-butaneboronyl)α-D-glucofuranose derivative by combined gas chromatography and mass spectrometry with selected ion monitoring. Tracer infusion was begun 90 min before the infusion of epinephrine with a priming dose calculated to produce 1.75% enrichment of the extracellular glucose pool, followed by continuous infusion of tracer at 1.75% of the estimated basal glucose turnover rate. Isotopic enrichment of plasma glucose reached a plateau before each epinephrine infusion. Glucose turnover rates in the basal state (before epinephrine infusion) were calculated using the standard isotope dilution equation (18). Rates of glucose production and glucose utilization were estimated by means of Steele's equations for nonsteady-state conditions (19) as validated for the glucose system (20). A value of 65% of the extracellular space was used as the mixing pool to correct for the lack of instantaneous mixing throughout the extracellular glucose pool (21). The plasma glucose clearance rate—an index of the ability of tissues to remove glucose from plasma, independent of the prevailing plasma glucose concentration—was calculated by dividing the rate of glucose utilization by the concurrent plasma glucose concentration (22).

Plasma epinephrine thresholds for its metabolic and hemodynamic effects were estimated by inspection of semilogarithmic plots of the steady-state plasma epinephrine concentration (p[E]ss)[1] vs. changes in each measured variable. On the premise that extrapolation of the central linear portion of the sigmoidal dose-response curve to the line of no change provides a maximum estimate of the threshold for that variable, regression lines through data points showing change from base-line values were extended to the line of no change. Fitting of data to curves by means of nonlinear least squares regression analysis tended to confirm values for the thresholds estimated in this fashion.

Plasma metabolic clearance rates of epinephrine ($pMCR_E$) were calculated by dividing the measured epinephrine infusion rate by the difference between the p[E]ss and the basal preinfusion plasma epinephrine concentration (5). Two points must be noted about this calculation. First, it requires the assumption that endogenous epinephrine released into the circulation at basal rates continues during the infusion of epinephrine. If endogenous release of epinephrine ceases during epinephrine infusion, this equation will overestimate the $pMCR_E$, especially at the lower p[E]ss levels. Second, to the extent that the extremity is an organ of epinephrine uptake (and net norepinephrine [NE] release), as suggested by arteriovenous concentration differences (23), this calculation will overestimate the $pMCR_E$ (and underestimate the $pMCR_{NE}$). From the data of our earlier study, using this method to calculate the $pMCR_{NE}$ (5), we calculate a value for the basal rate of metabolic clearance of norepinephrine (2.1 liter/min), which agrees with that found by Essler et al. (24) (2.8 liter/min), using an infusion of trace amounts of [^{3}H]norepinephrine. Mean $pMCR_E$ values were compared using a *t* test for unpaired data.

RESULTS

Mean (±SE) plasma epinephrine and norepinephrine concentrations at each of the five nominal epinephrine infusion rates are illustrated in Fig. 1. Achieved within 10 min, the mean (±SD) p[E]ss values were 54±30, 114±28, 219±83, 412±89, and 715±228 pg/ml at nominal epinephrine infusion rates of 0.1, 0.5, 1.0, 2.5, and 5.0 μg/min, respectively. The measured epinephrine infusion rates, determined from the infusate epinephrine concentrations, are given in Fig. 1. Mean plasma norepinephrine concentrations did not change significantly during the infusion of epinephrine.

These 30 epinephrine infusions produced p[E]ss levels ranging from 24 to 1,020 pg/ml. At p[E]ss levels of 24–74 pg/ml, values that overlap the basal normal range, the mean (±SE) $pMCR_E$ was 52±4 $ml \cdot min^{-1} \cdot kg^{-1}$. Notably, at p[E]ss levels of 90–1,020 pg/ml, the $pMCR_E$ values were comparable and significantly higher, averaging 89±6 $ml \cdot min^{-1} \cdot kg^{-1}$

[1] *Abbreviations used in this paper*: E, epinephrine, MCR, metabolic clearance rate; NE, norepinephrine; p, plasma; ss, steady-state.

