The Effects of Epinephrine on Norepinephrine Release in Essential Hypertension

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SUMMARY The effects of endogenous epinephrine (E), released by glucagon injection, and exogenously infused E on plasma norepinephrine (NE) and cardiovascular responses before and after C-blockade were studied in patients with essential hypertension and in age-matched normotensive controls. The resting plasma NE and E levels were significantly higher in the borderline hypertensive subjects (NE: 251 ± 21 pg/ml [SEM], p < 0.005; E: 57 ± 5, p < 0.05, n = 18) than in controls (NE: 129 ± 12; E: 39 ± 5, n = 18). An intravenous injection of glucagon (1.0 mg) induced a transient rise of both plasma catecholamine levels and blood pressure in every subject studied. Plasma E levels rose transiently and returned to the basal levels by 20 minutes after the injection, whereas plasma NE levels showed a more prolonged rise over 20 minutes. C-blockade with propranolol did not affect the plasma E response to glucagon, but inhibited the prolonged rise of plasma NE levels. An intravenous infusion of exogenous E (1.25-1.50 µg/min) for 30 minutes caused an apparent rise of both plasma NE levels and blood pressure, which lasted more than 60 minutes after stopping the E infusion. Propranolol did not affect the time course of plasma E but again inhibited the prolonged rise of both plasma NE levels and blood pressure. No significant differences could be observed in the cardiovascular or plasma NE responses to glucagon or to E infusion between normal and hypertensive subjects. These findings lend support to the view that plasma E can act physiologically as a sustained stimulator of presynaptic C-adrenergic receptors, which leads to an enhanced NE release from peripheral sympathetic nerve terminals and a rise of blood pressure in humans. (Hypertension 7: 187-195, 1985)

KEY WORDS • sympathoadrenal activity • glucagon • plasma catecholamines • presynaptic C-adrenergic receptor • propranolol

It has been well established that norepinephrine (NE) release from sympathetic nerve endings is regulated by feedback mechanisms operating through presynaptic α- and C-adrenergic receptors.1,2 Activation of the presynaptic α-adrenergic receptors by NE triggers a negative feedback loop that inhibits the further release of NE into the synaptic cleft. Activation of the presynaptic C-adrenergic receptors has the opposite effect. These receptors facilitate the release of the sympathetic transmitter during nerve stimulation. According to a recent hypothesis,4 circulating epinephrine (E) is taken up into the sympathetic transmitter stores and released as a cotransmitter to activate the presynaptic C-adrenergic receptors. These mechanisms may be important not only in the physiological control of sympathetic nerve activity but also in the pathogenesis of hypertension. In fact, the development of sustained hypertension has been induced in rats by prolonged intravenous infusion of E at physiological concentrations.5

To test the hypothesis that endogenous E plays a role in the physiological regulation of NE release in humans, this study examined the effects of glucagon-induced increases in endogenous E and the effects of exogenously infused E on plasma catecholamine (CA) levels and cardiovascular responses before and after C-blockade with propranolol. The results appear to lend support to the presynaptic C-adrenergic receptor hypothesis.
Motensive controls were studied in this procedure. In-

Epinephrine Procedure

asked to refrain from smoking. All subjects were stud-

of 20 mg, 120 minutes before the glucagon injection. 

and 4 borderline hypertensive subjects) following pre-

lowed to take a light breakfast without coffee and were 

ied while they were supine.

Glucagon Procedure

An indwelling catheter was placed in the antecubital vein through which isotonic saline solution was slowly infused at a rate of 1.0 ml/minute during the study. This catheter also was used for blood sampling and drug injection. Blood pressure (BP) and pulse rate (PR) were measured serially by an automated sphygmomanometer (BP 203X, Nipponcolin Co., Komaki, Japan) every 5 minutes. After a 60-minute observation period, blood (10 ml) was drawn for the measurement of plasma CA levels and 1.0 mg of glucagon (Novo Industri A/S, Copenhagen, Denmark) was injected intravenously. The BP and PR were then measured at 1-minute intervals, and blood specimens for plasma CA levels were obtained at 1, 2, 3, 5, and 20 minutes postinjection. The same procedure was repeated 1 week later in eight subjects (4 normotensive subjects and 4 borderline hypertensive subjects) following pre-

medication with propranolol given as a single oral dose of 20 mg, 120 minutes before the glucagon injection. Five motensive controls received isotonic saline instead of glucagon.

