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P Hjemdahl, E Belfrage, M Daleskog

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Research Article

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Vascular and Metabolic Effects of Circulating Epinephrine and Norepinephrine

CONCENTRATION-EFFECT STUDY IN DOGS

PAUL HJEMDAHL, ERIK BELFRAGE, and MAUD DALESKOG, *Department of Pharmacology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden*

A B S T R A C T Vascular and metabolic effects of circulating epinephrine and norepinephrine have been studied in relation to the plasma concentration of these amines in dogs. Intravenous infusion of epinephrine or norepinephrine (0.1, 0.5, and 2.5 nmol \times kg $^{-1}$ \times min $^{-1}$) raised the plasma concentration of the infused amine by 2.5, 13, and 63 nM from resting levels of 2.4 and 3.6 nM, respectively. Blood flow to isolated adipose tissue; skeletal muscle preparations; and plasma levels of glycerol, glucose, and cyclic AMP were measured.

Epinephrine and norepinephrine displayed a distinct selectivity with regard to both vascular and metabolic effects. Epinephrine caused significant vasoconstriction in adipose tissue already at a plasma concentration of 5 nM, whereas no significant effect was seen on skeletal muscle vascular resistance. Norepinephrine, on the other hand, caused significant vasoconstriction in skeletal muscle at 5 nM but had no vasoconstrictor effect in adipose tissue. Epinephrine was more potent than norepinephrine in increasing plasma cyclic AMP and glucose, whereas the converse was true for plasma glycerol. Epinephrine had significant effects on plasma cyclic AMP at 5 nM and on plasma glucose and glycerol at 15 nM. Norepinephrine, on the other hand, had significant effects on plasma glycerol at 5 nM, plasma cyclic AMP at 15 nM and plasma glucose only at 65 nM. It is suggested that these response patterns are related to a preferential action of epinephrine on β_2 -adrenoceptors and a preferential action of norepinephrine on β_1 -adrenoceptors. Our results support the view that both epinephrine and norepinephrine may act as circulating hormones, because vascular and metabolic effects of both amines were seen at plasma concentrations encountered during various kinds of stress in animals and man.

INTRODUCTION

Norepinephrine released from adrenergic nerve endings has its main site of action locally, whereas epinephrine released from the adrenal medulla acts as a circulating hormone (1, 2). Nevertheless, a significant proportion of the released norepinephrine enters the circulation from peripheral nerve endings and from the adrenal medulla and may act on distant target organs. Because the plasma concentrations of norepinephrine usually equal or exceed those of epinephrine one must consider the possibility that also norepinephrine acts as a circulating hormone. Difficulties associated with the measurement of catecholamines in small amounts of plasma have limited the information regarding the quantitative importance of circulating catecholamines. Recent methodological advances have, however, rendered such studies feasible and, we, therefore, decided to compare some vascular and metabolic actions of intravenously infused norepinephrine and epinephrine in the dog and relate these effects to the plasma concentrations of the amines.

Norepinephrine and epinephrine stimulate adrenergic receptors of both the α - and the β -type (3). Epinephrine is a more potent α -agonist than norepinephrine. There is a difference between norepinephrine and epinephrine with regard to the type of β -receptor which is stimulated. Thus, norepinephrine preferentially stimulates β_1 -receptors, whereas epinephrine rather selectively stimulates β_2 -receptors (4).

Blood vessels are usually endowed with both α - and β -receptors. Vascular β -receptors are usually of the β_2 -type. However, the vascular β -receptors of the adipose tissue differ from those of, for example, skeletal muscle, as they are of the β_1 -type (5). This may explain why it has been found in several species that intravenously infused norepinephrine may cause vasodilation in adipose tissue, whereas most other tissues

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respond with vasoconstriction (6–9). The β_2 -agonist properties of epinephrine, on the other hand, will make this amine a less powerful vasoconstrictor in skeletal muscle than in adipose tissue as a result of the simultaneous stimulation of vascular β_2 -receptors in the muscle (5). We, therefore, studied the vascular effects of norepinephrine and epinephrine in isolated subcutaneous adipose tissue and skeletal muscle preparations in parallel.