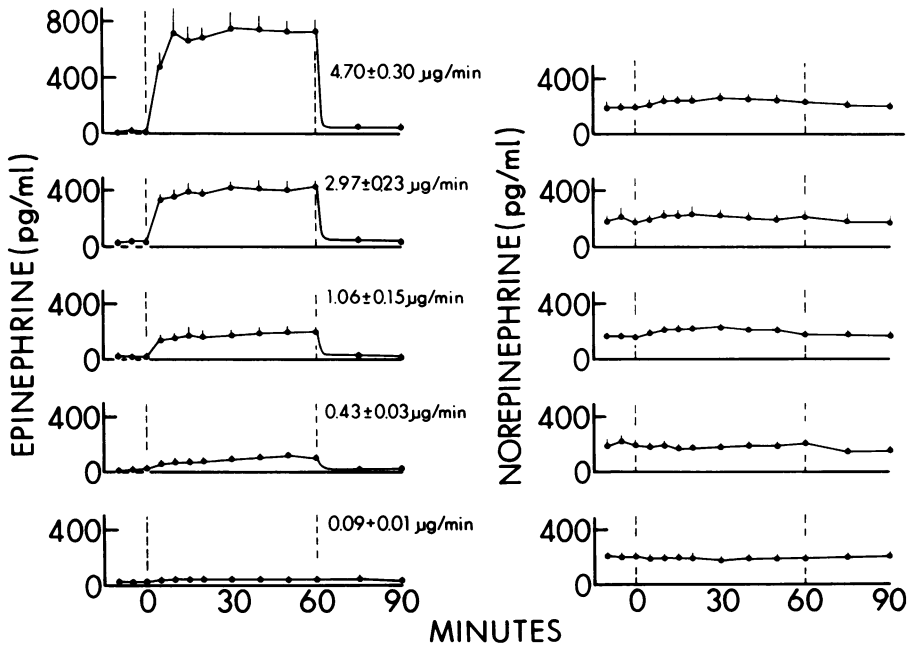

FIGURE 1 Mean (±SE) plasma epinephrine and norepinephrine concentrations before, during, and after 60-min epinephrine infusions at the five nominal infusion rates. The mean (±SE) measured infusion rates are listed at the right of the epinephrine plots.

($P < 0.01$). These findings are illustrated in Fig. 2. It should be noted that these differences are not explicable on the basis of the method of calculation because $pMCR_E$ calculations, assuming cessation of endogenous epinephrine release, would magnify the differences.

The means (±SE) of the measured metabolic and hemodynamic variables before and during epinephrine infusions at the five nominal rates are shown in Table II. At the higher infusion rates, epinephrine produced increments in heart rate and systolic blood pressure, and decrements in diastolic blood pressure, with increments in plasma glucose, blood lactate, blood glycerol, and blood β-hydroxybutyrate, and an initial decrement in plasma insulin. No significant changes in blood alanine or plasma glucagon, growth hormone, or cortisol were detected. As noted previously (25), glucose production rose transiently, returning to near base line by 60 min, glucose utilization did not change, and glucose clearance declined and remained suppressed during the infusion of epinephrine at the higher infusion rates (Fig. 3). The plasma insulin response to the larger doses of epinephrine was biphasic with an initial decline followed by a gradual rise and, after termination of the epinephrine infusions, a sharp rise (Fig. 4).

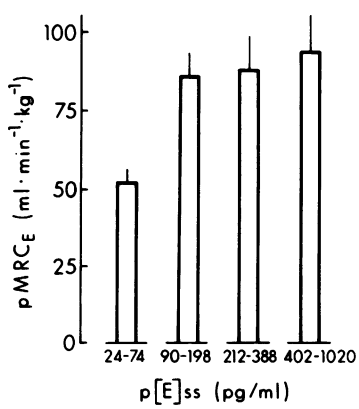

FIGURE 2 Epinephrine infusions. Mean (±SE) $pMCR_E$ at p[E]ss overlapping the basal normal range (left) and at three higher p[E]ss ranges, the latter including similar numbers of data points.

The data used to estimate the plasma epinephrine thresholds for its hemodynamic and metabolic actions are illustrated in Figs. 5–8, where the p[E]ss for each infusion is plotted against the change in each measured variable during that infusion. Except where indicated, changes in these variables represent the difference between the basal value and the value after 60 min of epinephrine infusion.