Epinephrine Procedure

Six borderline hypertensive patients and eight nor-

travenous catheters for E infusion and blood sampling were placed in the antecubital veins of the right and left arms respectively. After 60 minutes a continuous infu-

sion of $\alpha$-epinephrine was started and maintained for 30 minutes at a rate of 1.25 to 1.50 $\mu$g/minute. The BP and PR were measured at 3- to 5-minute intervals be-

ficials, and, after the infusion. Blood specimens (10 ml) for the plasma CA assay were obtained before the infusion, during the last minute of the infusion, and 5, 15, 30, and 60 minutes after stopping the infusion. A week later the same procedure was repeated follow-

ing propranolol pretreatment. To maintain a similar interval of 120 minutes from oral dosage of proprano-

ol to the time of the glucagon injection or to the end of 

E infusion, the E infusion was started 90 minutes after 

propranolol administration and continued for 30 min-

utes thereafter at a rate of 1.25 to 1.50 $\mu$g/minute. 

The effect of propranolol also was compared with that of placebo with the use of a randomized dosage schedule in eight normotensive subjects. Four of the eight subjects received propranolol (20 mg) first and placebo second, while the remaining four subjects received placebo first and propranolol second. The dosage 
schedule in each subject was randomly determined. The procedures for E infusion were similar to 
those described in the preceding paragraph, and a first 
and second study in each subject were performed at intervals of 1 week.

Chemical and Statistical Analysis

Immediately after blood sampling, blood specimens (10 ml) for CA assay were transferred into ice-chilled test tubes and plasma was separated by centrifugation at 3,000 g for 15 minutes at 4°C. Each plasma speci-

men (4.0 ml) was preserved with one-tenth volume of 1.0% sodium metabisulfate at —20°C until assayed. The assays of NE and E in 4.0 ml of plasma specimens were separately determined with a sensitive fluorometric method reported elsewhere. Every assay was car-

ried out within 14 days of blood sampling. No detect-
able decay in plasma CA levels was observed over this time. This assay method, which used a fluorescence spectrophotometer (model MPF-4, Hitachi Co., To-

kyo, Japan) installed with a high-sensitivity cell as-

sembly (Hitachi, product no. 018-0050), permitted an 

accurate measurement of levels as low as 25 to 50 pg of 

CA per cuvette, with a coefficient of interassay and 

intraassay variation of 5%. When the duplicate plasma 
specimens were measured simultaneously by fluoromet-

try and a radioenzymatic method, the corresponding 

values of NE and E were quite comparable and showed 

highly significant correlations (the fluorometry $[PNE, \ \ PE]$ versus the radioenzymatic assay $[PNE', PE']$: 

$PNE = 1.16 PNE' + 11.1, r = 0.914, p < 0.001; \ \ PE = 0.93 PE' + 10.7, r = 0.837, p < 0.001, \ \ n = 75$).

Statistical analyses were performed with Student's 
two-tailed paired $t$ test and analysis of variance for 

unpaired data. Values in this paper are expressed as 

means ± SEM. 

Methods

Subjects in this study consisted of 18 patients with 

borderline hypertension (12 men and 6 women), aged 

14 to 50 years with a mean of 32 ± 3 years (SEM), and 

18 patients with sustained essential hypertension (7 

men and 11 women), aged 19 to 57 years with a mean 

of 42 ± 3 years. Informed consent was obtained from 

each subject. Complete diagnostic evaluations were 

performed to exclude secondary forms of hyperten-

sion. All subjects were on an ad libitum diet, and any 

medications were discontinued at least 4 weeks before 

the studies began. The borderline hypertensive pa-

patients demonstrated intermittent hypertension of 140/ 

90 mm Hg or greater with intervening periods of nor-

mal blood pressure over an observation period of sev-

eral months. The sustained hypertensive patients dem-

onstrated blood pressures of 160/95 mm Hg or greater. 

