Desipramine Blocks Augmented Neurogenic Vasoconstrictor Responses to Epinephrine

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The forearm vasoconstrictor response to lower body negative pressure (LBNP), a reflex stimulus to norepinephrine release, can be augmented by a prior brachial artery infusion of epinephrine. We wished to determine whether this sustained aftereffect of epinephrine could be replicated by systemic infusion and, if so, whether it could be prevented by prior uptake-1 blockade with desipramine. Eight normal men (mean age 30 years) were studied on two separate study days at least 1 week apart, 2.5 hours after taking, at random, either desipramine (125 mg p.o.) or placebo. Forearm vascular resistance was measured at rest and at the end of 6 minutes of LBNP at —40 mm Hg. This was done both before and 30 minutes after a 60-minute infusion of epinephrine (1.5 μg/min i.v.). From similar baselines, the forearm vasoconstrictor response to LBNP was significantly augmented 30 minutes after epinephrine on the placebo day (+17±4 vs. +12±3 resistance units, mean±SEM, p<0.01) but not on the desipramine day (+14±2 vs. +16±3 resistance units). The heart rate response to LBNP was also greater after epinephrine infusion on the placebo day (+20±3 vs. +16±2 beats/min, p<0.05). Mean arterial pressure was higher after epinephrine infusion on the placebo (p<0.01) but not on the desipramine day. Thus, transient increases in epinephrine, which has a plasma half-life of only minutes, can have sustained aftereffects, increasing mean arterial pressure and augmenting vasoconstrictor and chronotropic responses to a reflex stimulus to norepinephrine release 30 minutes after its infusion. These effects appear to be mediated through the uptake of epinephrine by sympathetic nerves and its corelease with norepinephrine on subsequent nerve stimulation. Epinephrine then could act on prejunctional β-adrenergic receptors to facilitate norepinephrine release and augment neurogenic vasoconstriction. These observations provide further support for the concept that increases in plasma epinephrine concentration might contribute to the pathogenesis of essential hypertension by this mechanism. (Hypertension 1990;15:132-139)

Epinephrine facilitates noradrenergic transmission in isolated tissues and intact animals by stimulating prejunctional β-adrenergic receptors. These receptors appear to be β2 in most species, including humans.1-5 Because the affinity of epinephrine for β2 receptors is more than 200 times greater than that of norepinephrine, one of the physiological roles subserved by epinephrine may be to modulate norepinephrine release.6

Epinephrine can be taken up into postganglionic sympathetic nerves and released as a cotransmitter with norepinephrine up to 24 hours later.5-9 When released, epinephrine augments the simultaneous discharge of endogenous norepinephrine. Thus, the facilitated release of norepinephrine may occur after exogenous administration of epinephrine, even when its plasma concentrations have returned to basal levels.8 Endogenous epinephrine could also increase norepinephrine release by this mechanism both during and after episodes of sympathoadrenal activation. The concept that epinephrine can facilitate norepinephrine release in humans is supported by several studies that used different experimental strategies. For example, plasma norepinephrine concentrations have been measured during intravenous infusion of β-receptor agonists. However, when these catecholamines are given systemically, heart rate and blood pressure change and neurogenic reflex pathways are activated. These alterations may affect the release and clearance of norepinephrine independently of any prejunctional influence of these β-adrenergic agonists.
Further, an inappropriately high dose of epinephrine could inhibit norepinephrine release by stimulating prejunctional α2-adrenergic receptors. Not surprisingly, therefore, the results of such studies have been equivocal. Our strategy has been to explore the functional significance of these concepts as they relate to neurogenic vasoconstriction in humans. In a previous study, we compared the effects of epinephrine and isoproterenol on forearm vasoconstrictor responses to lower body negative pressure (LBNP), a reflex stimulus to norepinephrine release. To localize their action to the forearm these β-adrenergic receptor agonists were administered via a brachial artery catheter in low doses without systemic effect. The vasoconstrictor response to LBNP was augmented by 70% 30 minutes after termination of the epinephrine infusion. In contrast, prior infusion of isoproterenol, which is not taken up by sympathetic nerve terminals, had no effect on the vasoconstrictor response to LBNP. On the basis of experimental evidence, these sustained aftereffects of epinephrine were attributed to its uptake by forearm sympathetic nerves. When released later during subsequent reflex stimulation, we hypothesized that this epinephrine could then act on prejunctional β-receptors to augment norepinephrine release.