The plasma epinephrine threshold for increments in heart rate was 50–100 pg/ml, for increments in systolic blood pressure the threshold was 75–125 pg/ml, whereas for decrements in diastolic blood pressure, the threshold was 150–200 pg/ml (Fig. 5). Increments in the plasma glucose concentration and glucose production and decrements in glucose clearance occurred at threshold values of 150–200 pg/ml (Fig. 6). The

TABLE II

Mean (±SE) Hemodynamic and Metabolic Values before and during Epinephrine Infusions

Nominal infusion rate μg/min	0.1		0.5		1.0		2.5		5.0	
Measured infusion rate μg/min	0.09±0.01		0.43±0.03		1.06±0.15		2.97±0.23		4.70±0.30	
	B*	I‡	B	I	B	I	B	I	B	I
Heart rate, *beats/min*	66±5	69±6	63±3	72±4	61±2	70±4	68±4	81±4	63±3	84±6
Systolic blood pressure, *mm Hg*	109±3	115±3	109±2	117±2	114±4	120±3	111±2	127±3	111±2	133±5
Diastolic blood pressure, *mm Hg*	74±2	75±4	72±2	73±1	77±5	75±6	74±3	64±4	76±2	63±4
Glucose, *mg/dl*	86±4	87±3	90±4	92±3	85±3	97±3	86±2	122±4	84±1	152±10
Lactate, *μM*	682±85	696±81	768±40	830±103	869±62	1,000±86	681±56	1,100±120	857±112	2,560±178
Glycerol, *μM*	32±13	39±11	57±25	87±31	64±21	120±21	65±22	100±18	47±15	140±32
β-Hydroxybutyrate, *μM*	66±17	92±33	51±5	111±26	50±8	96±23	74±12	327±96	51±10	202±69
Alanine, *μM*	264±34	248±32	308±15	294±12	348±33	312±25	275±23	276±22	332±41	312±26
Insulin, *μU/ml*	10.0±1.5	9.8±0.9	10.9±1.4	9.5±1.2	9.0±0.8	9.6±1.1	9.9±3.2	8.1±1.0	10.8±3.0	5.9±0.8
Glucagon, *pg/ml*	124±20	136±12	112±13	105±15	112±14	102±12	109±22	100±16	141±8	125±6
Growth hormone, *ng/ml*	0.8±0.2	1.6±0.8	0.8±0.2	0.9±0.4	0.9±0.1	0.9±0.2	0.8±0.2	1.0±0.2	1.4±0.4	1.0±0.1
Cortisol, *μg/dl*	8.3±1.5	6.6±1.2	6.2±1.2	6.1±1.3	5.9±1.0	4.8±0.8	6.4±1.3	4.9±0.7	7.2±1.4	4.0±0.9

* Basal values before epinephrine infusion.

‡ Infusion values during the infusion of epinephrine at the indicated infusion rates. All are at 60 min except the glycerol (30 min) and insulin (10 min) values.

plasma epinephrine thresholds for increments in blood lactate and β-hydroxybutyrate (Fig. 7) were similar to those for glucose, but lower for increments in blood glycerol, 75–125 pg/ml (Fig. 7). The threshold for the initial suppression of plasma insulin was 400 pg/ml, higher than that of the other responsive variables (Fig.