Eighteen age-matched normotensive subjects (16 men 

and 2 women), aged 23 to 50 years with a mean of 33.9 

± 2 years, were also studied as controls. None of these 

subjects had a past history of hypertension. Their casu-

al blood pressures were 52 to 85 mm Hg (mean, 66 ± 2).

The experiment was started at 0900 hours to mini-

mize the effect of diurnal variation on plasma CA 

levels and cardiovascular responses. Subjects were al-

lowed to take a light breakfast without coffee and were 

asked to refrain from smoking. All subjects were stud-

ied while they were supine.

\[ PE = 0.93 PE' + 10.7, r = 0.837, p < 0.001, \ \ n = 75 \]

\[ PNE = 1.16 PNE' + 11.1, r = 0.914, p < 0.001 \]

\[ PE' \]
Results

Baseline Levels of Plasma Catecholamines

The baseline levels of plasma NE and E were 129 ± 12 and 39 ± 5 pg/ml (SEM) in 18 normotensive controls, 251 ± 21 and 57 ± 5 pg/ml in patients with borderline hypertension, and 176 ± 18 and 40 ± 6 pg/ml in patients with sustained hypertension. The mean plasma NE value was significantly higher in the borderline hypertensive patients (p < 0.005) and was slightly but not significantly higher in the sustained hypertensive patients when compared with the normotensive controls. The mean plasma E value was also significantly higher in the borderline hypertensive patients than in the normal subjects (p < 0.05). Although the mean value of plasma E in the sustained hypertensive patients was similar to that of normal subjects, raised plasma E levels, which exceeded the sum of the mean plus 2 standard deviations of the mean for normal subjects, were found in 16.7% of the sustained hypertensive patients.

Blood Pressure, Pulse Rate, and Catecholamine Levels

Effects of Glucagon

Figure 1 illustrates the effects of glucagon and isotonic saline on mean blood pressure (MBP), PR, and plasma CA levels in five normal subjects. Bolus intravenous injection of glucagon induced an immediate rise of MBP, PR, and plasma CA levels in every subject studied, whereas these parameters remained unaltered after saline injection. An apparent difference was observed in the time courses between the plasma NE and E response to glucagon. Plasma E reached a peak concentration 2 to 3 minutes after glucagon injection and thereafter declined rapidly to the baseline; plasma NE concentrations were maximal 2 to 5 minutes after glucagon infusion and declined more slowly. A significant elevation of plasma NE levels (p < 0.05) lasted for 20 minutes or more after intravenous glucagon administration.

The response of BP, PR, and plasma CA glucagon administration in 10 normal and 36 hypertensive subjects is summarized in Table 1. When the changes in these variables are expressed in terms of percentage of the baseline, MBP, PR, and plasma NE levels showed a modest but significant rise (p < 0.05) in the 20 minutes after glucagon injection in both normotensive and hypertensive subjects. The changes in plasma E levels were most prominent but were not sustained. There was no noticeable time difference in the response of MBP, PR, and plasma CA before and after /3-blockade, statistical analyses were performed on the combined data from two groups. The early MBP response to glucagon tended to be greater after /3-blockade, but was short-lived. The PR changes also were diminished after /3-blockade. The baseline levels of plasma NE and E were similar before and after /3-blockade. The peak values (percentage of baseline) of both plasma NE and E tended to correlate inversely with their baseline levels in normotensive as well as hypertensive subjects, although the slopes of their linear regressions differed among the various groups (Table 3).

Effects of /3-Blockade on Glucagon-Induced Changes

Figure 2 illustrates the effect of /3-blockade with propranolol on glucagon-induced changes of MBP, PR, and plasma CA levels in four normotensive and four hypertensive patients. As these variables in both groups showed similar responses to glucagon before and after /3-blockade, statistical analyses were performed on the combined data from two groups. The early MBP response to glucagon tended to be greater after /3-blockade, but was short-lived. The PR changes also were diminished after /3-blockade. The baseline levels of plasma NE and E were similar before and after /3-blockade.
TABLE 1. Response of Blood Pressure, Pulse Rate, and Plasma Catecholamines to Glucagon Administration in Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline levels (0 min)</th>
<th>Responses to glucagon (% of baseline levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Min</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>83 ± 2.8</td>
<td>110 ± 1.4</td>
</tr>
<tr>
<td>B</td>
<td>94 ± 2.7†</td>
<td>106 ± 1.6</td>
</tr>
<tr>
<td>H</td>
<td>105 ± 2.7†</td>
<td>105 ± 1.5†</td>
</tr>
</tbody>
</table>