Our aim in the current series of experiments was to determine whether the sustained local aftereffects of epinephrine 1) could be replicated by systemic infusion of epinephrine to achieve plasma levels seen during physiological stress and 2) could be prevented by prior neuronal uptake-1 blockade with desipramine. Our hypotheses were 1) that we would detect augmentation of the forearm vasoconstrictor and heart rate responses to LBNP 30 minutes after prior infusion of epinephrine and 2) that the sustained effects of epinephrine would not be seen after prior uptake-1 blockade with desipramine.

Methods

Subjects

Eight healthy consenting male volunteers 20–37 years old (mean age 30 years) were studied according to a protocol approved by the Human Subjects Review Committee of the Toronto General Hospital. Informed written consent was obtained after the rationale, nature, and potential risks of this research were explained.

Subjects participated on 2 study days at least 1 week apart. After a light breakfast, subjects were given either placebo or desipramine (125 mg p.o.) according to a random, double-blind schedule prepared by our pharmacy.

Procedures

Subjects rested supine during the study. Blood pressure was measured from the left arm by an automatic cuff recorder (Lifestat 200, Physio-Control Corp., Redmond, Washington). An intravenous catheter was placed in a left forearm vein for infusions. After local anesthesia, a central venous catheter was introduced into the antecubital vein of the left arm and advanced to an intrathoracic position. Central venous pressures and respiratory excursions were measured continuously by Statham P23ID pressure transducers (Gould Inc., Cleveland, Ohio) and recorded simultaneously with the heart rate, electrocardiogram, and forearm blood flow (Gould 2800 S ink recorder, Gould Inc.).

Forearm blood flow was measured in the right arm by venous occlusion plethysmography as described in detail previously. Four measurements of forearm blood flow were obtained each minute. Forearm vascular resistance, expressed as resistance units (units), was calculated by dividing mean arterial pressure by the average of four to six measures of forearm blood flow (ml/min/100 ml of forearm volume).

An LBNP chamber was placed over the patient’s body below the iliac crest and sealed. LBNP at −40 mm Hg was used to lower both central venous and mean arterial pressure and thus unload both arterial and cardiopulmonary receptors. The reflex response to this stimulus includes forearm vasoconstriction and tachycardia.

Protocol

Our experimental strategy is summarized by Figure 1. The protocol began 2.5 hours after tablets (placebo or desipramine) were taken. Responses to LBNP were compared before and 30 minutes after a 60-minute intravenous infusion of 1.5 μg/min (approximately 20 ng/kg/min) epinephrine hydrochloride in saline (0.76 ml/min). At all other times saline, as control, was infused at 0.76 ml/min.

Blood pressure and heart rate were recorded automatically at 1-minute intervals during the rest period and during LBNP and at 3-minute intervals during the epinephrine infusion. Forearm blood flow was recorded at rest, immediately before the onset of LBNP and during the last 2 minutes of 6 minutes of LBNP at −40 mm Hg. The vasoconstrictor response to LBNP was determined from the difference between forearm vascular resistance at rest and during the last 2 minutes of LBNP. The chronotrop response to LBNP was calculated as the difference between heart rate over the minute immediately before LBNP and the heart rate recorded over the last minute of LBNP.

Plasma Catecholamines

Venous blood (10 ml) was sampled before and in the last minute of LBNP, placed in chilled 15 ml polypropylene tubes containing reduced glutathione (25 mg), EGTA (100 μl;100 mg/ml), and heparin (100 units). Tubes were then centrifuged at 4°C at 3,000 rpm for 10 minutes. Plasma was then separated and stored at −70°C. Plasma concentrations of norepinephrine and epinephrine were determined via high-performance liquid chromatography (HPLC) using modifications of the methods of...
Ericksson and Persson\textsuperscript{20} and Weicker et al.\textsuperscript{21} This assay is sensitive to 20 pg/ml of norepinephrine and 20 pg/ml of epinephrine. Both the interassay and intra-assay coefficients of variation of this technique have been calculated to be 7.5%.