To study the metabolic effects of circulating catecholamines, three parameters were chosen: First, we measured plasma glycerol, because lipolysis has been claimed to be mediated mainly by β_1 -receptors (4). Second, we measured plasma glucose, because glycogenolysis is mediated by α - and β_2 -receptors (10, 11). As a third "metabolic" parameter we measured plasma cyclic AMP, because changes in the levels of this nucleotide may reflect changes in plasma catecholamines during various kinds of stress (12) and shock (13, 14). The aim of our study was thus twofold: to study the selectivity of the endogenous catecholamines norepinephrine and epinephrine with regard to

vascular and metabolic actions, and to evaluate the relative importance of the circulating catecholamines by studying the plasma concentrations required for effects.

METHODS

Experiments were performed on seven female mongrel dogs weighing 17–29 kg (average: 22.5 kg). The dogs were anesthetized with sodium pentobarbital 30 mg/kg i.v. with small supplements as required during experiments. A tracheotomy was performed, and the dogs were mechanically ventilated with a Braun Melsungen 74052 respirator (B. Braun Instruments, San Francisco, Calif.). Fluid losses as a result of sampling and trauma were counteracted by replacement with isotonic saline. The hematocrit remained essentially unchanged during experiments.

Subcutaneous adipose tissue in the right inguinal region was isolated from surrounding tissues as described by Rosell (15). The weight of the adipose tissue preparation averaged 59 g (range: 20–112 g). The contralateral gracilis muscle was subsequently isolated from surrounding tissues (16), with care being taken to minimize bleeding by leaving the fascia as intact as possible. The muscle preparations weighed 45–108 g (average: 76 g). After the administration of heparin (2,500 U/kg), the blood vessels supplying both tissues were