Pulse rate (beats/min)

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline levels (0 min)</th>
<th>Responses to glucagon (% of baseline levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Min</td>
</tr>
<tr>
<td>N</td>
<td>63 ± 2.7</td>
<td>118 ± 3.1</td>
</tr>
<tr>
<td>B</td>
<td>69 ± 2.3</td>
<td>114 ± 1.7</td>
</tr>
<tr>
<td>H</td>
<td>67 ± 1.4</td>
<td>108 ± 1.5†</td>
</tr>
</tbody>
</table>

Plasma norepinephrine levels (pg/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline levels (0 min)</th>
<th>Responses to glucagon (% of baseline levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Min</td>
</tr>
<tr>
<td>N</td>
<td>127 ± 17</td>
<td>105 ± 4‡</td>
</tr>
<tr>
<td>B</td>
<td>251 ± 21†</td>
<td>106 ± 3‡</td>
</tr>
<tr>
<td>H</td>
<td>176 ± 17</td>
<td>104 ± 4‡</td>
</tr>
</tbody>
</table>

Plasma epinephrine levels (pg/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline levels (0 min)</th>
<th>Responses to glucagon (% of baseline levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Min</td>
</tr>
<tr>
<td>N</td>
<td>38 ± 6</td>
<td>146 ± 22‡</td>
</tr>
<tr>
<td>B</td>
<td>57 ± 5*</td>
<td>134 ± 9</td>
</tr>
<tr>
<td>H</td>
<td>40 ± 6</td>
<td>126 ± 10</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01: statistical significance between the values of normotensive and hypertensive subjects. Values are means ± SEM.

All values (percentage of baseline) except for those with a † are significantly different (p < 0.05) from their baselines.

B = borderline subjects (n = 18); H = hypertensive subjects (n = 18); N = normotensive subjects (n = 10).

TABLE 2. Maximal Responses of Blood Pressure, Pulse Rate, and Plasma Catecholamines to Glucagon Injection in Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive subjects (n = 10)</th>
<th>Borderline subjects (n = 18)</th>
<th>Hypertensive subjects (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mm Hg)</td>
<td>83 ± 3.0</td>
<td>94 ± 2.8†</td>
<td>105 ± 2.8‡</td>
</tr>
<tr>
<td>Peak (mm Hg)</td>
<td>93 ± 3.4</td>
<td>105 ± 3.4*</td>
<td>114 ± 3.3‡</td>
</tr>
<tr>
<td>Percentage of baseline</td>
<td>113 ± 1.1</td>
<td>111 ± 1.1</td>
<td>108 ± 1.0‡</td>
</tr>
<tr>
<td>Pulse rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (beats/min)</td>
<td>63 ± 2.9</td>
<td>69 ± 2.4</td>
<td>67 ± 1.5</td>
</tr>
<tr>
<td>Peak (beats/min)</td>
<td>79 ± 1.7</td>
<td>82 ± 3.0</td>
<td>76 ± 1.5</td>
</tr>
<tr>
<td>Percentage of baseline</td>
<td>126 ± 3.9</td>
<td>119 ± 2.1</td>
<td>112 ± 1.3‡</td>
</tr>
<tr>
<td>Plasma norepinephrine levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (pg/ml)</td>
<td>127 ± 18</td>
<td>251 ± 21†</td>
<td>176 ± 18</td>
</tr>
<tr>
<td>Peak (pg/ml)</td>
<td>181 ± 22</td>
<td>302 ± 23†</td>
<td>232 ± 20</td>
</tr>
<tr>
<td>Percentage of baseline</td>
<td>148 ± 10</td>
<td>123 ± 4†</td>
<td>143 ± 11</td>
</tr>
<tr>
<td>Plasma epinephrine levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (pg/ml)</td>
<td>38 ± 7</td>
<td>57 ± 5*</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>Peak (pg/ml)</td>
<td>128 ± 15</td>
<td>119 ± 10</td>
<td>73 ± 8‡</td>
</tr>
<tr>
<td>Percentage of baseline</td>
<td>404 ± 59</td>
<td>240 ± 31*</td>
<td>216 ± 21‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*p < 0.05, †p < 0.01, ‡p < 0.005: the statistical significance between the values of normotensive and hypertensive subjects.
TABLE 3. Correlations Between Basal Plasma Catecholamine Levels and Their Maximal Responses to Glucagon