**Statistics**

Means and their standard errors are reported. The effects of period (before epinephrine, after epinephrine), condition (rest, LBNP), and the eight subjects on the overall variance were assessed by three-way analysis of variance. When $F$ tests revealed significant actions and interactions, the nature of the effects of prior infusion of epinephrine was determined by Student's paired $t$ test. The paired $t$ test was also used to assess the effect of desipramine on initial resting values. Values of $p<0.05$ were required for statistical significance.

**Results**

**After Placebo**

Epinephrine infusion increased pulse pressure, heart rate, and forearm blood flow. Blood pressure was 117±2/69±3 mm Hg before and 124±6/66±2 mm Hg during epinephrine infusion. Central venous pressure increased from 3±1 to 4±1 mm Hg ($p<0.05$) and heart rate from 59±3 to 65±4 ($p<0.01$). Forearm vascular resistance fell from 31.3±3.3 to 17.9±1.8 units ($p<0.01$).

Prior infusion of epinephrine resulted in several hemodynamic changes: an increase in mean arterial pressure ($F=6.92$, $p=0.034$), a decrease in central venous pressure ($F=25.14$, $p=0.0015$), and an increase in heart rate ($F=13.11$, $p=0.0085$). Systolic ($p=0.08$) and diastolic ($p=0.06$) blood pressure tended to be higher after epinephrine infusion, whereas forearm blood flow, forearm vascular resistance, and plasma norepinephrine concentrations were not altered (Table 1).

Plasma epinephrine concentrations during LBNP were somewhat higher after epinephrine (117±20 ng/μl) than before its infusion (78±24 ng/μl, $p<0.005$).

Effects of LBNP at −40 mm Hg on study variables were as expected (Table 1). Systolic blood pressure fell ($F=34.2$, $p=0.006$), as did central venous pressure ($F=27.02$, $p=0.0013$) and forearm blood flow ($F=30.90$, $p=0.0009$). Mean ($p=0.16$) and diastolic blood pressure ($p=0.83$) tended to remain constant. There were reflex increases in heart rate ($F=52.22$, $p=0.00017$), forearm vascular resistance ($F=17.95$, $p=0.0039$), and plasma norepinephrine concentrations ($F=70.54$, $p=0.00007$) (Table 1). Significant interactions between epinephrine and LBNP were documented for central venous pressure ($F=23.82$, $p=0.0018$), forearm blood flow ($F=8.18$, $p=0.024$), forearm vascular resistance ($F=41.67$, $p=0.0035$), and heart rate ($F=6.52$, $p=0.038$). In other words, prior infusion of epinephrine attenuated the fall in central venous pressure with LBNP but augmented the forearm vasoconstrictor and heart rate responses to this stimulus (+17.4±3.7 units after, as opposed to +11.7±3.2 units before, epinephrine; $p<0.01$; +20±3 beats/min after, as opposed to +16±2 beats/min before, epinephrine infusion; $p<0.05$) (Table 1, Figure 2).

Prior infusion of epinephrine also tended to increase plasma norepinephrine concentrations during LBNP ($F=4.74$, $p=0.066$).
After Desipramine

Initial resting values for blood pressure and heart rate were higher 2.5 hours after desipramine than after placebo, whereas resting values for other study variables were similar on the 2 days (Table 1).

Epinephrine infusion increased pulse pressure, heart rate, and forearm blood flow. Blood pressure was 125±2/76±3 mm Hg before and 130±2/67±3 mm Hg during epinephrine infusion. Epinephrine increased heart rate from 74±5 to 82±4 beats/min (p<0.01), tended to reduce central venous pressure (from 3±2 to 2±1 mm Hg), and lowered forearm vascular resistance (from 25.5±2.3 to 11.9±1.1 units, p<0.0001).