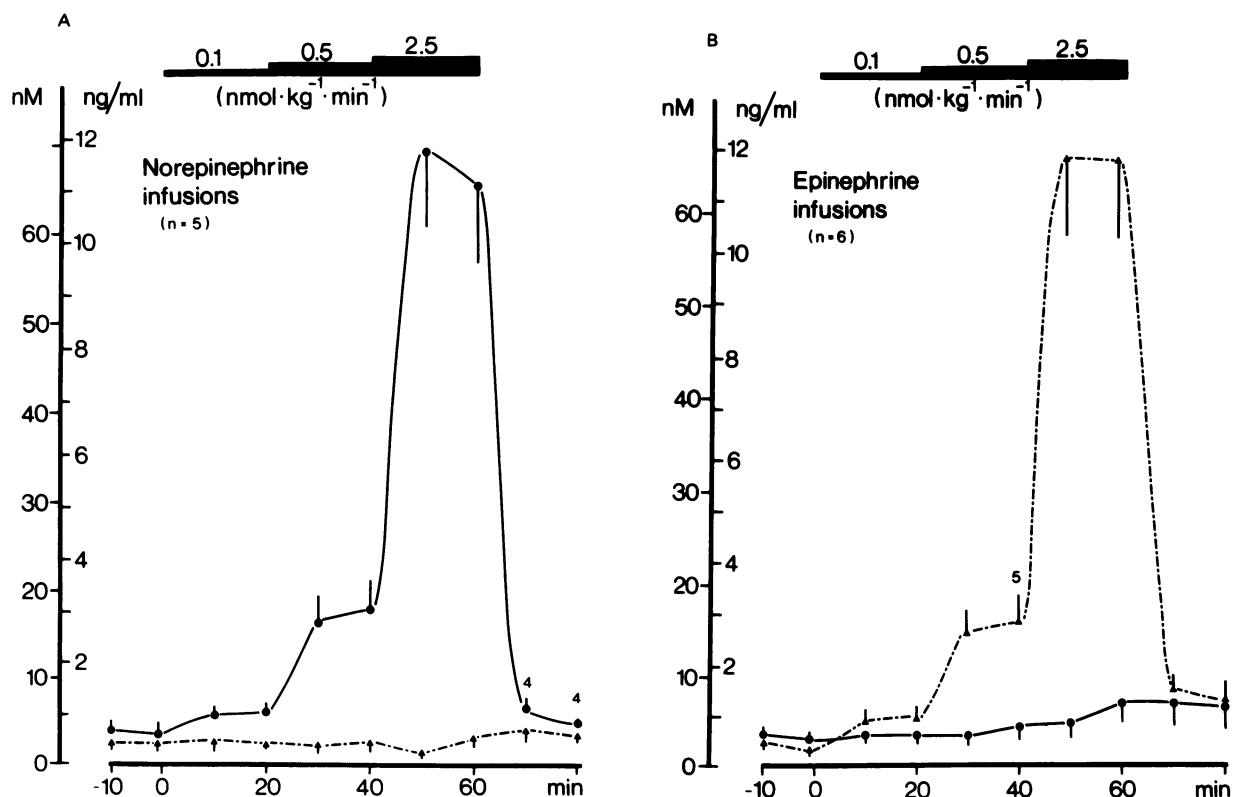


FIGURE 1. Plasma catecholamine concentrations in connection with intravenous infusion of (A) norepinephrine and (B) epinephrine. In five experiments, norepinephrine was infused intravenously in a step-wise fashion at the rates of 0.1, 0.5, and 2.5 $\text{nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, each step lasting 20 min. In six experiments, epinephrine was infused in a similar fashion. Catecholamine concentrations are shown both in nanomolars and in nanograms per milliliter plasma. Vertical bars indicate the SEM.

cannulated with polyethylene tubing. In both cases arterial blood was diverted from the ipsilateral femoral artery and the venous effluent was returned to the ipsilateral femoral vein. Blood pressure was measured from one of the arterial loops with a Statham P23Ac transducer (Statham Instruments, Inc., Oxnard, Calif.). Blood flow was measured with drop counters that contained silicon oil inserted into the arterial loops and was recorded together with blood pressure on a Grass model 7B polygraph (Grass Instrument Co., Quincy, Mass.). Vascular resistance in the adipose tissue and in the skeletal muscle was calculated by dividing the blood pressure in mm Hg by the blood flow in $\text{ml} \times \text{min}^{-1} \times 100 \text{ g}^{-1}$. After the cannulation procedure, both tissues were denervated and allowed to rest for 20–30 min before the first experimental run.

Norepinephrine (1-arterenol HCl, Sigma Chemical Co., St. Louis, Mo.) and epinephrine (as bitartrate; Sigma Chemical Co.) were diluted in ice-cold isotonic saline that contained 20 $\mu\text{g}/\text{ml}$ ascorbic acid to prevent oxidation. In four experiments 0.2 ml of both amines (10^{-10} – 4×10^{-10} mol) were injected into the arterial blood supplying the adipose tissue before and after systemic β -adrenoceptor blockade with propranolol (2 mg $\times \text{kg}^{-1}$ i.v.). In the remaining experiments, both amines were infused into a foreleg vein at infusion rates of 0.1, 0.5, and 2.5 nmol $\times \text{kg}^{-1} \times \text{min}^{-1}$. The infusions were performed in a step-wise fashion, each step lasting 20 min, in a constant volume (0.23 ml/min). At the end of six experiments, the dogs were rapidly hemorrhaged to a blood pressure of 50–60/30–35 mm Hg to obtain a crude estimate of sympathoadrenal reactivity. Arterial blood was removed at the times indicated in Fig. 1 for the determination of plasma concentrations of norepinephrine, epinephrine, glycerol, glucose, and cyclic AMP.

For the determination of catecholamines, 1 ml of blood was collected in an ice-cold plastic tube that contained glutathione and EGTA, as described by Peuler and Johnson (17). Norepinephrine and epinephrine were determined on $3 \times 50 \mu\text{l}$ of plasma by the radioenzymatic (catechol-O-methyl transferase) method of Peuler and Johnson (17) with a few modifications described elsewhere (18). [$S^{-3}\text{H}$]Adenosyl methionine (6.9–10.8 Ci/mmol) was obtained from New England Nuclear, Boston, Mass. All chemicals used were of reagent grade and were usually purchased from Merck AG, Darmstadt, West Germany. All samples, standards and blanks, were run in triplicates. Standards were run as internal standards in pool plasma. Blanks consisted of water. The method used in this study has been validated against an entirely different assay method based on electrochemical detection after separation of the catecholamines by high-pressure liquid chromatography. This comparison showed an excellent agreement between results obtained with the two methods on a set of plasma samples (18).

For determination of cyclic AMP, 1 ml of blood was collected in ice-cold plastic tubes with 50 μl of an EDTA solution that yielded a final concentration of 10 mM. Cyclic AMP was determined on duplicates of 50 μl of plasma with the protein-binding method of Brown et al. (19). The recovery of unlabeled cyclic AMP added to plasma that contained 10 mM of EDTA was essentially complete, as has been shown previously (12). Glycerol was determined on deproteinized ($\text{ZnSO}_4 + \text{Ba}(\text{OH})_2$) plasma from the heparinized dogs according to Laurell and Tibbling (20). Glucose was determined in the same deproteinized plasma with a commercially available glucose-oxidase method (Glox, A. B. Kabi, Stockholm). Data are presented as mean values \pm SEM. Statistical evaluation of the data was performed with Student's *t* test.