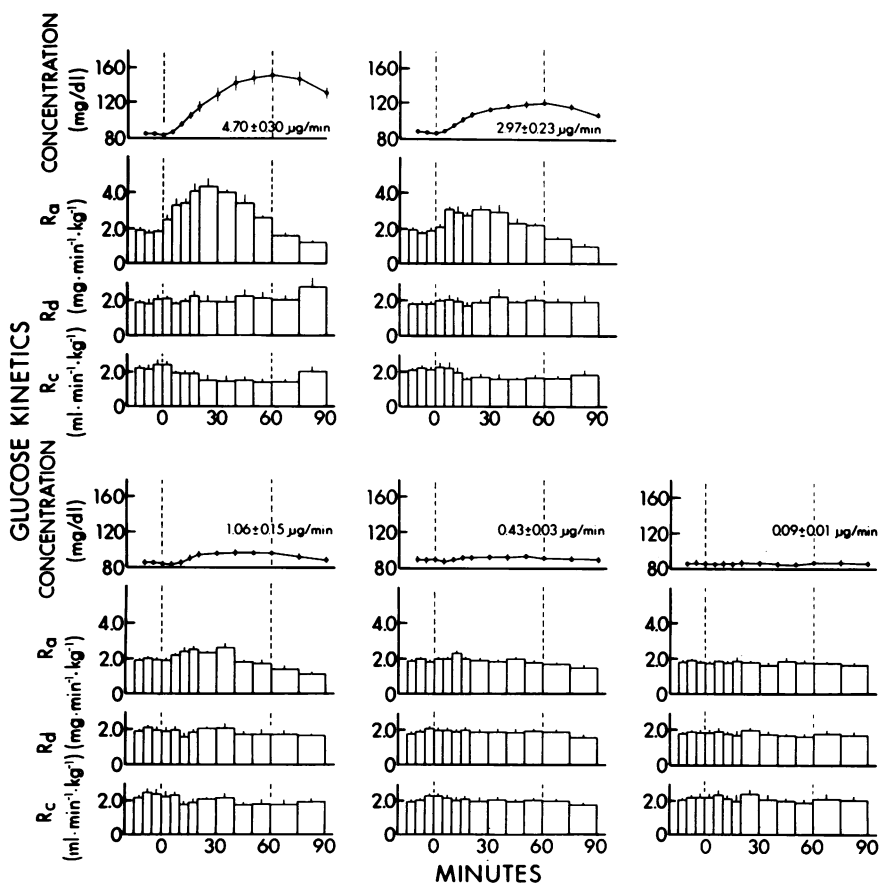

FIGURE 3 Mean (±SE) plasma glucose concentrations and glucose production (R_a), utilization (R_d), and clearance (R_c) rates before, during, and after 60-min epinephrine infusions at the five nominal infusion rates. The mean (±SE) measured infusion rates are listed at the right of each panel.

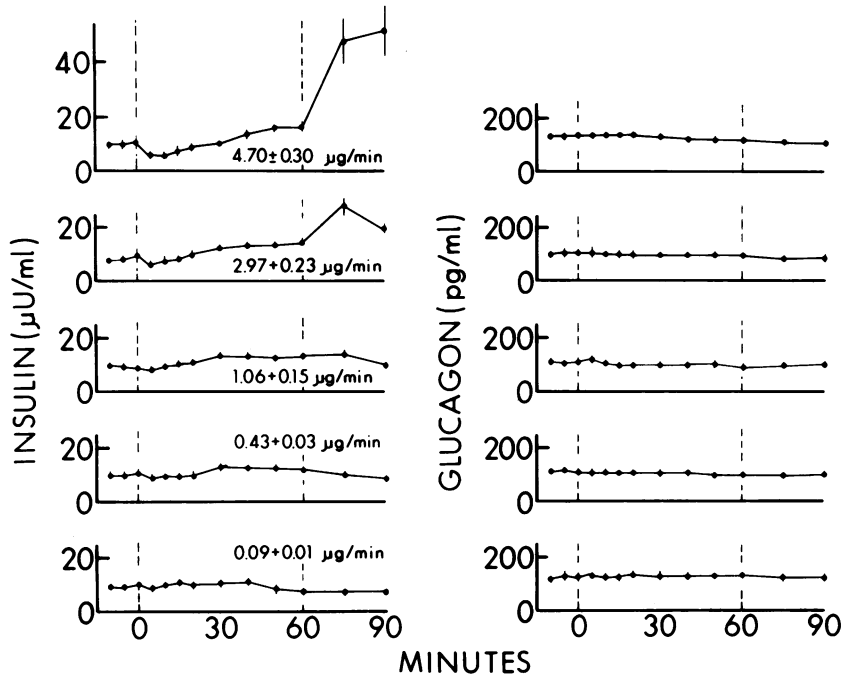

FIGURE 4 Mean (±SE) plasma insulin and glucagon concentrations before, during, and after 60-min epinephrine infusions at the five nominal infusion rates. The mean (±SE) measured infusion rates are listed at the right of the insulin plots.