Prior infusion of epinephrine resulted in a decrease of central venous pressure (F=8.72, p=0.021) and an increase in heart rate (F=22.06, p=0.0022) but had no effect on mean arterial blood pressure or on the other study variables (Table 1).

Plasma epinephrine concentrations during LBNP were similar before (92±22 μg/ml) and after infusion (128±52 μg/ml) its infusion (p=0.55).

LBNP lowered systolic (F=29.72, p=0.00095) and mean arterial blood pressure (F=6.52, p=0.038), central venous pressure (F=16.56, p=0.005), and forearm blood flow (F=7.63, p=0.00085). Diastolic blood pressure (F=1.28, p=0.30) held constant. There were reflex increases in heart rate (F=94.69, p=0.00003), forearm vascular resistance (F=50.81, p=0.00019), and plasma norepinephrine concentrations (F=40.995, p=0.0004). (Table 1).

Significant interaction between epinephrine and LBNP were documented for central venous pressure (F=9.67, p=0.017) and heart rate (F=5.80, p=0.0047). In contrast to the placebo study day, there were no significant interactions between epinephrine and LBNP for forearm blood flow (F=1.40, p=0.28), forearm vascular resistance (F=0.25, p=0.63), or plasma norepinephrine concentration (F=1.49, p=0.26). Indeed, the forearm vasoconstrictor response to LBNP tended to be less after prior infusion of epinephrine, whereas the heart rate response to LBNP tended to be greater (p=0.05), albeit from a higher basal level (Table 1, Figure 2). As after placebo, prior infusion of epinephrine attenuated the fall in central venous pressure with LBNP after desipramine.

Discussion

Several groups have focused on the effects of exogenous epinephrine infusion on responses to stimuli that increase sympathetic outflow. For example, increases in blood pressure and plasma norepinephrine evoked by the cold pressor test and isometric exercise can be amplified by systemic infusion of epinephrine and prevented if propranolol is also given. Our study differs from these in that we have directed our attention specifically to responses to a reflex stimulus to norepinephrine release after, rather than during, epinephrine infusion.
On the placebo day of this study we observed 1) augmented reflex forearm vasoconstrictor and heart rate responses to LBNP 30 minutes after the systemic infusion of epinephrine and 2) higher mean arterial pressure after epinephrine infusion. The noradrenergic response to LBNP also seemed to be amplified (p=0.066). The extent to which the forearm vasoconstrictor responses to LBNP could be augmented by prior infusion of epinephrine was similar to that observed in our previous study14 in which we examined the direct and the sustained local aftereffects of intra-arterial epinephrine infusion on neurogenic vasoconstriction.

These findings cannot be attributed to temporal factors for three reasons. First, the hemodynamic stimuli to neurogenic vasoconstriction and reflex tachycardia (i.e., reductions in arterial and central venous pressure) before and after the epinephrine infusion were similar on both study days. Second, this pattern of responses was not replicated after desipramine administration. Third, in our previous studies of the local effects of brachial artery infusion of low dose epinephrine increases in vascular resistance with LBNP -40 mm Hg in the contralateral forearm did not differ before and after an epinephrine infusion of similar duration, indicating the reproducibility of this stimulus and of the responses to LBNP over time.

As the dose of epinephrine infused in these experiments has been reported to raise its plasma concentrations to levels achieved during physiological stresses13,24-26 and to increase plasma norepinephrine concentrations by a β-adrenergic mechanism,13,22 these findings suggest that transient increases in plasma epinephrine can have sustained aftereffects on mean arterial pressure and on neurogenic vasoconstriction and tachycardia in normal humans. These findings are consistent with those reported recently by Fellows et al.20 Intravenous infusion of epinephrine (50 ng/kg/min for 30 minutes) increased venous epinephrine concentrations from 90±31 to 522±41 pg/ml and heart rate from 58±4 to 67±4 beats/min. The chronotropic response to graded LBNP -50 mm Hg was augmented 30 minutes after epinephrine; the forearm vasoconstrictor response to this stimulus, expressed proportionate to baseline, was amplified 15 but not 30 minutes after the infusion.