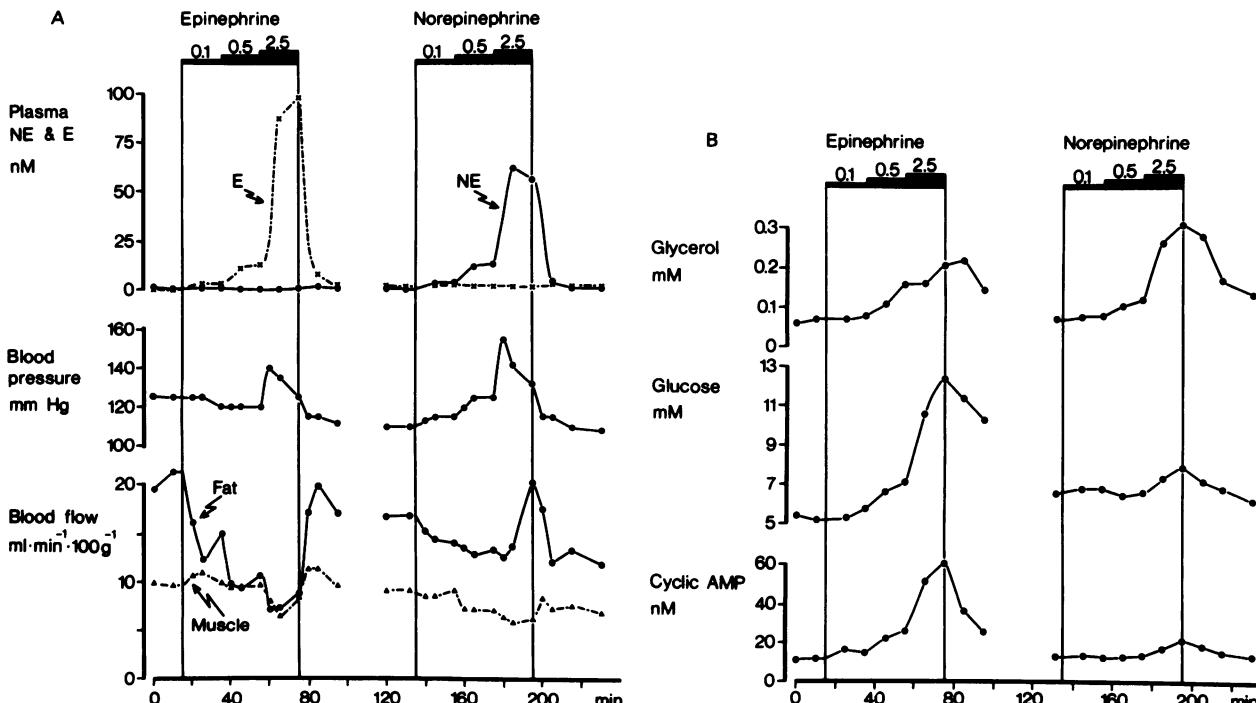


FIGURE 2. (A) Plasma norepinephrine (NE) and epinephrine (E) concentrations, blood pressure, and blood flow to the isolated subcutaneous adipose tissue and the isolated gracilis muscle in a typical experiment in which epinephrine and norepinephrine were infused intravenously. (B) Plasma concentrations of glycerol, glucose, and cyclic AMP in the same experiment.