8). These plasma epinephrine thresholds are summarized in Table III.

DISCUSSION

From mean (±SD) basal values of 34±18 in 60 normal subjects studied in our laboratory, mean plasma epinephrine concentrations rise nearly 2-fold during quiet standing (6), ~3-fold during cigarette smoking (26), from 2–13-fold during mild to heavy exercise (27), and 50-fold during insulin-induced hypoglycemia (28). Notably, physiologic decrements in the plasma glucose concentration—from 95 to 60 mg/dl—were associated with a nearly seven-fold rise in plasma epinephrine levels, with a maximum mean value of 230 pg/ml (29). Similar values are achieved during elective cholecystectomy,[2] and higher values occur in various pathophysiologic states such as diabetic ketoacidosis (30), acute myocardial infarction (31), and pheochromocytoma (32). Clearly, interpretation of the biologic significance of these plasma epinephrine measurements requires knowledge of the plasma epinephrine concentrations necessary to produce measurable biologic actions.

In the present studies, infusions of graded doses of epinephrine into normal human subjects generally produced the effects anticipated (3, 4). These included increments in heart rate, widening of the pulse pressure, increments in plasma glucose (the resultant of a transient increase in glucose production and a sus-

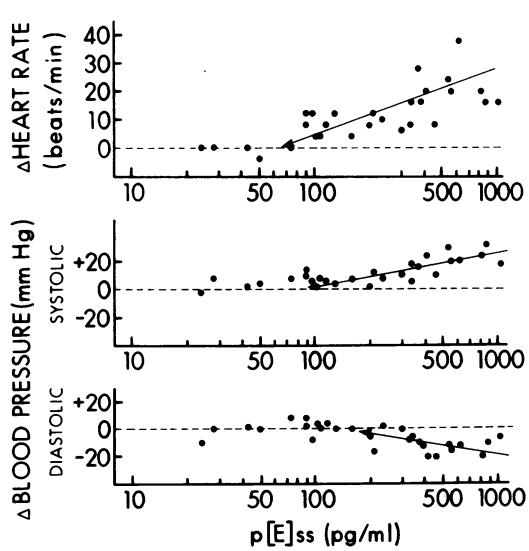

FIGURE 5 Epinephrine infusions. Changes (Δ) in heart rate, systolic blood pressure, and diastolic blood pressure at p[E]ss ranging from 24 to 1,020 pg/ml. The arrows indicate the estimated plasma epinephrine thresholds for these variables.

[2] Brown, F. F., W. D. Owens, J. A. Felts, E. I. Spitznagel, and P. E. Cryer. Unpublished observations.

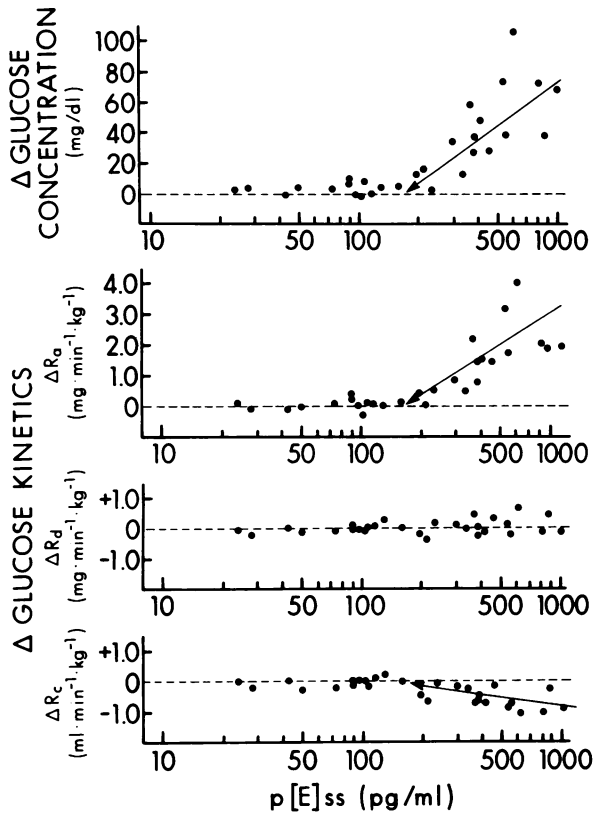

FIGURE 6 Epinephrine infusions. Changes (Δ) in plasma glucose, production (R_a), glucose utilization (R_d), and glucose clearance (R_c) at p[E]ss ranging from 24 to 1,020 pg/ml. The R_a values are from 30 min. The arrows indicate the estimated plasma epinephrine thresholds for the epinephrine-responsive variables.