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal PNE levels*</th>
<th>Basal PE levels†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficients of correlation</td>
<td>Linear regression [Y = aX + b]</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>Slope (a)</td>
</tr>
<tr>
<td>Normotensive subjects</td>
<td>0.471</td>
<td>-86.0</td>
</tr>
<tr>
<td>Borderline subjects</td>
<td>0.479</td>
<td>-52.2</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>0.693</td>
<td>-140.9</td>
</tr>
<tr>
<td>Total subjects</td>
<td>0.639</td>
<td>-103.3</td>
</tr>
<tr>
<td>Normotensive subjects</td>
<td>-0.797</td>
<td>-530</td>
</tr>
<tr>
<td>Borderline subjects</td>
<td>-0.597</td>
<td>-431</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>-0.671</td>
<td>-203</td>
</tr>
<tr>
<td>Total subjects</td>
<td>-0.572</td>
<td>-318</td>
</tr>
</tbody>
</table>

*Basal plasma norepinephrine (log PNE; X axis) versus peak values of PNE (percentage of basal PNE; Y axis).
†Basal plasma epinephrine levels (log PE; X axis) versus peak values of PE (percentage of basal PE; Y axis).

PNE = plasma norepinephrine; PE = plasma epinephrine.

Figure 2. Response of MBP, PR, and plasma CA to a bolus intravenous injection of glucagon (1.0 mg) before (closed circles) and after β-blockade with propranolol (open circles) in normal and hypertensive subjects. Each circle and vertical line indicates means and SEM for all subjects respectively. Asterisks indicate the statistical significance when compared with the baseline values.

After β-blockade (204 ± 20 versus 200 ± 21 pg/ml, 40 ± 9 versus 38 ± 8 pg/ml respectively), β-Blockade did not appreciably affect the plasma E response to glucagon, but resulted in a remarkable change in the time course of the plasma NE response. The prolonged rise of plasma NE levels induced by glucagon administration was completely inhibited by β-blockade.

Responses to Exogenous Epinephrine Infusion and the Effects of β-Blockade

The time course of cardiovascular responses to exogenous E infusion and the effects of β-blockade on these responses are illustrated in Figure 3 for eight normotensive subjects and in Figure 4 for six hypertensive patients. In normal controls receiving placebo as well as in the hypertensive subjects before β-blockade, E infusion induced a slight but significant rise (p < 0.01) of both systolic BP and PR, while diastolic BP tended to fall. After stopping the E infusion, both systolic and diastolic BP showed a gradual and sustained rise for 60 minutes or more, while PR decreased gradually to the baseline levels.

When the changes of BP were expressed as a percentage of the baseline, systolic BP and diastolic BP levels were 106 ± 1.8% and 111 ± 3.5% of the normal control values 60 minutes after stopping the E infusion. Respective values in the hypertensive patients were 113 ± 4.0% and 114 ± 2.2%. These values were significantly greater than the baseline levels (p < 0.01 for each value), but no significant difference was found between the values of normal and hypertensive subjects.

After β-blockade, both systolic BP and diastolic BP in normal and hypertensive subjects showed a significant rise (p < 0.05) during E infusion and returned promptly to baselines after stopping the E infusion. The PR tended to fall during E infusion and remained...
Figure 3. Cardiovascular responses to the intravenous infusion of epinephrine (1.25–1.50 μg/min) in normal subjects. Open or closed circles indicate the responses when examined after premedication with propranolol or its placebo respectively. Each circle and vertical line indicates means and SEM respectively. Asterisks indicate the statistical significance when compared with the baseline values.