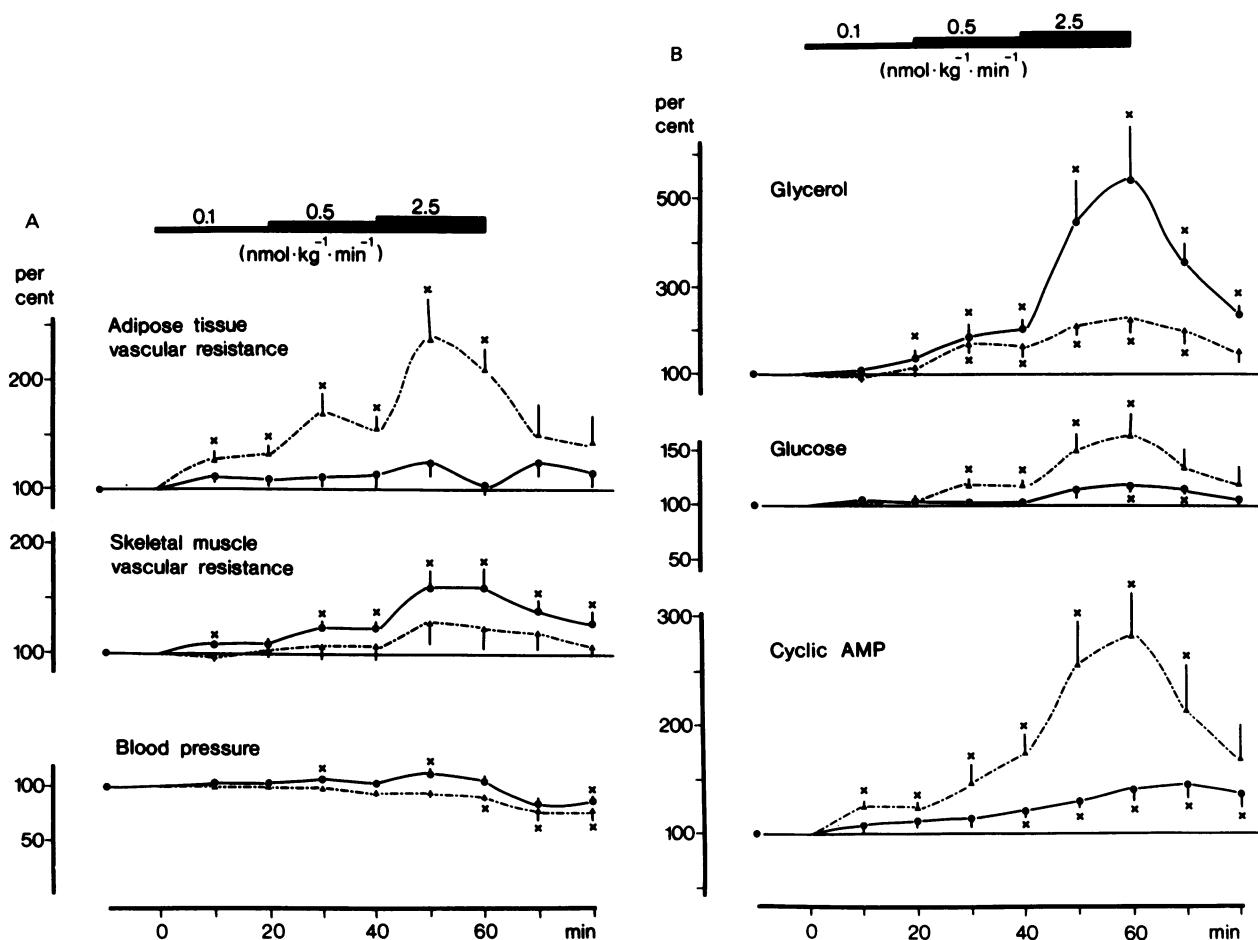


FIGURE 3 Effects of intravenous infusion of norepinephrine (solid lines) and epinephrine (broken lines). Results are expressed in percent of preinfusion values \pm SE to counteract interindividual variations. Statistically significant ($P < 0.05$) deviations from preinfusion values are denoted with a cross. (A) Vascular resistance in subcutaneous adipose tissue and skeletal muscle and blood pressure. (B) Plasma levels of glycerol, glucose, and cyclic AMP.

RESULTS

To minimize the influence of interindividual variation of levels of vascular resistance and plasma concentrations of substances determined, we chose to present one typical experiment (Fig. 2), whereas the compiled results regarding the effects of the catecholamines are expressed as percent change from the resting level before infusion in each dog (Fig. 3). Resting levels of the parameters studied are given in Table I.

Plasma catecholamine concentrations. The basal plasma levels of norepinephrine and epinephrine in our experiments are shown in Table I. These levels are close to the levels previously reported in unanesthetized dogs not exposed to the trauma of isolating tissue preparations (21).