Intra-arterial isoproterenol, which is not taken up by sympathetic nerve endings, did not alter the reflex vasoconstrictor response to LBNP 30 minutes after its infusion in our earlier study. On the basis of experimental4-5,8 and clinical13 literature, we attributed the sustained local aftereffects of epinephrine to its uptake by forehead sympathetic nerve terminals and its corelease with norepinephrine on subsequent nerve stimulation.5,8,27 Epinephrine could then act on prejunctional β-adrenergic receptors to facilitate norepinephrine release and augment neurogenic vasoconstriction. We wished to test this hypothesis directly in these experiments. Because experimental studies indicate that these sustained aftereffects of epinephrine do not occur in the presence of uptake-1 blockade5,8 our aim was to determine if these aftereffects of infused epinephrine could be prevented if its neuronal uptake were blocked by prior administration of desipramine. We gave a single dose of desipramine (125 mg p.o.), which has been shown to block completely neuronal reuptake of norepinephrine in the forearm.17,18 When this was done, the reflex response to LBNP tended to be less, not greater, after the epinephrine infusion, and no effects on plasma norepinephrine concentration were detected (F=1.49, p=0.26). These experiments therefore provide further support for the concept that the delayed effects of epinephrine on vascular responses to LBNP were due to its neuronal uptake, subsequent release as a cotransmitter with norepinephrine, and facilitation of norepinephrine release by its action on prejunctional β-adrenergic receptors.

Several alternative mechanisms for these observations can be dismissed. The attenuated forearm vasoconstrictor response to LBNP after desipramine and epinephrine cannot be attributed to differing baseline forearm vascular resistances, as these were similar before and after epinephrine infusion on the 2 study days. Nor can they be attributed to an attenuated effect of LBNP on arterial or central venous pressure after desipramine. Indeed, we observed the opposite. LBNP decreased mean arterial pressure after desipramine (F=6.52, p=0.038),
whereas after placebo mean arterial pressure was stable during LBNP ($F=2.43$, $p=0.16$). Central venous pressure was $3 \pm 2$ mm Hg before epinephrine and $1 \pm 1$ mm Hg after epinephrine on both study days, and identical effects of LBNP on central venous pressure were seen after placebo and after desipramine; before epinephrine LBNP lowered central venous pressure by $7$ mm Hg, and after epinephrine LBNP lowered central venous pressure by $5$ mm Hg. As a result, the absolute level of central venous pressure achieved with LBNP ($-4$ mm Hg) and thus, this particular hemodynamic stimulus to neurogenic vasoconstriction was identical on both study days—both before and after epinephrine infusion (Table 1). This was the key consideration in interpreting the results of these experiments—not whether the proximate stimulus to reflex forearm vasoconstriction with LBNP is the change in central venous pressure that it elicits or the absolute level of central venous pressure achieved. If it were the former, observing an attenuated forearm vasoconstrictor response to LBNP after epinephrine on the placebo day could be anticipated, and if it were the latter, similar responses on the study days should be detected. However, the forearm vascular response to LBNP was augmented after LBNP on the placebo day only, an effect that cannot be attributed to differences in baseline central venous pressure (caused by either the prior infusion of epinephrine or the protracted supine state) or to the effects of LBNP on this variable. The augmented vasoconstrictor response seen after epinephrine may represent an aggregate of the central neural and the peripheral adrenergic effects of epinephrine. As we did not examine the effects of locally administered epinephrine, we cannot assess this potential interaction in these particular experiments.

A final possibility, raised by the observation that plasma epinephrine concentrations during LBNP had returned to preinfusion values on the placebo day but not on the desipramine day, is that the augmented vasoconstrictor and chronotropic responses to LBNP were due to a direct action of circulating epinephrine on prejunctional $\beta$-adrenergic receptors in the forearm, or prejunctional and postjunctional $\alpha$-adrenergic receptors in the sinoatrial node, rather than because of its prior uptake and subsequent discharge from sympathetic nerves during LBNP. We consider this to be unlikely, as plasma epinephrine concentrations during LBNP, but after its infusion, were similar on the placebo ($117 \pm 20$ pg/ml) and desipramine days ($128 \pm 52$ pg/ml, $p=0.80$), yet the reflex responses to LBNP were greater on the placebo day.