Figure 4. Cardiovascular responses to the intravenous infusion of epinephrine (1.25–1.50 μg/ml) in hypertensive subjects before (closed circles) and after β-blockade with propranolol (open circles). Each circle and vertical line indicates means and SEM respectively. Asterisks indicate the statistical significance when compared with the baseline values.

at the baseline levels thereafter, which presumably reflects a baroreflex-mediated suppression of PR rather than an exogenous E-induced stimulation of cardiac β-adrenergic receptors, which had been blocked by premedication with propranolol. Thus, β-blockade modified the cardiovascular responses to E infusion in both normotensive and hypertensive subjects, which eliminated the prolonged rise of BP during the postinfusion period.

The time course of plasma CA concentrations during and after E infusion are summarized in Table 4. During E infusion, plasma CA concentrations increased to similar levels in both normotensive and hypertensive subjects, whether they were tested while they were receiving placebo or premedication. After stopping the infusion, plasma E declined promptly to the baseline levels within 15 to 30 minutes. Interestingly, a concomitant rise of plasma NE levels was observed during and after E infusion. A marked rise of plasma NE levels lasted for 60 minutes or more after stopping the E infusion. When plasma NE levels were expressed as a percentage of the baseline, these values at 60 minutes after stopping the E infusion were similar for both normotensive and hypertensive subjects (126 ± 7% and 129 ± 8% respectively).

Propranolol-induced β-blockade did not affect the time course of the change in plasma E levels either during or after E infusion in both normotensive and hypertensive subjects. By contrast, the increase in plasma NE levels during and after E infusion was attenuated by β-blockade in both normotensive and hypertensive subjects.

Discussion

A number of reports have suggested that neurogenic factors may play a role in the pathogenesis of essential hypertension. The levels of plasma CA, a neurotransmitter released from the peripheral sympathoadrenal system into the circulation, have been studied as a useful marker to measure overall activity of the system, although its importance remains widely controversial.

In the present study, the basal levels of plasma NE and E tended to be higher in some patients with essential hypertension than in age-matched normotensive controls. The mean concentration of plasma E was significantly greater (p < 0.05) in the borderline hypertensive subjects than in age-matched normotensive controls. These findings are in agreement with previous reports. An attenuated response of plasma E to glucagon injection was observed in both the sustained and borderline hypertensive patients (Table 2), and an inverse correlation was also found between the basal levels of plasma CA and its responsiveness to glucagon administration (Table 3). A reduced re-
TABLE 4. Response of Plasma Catecholamines During and After Intravenous Infusion of Epinephrine in Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline levels</th>
<th>During E infusion</th>
<th>Postinfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10 Min 0 Min</td>
<td>30 Min 5 Min 15 Min 30 Min 60 Min</td>
<td></td>
</tr>
<tr>
<td>Plasma epinephrine levels (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive subjects (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (placebo)</td>
<td>29 ± 2 41 ± 7</td>
<td>327 ± 34† 73 ± 8† 45 ± 4* 42 ± 6</td>
<td>39 ± 5</td>
</tr>
<tr>
<td>Propranolol</td>
<td>36 ± 3 37 ± 5</td>
<td>392 ± 42† 102 ± 15† 54 ± 4† 39 ± 5</td>
<td>36 ± 3</td>
</tr>
<tr>
<td>Hypertensive subjects (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>— 44 ± 4</td>
<td>312 ± 34† 71 ± 6† — 55 ± 6*</td>
<td>46 ± 7</td>
</tr>
<tr>
<td>Propranolol</td>
<td>— 45 ± 7</td>
<td>290 ± 35† 70 ± 11† — 50 ± 11</td>
<td>48 ± 10</td>
</tr>
<tr>
<td>Plasma norepinephrine levels (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive subjects (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (placebo)</td>
<td>130 ± 17 132 ± 17</td>
<td>183 ± 34† 195 ± 34* 165 ± 27* 158 ± 23* 169 ± 29* (126 ± 7%)†</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>149 ± 18 152 ± 14</td>
<td>123 ± 16 133 ± 14‡ 149 ± 16 131 ± 13 131 ± 14 (91 ± 8%)§</td>
<td></td>
</tr>
<tr>
<td>Hypertensive subjects (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>— 129 ± 11</td>
<td>177 ± 20* 187 ± 19* — 162 ± 13* 156 ± 9* (129 ± 8%)§</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>— 144 ± 13</td>
<td>139 ± 22‡ 125 ± 14§ — 127 ± 15§ 129 ± 23§ (93 ± 6%)§</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01: versus baselines.
‡p < 0.05, §p < 0.01 versus control.
Values are means ± SEM.
E = epinephrine.