Norepinephrine and epinephrine were infused intravenously in a step-wise fashion at the rates of 0.1,

0.5, and 2.5 $\text{nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$, as indicated in Fig. 1. This infusion rate corresponds to 0.017, 0.085, and 0.42 μg norepinephrine and 0.018, 0.091, and 0.46 μg epinephrine per kilogram body weight and minute. The order of the infusions was varied when effects of both norepinephrine and epinephrine were studied in the same experiment. Infusion of norepinephrine increased the plasma concentration by, on the average, 2.2, 14, and 64 nM during infusion of 0.1, 0.5, and 2.5 $\text{nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$, respectively. Infusion of epinephrine in a similar fashion increased plasma concentrations by 2.7, 13, and 62 nM (Fig. 1). Thus, a fivefold increase in the rate of administration caused a fivefold increase in the plasma concentration of either catecholamine. Steady-state levels appear to have been reached within 10 min during infusions of both amines. These observations indicate that plasma levels of either amine in the order of 60 nM are well below the

TABLE I

Resting Values for the Parameters Studied before Infusion of Norepinephrine or Epinephrine

	Before norepinephrine*	Before epinephrine†
Epinephrine, nM	2.39±0.61	2.43±0.73§
Norepinephrine, nM	3.72±1.09	3.57±0.61§
Blood pressure, mm Hg	112±5	106±6§
Adipose tissue vascular resistance, PRU ₁₀₀	20.5±6.2	16.6±3.5§
Skeletal muscle vascular resistance, PRU ₁₀₀	11.4±1.2	14.6±2.5§
Glycerol, mM	0.052±0.012	0.083±0.011§
Glucose, mM	7.39±1.26	6.24±0.46§
Cyclic AMP, nM	22.8±4.2	27.3±7.2§

* n = 5.

† n = 6.

§ Not significantly different from resting levels before norepinephrine infusions.

saturating level for the inactivation mechanisms. The only statistically significant ($P < 0.05$) effect of catecholamine infusions on the noninfused amine was a reduction in the epinephrine levels after 10 min of infusion of norepinephrine $2.5 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$. The return of these levels to control values at 20 min indicates that this is not an artifact associated with the catecholamine assay.

Six experiments were terminated by rapidly hemorrhaging the dog to a blood pressure of 50–60/30–35 mm Hg for 1.5 min, after which arterial samples were drawn for catecholamine determinations. This rapid and profound stress increased plasma norepinephrine to $11.7 \pm 2.7 \text{ nM}$ and plasma epinephrine to $45.7 \pm 12.7 \text{ nM}$.

Circulatory effects of infused norepinephrine and epinephrine. As expected, norepinephrine caused an increase in mean blood pressure, whereas epinephrine tended to reduce mean blood pressure (Figs. 2A and 3A). When the infusion of either amine was terminated, there was usually a drop in blood pressure. The effects of the two catecholamines on blood flow to the denervated adipose tissue and skeletal-muscle preparations clearly differed.

In the adipose tissue, epinephrine invariably caused vasoconstriction (Figs. 2A and 3A). This effect was already statistically significant at the lowest rate of infusion. During infusion of norepinephrine at the two lowest infusion rates there was either only a slight vasoconstriction or no effect at all (Figs. 2A and 3A). As can be seen in Fig. 2A, norepinephrine could cause a vasodilator effect in adipose tissue after ≈ 20 min of infusion at the highest rate ($2.5 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$). This tendency towards vasodilation, or at least a reduction in vasoconstriction, when the adipose tissue had been exposed to high concentrations of norepi-

nephrine for more than 10 min was a constant finding (Fig. 3A). Intra-arterial injection of both amines caused vasoconstriction in adipose tissue (Table II). β_1 -selective blockade with practolol potentiated the vasoconstrictor effects of norepinephrine but not those of epinephrine (Table II).

In the skeletal muscle, norepinephrine caused statistically significant vasoconstrictor responses at all infusion rates (Fig. 3A). Epinephrine caused either slight vasodilatation or vasoconstriction at the two lowest infusion rates (Fig. 3A). At the highest infusion rate there was a clear but not significant tendency towards vasoconstriction in the skeletal muscle (Figs. 2A and 3A).

Metabolic effects of infused norepinephrine and epinephrine. Resting values for glycerol, glucose, and cyclic AMP in plasma are given in Table I. Norepinephrine and epinephrine increased the plasma concentrations of glycerol, glucose, and cyclic AMP. There was, however, a distinct selectivity with regard to these responses as well (Figs. 2B and 3B). Thus, norepinephrine significantly increased plasma glycerol already at an infusion rate of $0.1 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$, whereas infusion of $0.5 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$ of epinephrine was required for a significant response (Fig. 3B). Plasma cyclic AMP was significantly increased by epinephrine at all infusion rates, whereas $0.5 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$ was required for a significant response during norepinephrine infusions (Fig. 3B). Plasma glucose was the parameter least easily affected by circulating catecholamines as epinephrine caused a significant increase only at the two highest and norepinephrine at the highest rate of infusion.