tained decrease in glucose clearance), blood lactate, blood glycerol, and blood β-hydroxybutyrate, and initial decrements in plasma insulin. One discrepancy with earlier studies (25, 33, 34) was the absence of an increase in plasma glucagon during epinephrine infusions.

These 30 epinephrine infusions resulted in p[E]ss ranging from 24 to 1,020 pg/ml, thus permitting estimation of the plasma epinephrine thresholds for its metabolic and hemodynamic actions. As summarized in Table III, the plasma epinephrine thresholds for increments in heart rate (50–100 pg/ml) and in systolic blood pressure and blood glycerol (75–125 pg/ml) were the lowest among the variables tested. Thus, the cardiac chronotropic and lipolytic effects of epinephrine occur at p[E]ss levels only 2–3-fold basal values. The plasma epinephrine thresholds for the remaining direct metabolic effects—increments in glucose production and decrements in glucose clearance resulting in increments in the plasma glucose concentration, and increments in blood lactate and blood β-hydroxybutyrate—were intermediate at 150–200 pg/ml. Thus, the hyperglycemic, glycolytic, and ketogenic effects of epinephrine occur at p[E]ss levels 4–5-fold basal values. Clearly, then, the plasma thresholds for the direct metabolic actions of epinephrine lie within the commonly achieved physiologic range. The plasma epinephrine threshold for indirect metabolic actions—those mediated through suppression of insulin secretion—was the highest among the variables tested, >400 pg/ml or 12-fold basal values. As noted earlier, plasma epinephrine concentrations of this magnitude do occur during heavy exercise and absolute hypoglycemia, as well as during a variety of acute illnesses.

These plasma thresholds for direct metabolic and hemodynamic effects of epinephrine (<200 pg/ml) are ~10% of those previously determined (5) for norepinephrine (1,500–2,000 pg/ml). Thus, epinephrine is ~10-fold more potent than norepinephrine in humans.

Catecholamines are rapidly cleared from the extracellular fluid. In the present study, at p[E]ss values overlapping the basal normal range, the mean $pMCR_E$ was 52±4 ml·min^{-1}·kg^{-1}. Notably, the $pMCR_E$ values were significantly higher, averaging 89±6 ml·min^{-1}·kg^{-1}, at p[E]ss levels ranging from 90 to 1,020 pg/ml. Thus, epinephrine accelerates its own metabolic clear-

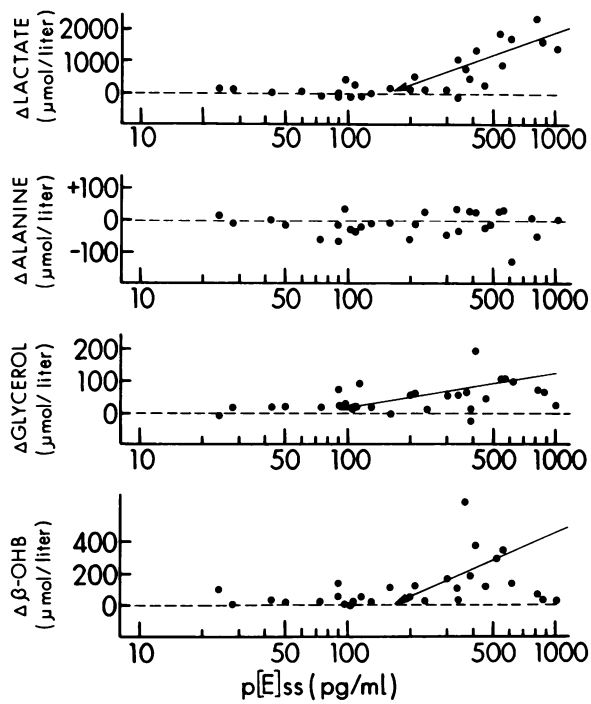

FIGURE 7 Epinephrine infusions. Changes (Δ) in blood lactate, alanine, glycerol, and β-hydroxybutyrate at p[E]ss ranging from 24 to 1,020 pg/ml. The blood glycerol values are from 30 min. The arrows indicate the estimated plasma epinephrine thresholds for the epinephrine-responsive variables.