The reflex chronotropic response to LBNP was also enhanced after prior infusion of epinephrine. Brown and his colleagues reported that tachycardia persisted after epinephrine, infused at $100$ ng/kg/min, was stopped, even though its plasma concentration returned to basal levels within minutes. This sustained tachycardia was not observed in a small number of subjects pretreated with desipramine or when isoproterenol was substituted for epinephrine in these experiments providing further support for the “epinephrine hypothesis.” In our studies, prior infusion of epinephrine after placebo had significant effects on heart rate ($F=13.31$, $p=0.0085$), but overall such effects were modest, likely reflecting the lower infusion rate in our study (about $20$ ng/kg/min). Other authors using similar epinephrine infusion rates to ours, also reported a return of heart rate to initial values rather than a persisting resting tachycardia after these infusions were stopped. The absence of persistent resting tachycardia and forearm vasoconstriction in our own work and in those previous studies using these lower doses that did demonstrate sustained aftereffects of epinephrine suggest that the dose administered in these experiments was insufficient to maintain the synaptic concentrations of epinephrine at levels necessary to facilitate norepinephrine release at rest but caused sufficient loading of the sympathetic neuron to achieve such concentrations during LBNP, the reflex stimulus to norepinephrine release, and presumably, epinephrine clearance.

Several factors could contribute to the contrasting effects of epinephrine and desipramine on heart rate and vascular responses to LBNP. As well as blocking uptake-1, desipramine also has antimuscarinic properties. Because the heart rate response to LBNP represents the net effect of sympathetic activation and vagal withdrawal, these dual effects of desipramine on vagal tone and neuronal reuptake of norepinephrine make interpretation of heart rate responses to LBNP on that day more complex. Resting heart rates were higher after desipramine than after placebo. The increased heart rate seen at rest is not only a function of the anticholinergic action of desipramine and augmented postjunctional effects of neurally released norepinephrine, but also the interaction between these two neural pathways, termed “accentuated antagonism.” The augmented heart rate responses to LBNP on the desipramine day might in part be due to the reduction of mean arterial pressure elicited by this stimulus on that day only, and in part, due to such accentuated antagonism, as the effect of increased sympathetic discharge on heart rate would be augmented if vagal tone during LBNP were, indeed, less on the desipramine day than after placebo.

The proportion of circulating norepinephrine removed by uptake-1 in the human forearm is about $15\%$. This ratio is similar to that seen in vivo in most other organs. A notable exception is the human heart, which clears about $70\%$ of the norepinephrine it receives by uptake-1. This fivefold difference indicates that the heart is unique in its dependence on neuronal reuptake for in vivo removal of circulating norepinephrine. If the sinus node shares these uptake-1 characteristics with the myocardium, it might be anticipated that after desipramine the postjunctional chronotropic response to
neurally released norepinephrine would be greater than the forearm vascular response. Although desipramine (125 mg) blocks uptake-1 in the forearm,17,18 less complete blockade of epinephrine uptake in the sinus node could also account for the tendency for the chronotropic response to LBNP to be greater after the combination of epinephrine and desipramine.

Long-term infusion of epinephrine in low doses that do not increase its plasma concentration can induce hypertension in rats.6–8 Two clinical studies have reported sustained elevations of blood pressure after intravenous infusion of epinephrine.13,23 Blankenstein et al23 noted that the pressor aftereffects of epinephrine infusion were only evident during periods of increased sympathetic activity, such as ambulation, rapid eye movement sleep, and attendance at hospital. Our data indicate 1) that prior infusion of epinephrine can have a sustained, albeit modest, pressor effect and 2) that physiological increases in plasma epinephrine can have sustained effects on both heart rate and forearm vasoconstrictor responses to reflex stimuli to norepinephrine release. By facilitating the release of norepinephrine during periods of increased central sympathetic outflow, these observations suggest a potential mechanism by which endogenous epinephrine might contribute to the pathogenesis of essential hypertension.

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References


KEY WORDS • baroreceptor reflex • essential hypertension • norepinephrine • vascular resistance
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