DISCUSSION

Circulating catecholamines, as measured by radioenzymatic methods, are elevated by several physio-

TABLE II
Vasoconstrictor Effects in Isolated Adipose Tissue

	Vasoconstriction	
	Epinephrine	Norepinephrine
Control	57±12	46±4
Practolol	54±12	54±4

Vasoconstrictor effects in isolated adipose tissue of intra-arterial bolus injections of epinephrine ($1-2 \times 10^{-10} \text{ mol}$) and norepinephrine ($2-4 \times 10^{-10} \text{ mol}$) before and after intravenous injection of practolol $2 \text{ mg} \times \text{kg}^{-1}$. Mean values $\pm \text{SE}$ from four experiments are shown.

logical stimuli. In healthy humans, vigorous exercise may increase plasma norepinephrine to >10 nM and epinephrine to >2 nM (22, 23). This response to exercise is further increased by autonomic blockade (24, 25). Insulin-induced hypoglycemia increased plasma norepinephrine to ≈ 4.6 nM and epinephrine to 12 nM in the study of Garber et al. (26). Orthostatic provocation by tilting may increase plasma norepinephrine to as much as 13 nM (27) and immersion in cold water may increase plasma norepinephrine to 6.9 nM (28). These examples illustrate that the plasma levels observed by us during infusion of norepinephrine or epinephrine, at least at the two lower infusion rates ($0.1-0.5 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$), may be encountered in man exposed to moderate degrees of physical stress. Our experiments have demonstrated both vascular and metabolic effects of circulating norepinephrine and epinephrine in the concentration range mentioned above.

Vascular effects of circulating catecholamines in isolated and denervated tissue preparations will be governed by the relative activity of each catecholamine on α -receptors mediating vasoconstriction and on β -receptors mediating vasodilation. Previously performed comparisons of the vascular α -adrenoceptors in adipose tissue and skeletal muscle have revealed no differences (5, 29). The β -adrenoceptors mediating vasodilatation in adipose tissue are predominantly of the β_1 -type, whereas those in skeletal muscle are of the β_2 -type (5). This and an earlier (5) demonstration that infused epinephrine, but not norepinephrine, causes pronounced vasoconstriction in adipose tissue agrees with this concept, because epinephrine is a less-potent β_1 -receptoragonist (4) and a more-potent α -receptor agonist (3) than norepinephrine. This is further supported by our demonstration that propranolol potentiates the vasoconstrictor effect of norepinephrine but not that of epinephrine in the adipose tissue. In skeletal muscle, on the other hand, the predominance of vascular β_2 -receptors explains why norepinephrine is a more powerful vasoconstrictor than epinephrine and why epinephrine even tends to cause vasodilatation in this tissue (30). Our finding that vascular effects of both norepinephrine and epinephrine are detectable in isolated tissue preparations at plasma concentrations of 5–10 nM clearly suggests that both of these circulating catecholamines may be of physiological importance for the regulation of peripheral circulation.

The vasodilating effect of norepinephrine in the adipose tissue of the dog is usually seen during infusion at rates which, according to our results, would produce plasma concentrations in the order of 50 nM or more (8, 9, 31), whereas lower infusion rates cause vasoconstriction (32). Furthermore, the vasodilatation seen with high concentrations of norepinephrine is pre-

ceded by a period of vasoconstriction (9), which suggests that there may be a metabolic component in the β -adrenergic vasodilator response of adipose tissue to circulating norepinephrine, as is also suggested by experiments with acidosis (29) and cooling (33). In our experiments there was only a tendency towards vasodilatation in the adipose tissue after 20 min of infusion of norepinephrine at the highest infusion rate (Fig. 3). Because the plasma norepinephrine concentration had not changed significantly between 10 and 20 min of infusion (69 ± 6 vs. 65 ± 8.5 nM) it is conceivable that factors other than the degree of direct β -adrenergic vasodilatation, e.g., metabolic factors, may also be of importance for this vasodilator response.