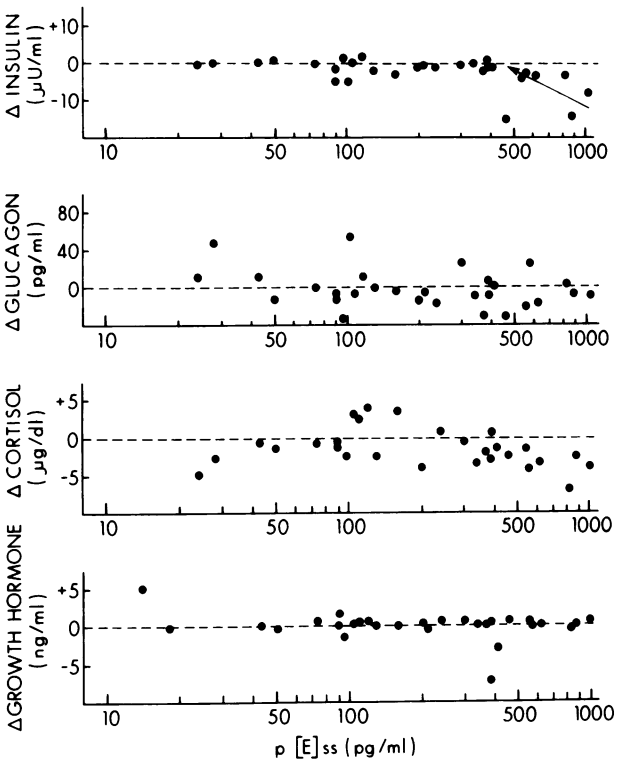

FIGURE 8 Epinephrine infusions. Changes (Δ) in plasma insulin, glucagon, growth hormone, and cortisol at p[E]ss ranging from 24 to 1,020 pg/ml. The plasma insulin values are from the average of the 5- and 10-min levels. The arrow indicates the estimated plasma epinephrine threshold for the epinephrine-responsive variable.

ance by ~70%. Analysis of the primary data from an earlier study (5) from our laboratory revealed a similar effect of norepinephrine on its metabolic clearance. At p[NE]ss of 229–345 pg/ml, the $pMCR_{NE}$ was 25±4 $ml \cdot min^{-1} \cdot kg^{-1}$; at higher p[NE]ss the $pMCR_{NE}$ was 39±3 $ml \cdot min^{-1} \cdot kg^{-1}$ ($P < 0.02$). These findings are complementary to the recent observation that the clearances of epinephrine and norepinephrine are sharply reduced during β-adrenergic blockade (but unaltered during α-adrenergic blockade) in humans (35). Thus, the catecholamines appear to regulate their own metabolic clearance through β-adrenergic mechanisms, a potentially important level of modulation of the biologic expression of sympathoadrenal activity.

We conclude that in human subjects: (*a*) the plasma epinephrine thresholds for its hemodynamic and metabolic actions lie within the physiologic range, (*b*) epinephrine and norepinephrine accelerate their own metabolic clearance, and (*c*) epinephrine is ~10 times more potent than norepinephrine.

TABLE III
Plasma Epinephrine Thresholds for Hemodynamic and Metabolic Actions

p[E]ss =	50–100 pg/ml
	Increment in heart rate
p[E]ss =	75–125 pg/ml
	Increment in systolic blood pressure
	Increment in blood glycerol
p[E]ss =	150–200 pg/ml
	Decrement in diastolic blood pressure
	Increment in plasma glucose and glucose production; decrement in glucose clearance
	Increment in blood lactate
	Increment in blood β-hydroxybutyrate
p[E]ss =	>400 pg/ml
	Initial decrement in plasma insulin

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