Adipose tissue is one of the tissues most sensitive to the adverse effects of hemorrhagic shock (34). Thus, during hypotension, blood flow to the adipose tissue is more severely compromised than the blood flow to several other tissues, including skeletal muscle (34). Hemorrhage is a profound stimulus to catecholamine secretion, epinephrine levels in plasma being considerably more elevated than norepinephrine levels (35). In keeping with this, we observed an extremely rapid (<2 min) increase in plasma epinephrine to ≈ 45 nM, whereas norepinephrine increased to 12 nM during hemorrhage. Our results, which show a powerful vasoconstrictor effect of epinephrine in adipose tissue at plasma concentrations easily attained during shock, suggest that circulating epinephrine is at least partially responsible for the exquisite sensitivity of adipose tissue circulation to hemorrhagic shock.

The sympathetic nervous system appears to be of considerable importance for the regulation of metabolic processes such as lipolysis and glucose turnover (36). Our results indicate that circulating epinephrine and norepinephrine may cause metabolic activation at concentrations in the order of 10 nM. As was seen for the vascular effects, these amines also possessed a clear-cut selectivity with regard to metabolic effects. Thus, norepinephrine was the more potent lipolytic agent, whereas epinephrine was more active with regard to plasma glucose and, in particular, plasma cyclic AMP.

Plasma glycerol, the levels of which reflect the outflow of glycerol from the isolated subcutaneous adipose tissue during intravenous infusion of norepinephrine (9), was already significantly increased by norepinephrine during infusion of $0.1 \text{ nmol} \times \text{kg}^{-1} \times \text{min}^{-1}$, i.e., at plasma concentrations in the order of 5 nM. At the medium rate of infusion, epinephrine was almost as effective as norepinephrine in increasing plasma glycerol, whereas norepinephrine was clearly more effective at the highest concentration studied. The tendency towards a stronger lipolytic response to norepinephrine than to epinephrine at plasma concentrations of up to ≈ 15 nM may be explained by the β_1 -receptor selectivity

of norepinephrine (4). The strong dissociation of the lipolytic effect of these amines seen at higher plasma concentrations would, however, seem to call for an additional explanation. It has previously been noted (31) that the lipolytic response to circulating norepinephrine is determined not only by the arterial plasma concentration of the amine but also by the total amount delivered to the tissue. The comparatively poor lipolytic effect of epinephrine at plasma concentrations in the order of 60 nM may thus be explained by the reduction in blood flow to the adipose tissue, which is induced by epinephrine but not by norepinephrine.

Several hormones may cause increases in plasma cyclic AMP, and it is assumed that these increases in extracellular cyclic AMP mirror changes in intracellular cyclic AMP in the target organs of the hormone in question (12). Even though extracellular cyclic AMP has no known physiological function, plasma cyclic AMP may be a sensitive indicator of hormonal changes and stress (12). For example, Nistrup Madsen et al. (37) found increases in plasma cyclic AMP that were correlated to changes in plasma epinephrine in connection with surgery. Hemorrhagic shock in the rat induces a rapid and pronounced increase in plasma cyclic AMP (13), which has been attributed to an increase in epinephrine (14). Our results confirm earlier findings that catecholamines increase plasma cyclic AMP (38, 39). The marked sensitivity of plasma cyclic AMP to increases in circulating epinephrine suggests that this hormone may be one of the more important hormones in the regulation of plasma cyclic AMP. Similarly, plasma glucose was selectively increased by epinephrine. Because the selective β_2 -agonist, salbutamol, increases plasma glucose and cyclic AMP in a similar fashion (40, 41), it may be inferred that the β_2 -agonist properties of epinephrine are of importance for these actions.

Intravenous infusion of epinephrine (42) or norepinephrine (43, 44) in doses comparable to our intermediate dose causes metabolic activation in man. In addition, Silverberg et al. (43) measured plasma norepinephrine concentrations, finding increases during infusion that were similar to ours. They concluded that norepinephrine might subserve a role as a circulation hormone in man during stress. By using anesthetized dogs we have found metabolic effects at still lower concentrations of circulating norepinephrine and epinephrine. Furthermore, we have demonstrated effects of low concentrations of both amines on peripheral blood vessels. Thus, our results strengthen the view that both of these catecholamines act as circulating hormones. Their selective actions on different vascular beds and different metabolic events facilitate a differentiated response pattern in connection with various kinds of stress.

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