Response of plasma E to glucagon may be due either to diminished capacity of the adrenal to release E or to blunted sensitivity of glucagon-mediated reactions in the adrenal. The attenuated response of plasma E to glucagon was evident in the sustained hypertensive patients, who showed normal response of plasma NE but not in plasma E. Such a nonparallelism suggests that a blunted sensitivity of glucagon-mediated reactions in the adrenal could not account for the diminished response of plasma E in the hypertensive patients. An enhanced turnover of adrenal CA by raised sympathoadrenal activity could result in a reduction in the releasable pool of E. An inverse correlation between basal levels of plasma CA and its responsiveness to glucagon might support the latter possibility. An increased uptake of arterial E by the peripheral vascular beds could be an alternative possibility, as proposed previously in a study of hypertensive subjects. This process, however, cannot easily explain the inverse correlation between basal levels of plasma E and its responsiveness to glucagon. It is also unlikely that glucagon administration accelerates an inactivation of plasma E only in the hypertensive subjects. It is thus conceivable that a depletion of the releasable pool of adrenal E might be the predominant factor accounting for the attenuated response of plasma E to glucagon in the hypertensive subjects.

It is noteworthy that the plasma NE and E responses to glucagon showed different time courses. Plasma E rose immediately after glucagon injection and then returned promptly to basal levels. A concomitant rise of plasma NE levels was also observed after glucagon injection, but it tended to fall more slowly to the baseline. Its apparent rise lasted for at least 20 minutes after the glucagon injection, which suggests extramedullary NE release rather than a prolonged adrenomedullary response or delayed clearance of plasma NE. In fact, a parallel time course of NE and E response has been shown when glucagon-stimulated CA secretion was examined in the isolated adrenal. Furthermore, the premedication with propranolol, a nonselective β-blocker, failed to affect the response of plasma E after glucagon but completely inhibited the prolonged rise of plasma NE levels. These findings could be compatible with the view that the prolonged rise of plasma NE levels after glucagon administration is caused by a β-adrenergic receptor mediated NE release from sympathetic nerve terminals. The BP responses induced by glucagon were almost parallel with the plasma NE changes, while changes in PR could be due to the combined chronotropic actions of plasma CA as well as of glucagon itself.

An intravenous E infusion caused not only the anticipated responses of the cardiovascular system but also an unexpected rise in the plasma NE concentration. Raised plasma NE levels lasted for a prolonged period after stopping the E infusion and accompanied a further elevation of BP. Baroreflex stimulation of peripheral sympathoadrenal activity triggered by the decrease in diastolic BP during E infusion might cause a rise of plasma NE. Changes of BP during E infusion, however, were more evident in pulse pressures (+10
± 2 mm Hg) than in MBP (−1.0 ± 0.8 mm Hg). These changes might cause suppression rather than stimulation of baroreflex-mediated sympathetic activity. With β-blockade, changes of BP during E infusion tended to be greater (Figures 3 and 4), but no significant fluctuation of plasma NE could be detected throughout these periods (Table 4), which indicates that the baroreflex-mediated changes of peripheral sympathetic nerve activity might not be so influential as to affect the plasma NE concentration.

β-Blockade completely inhibited the rise in plasma NE levels during and after E infusion. A prolonged rise of BP after stopping the E infusion also disappeared during β-blockade. These results are consistent with some previous studies in experimental animals and in humans, but inconsistent with others, which did not detect any marked change in plasma NE during E infusion in humans. These studies evaluated neither the effects of β-blockade, however, which might unmask an effect of E infusion on plasma NE levels, nor the time courses of plasma NE levels and BP after stopping the E infusion.

It is also possible that changes in the metabolic clearance of plasma NE may be an explanation for the present observations. Raised plasma CA levels have been proposed to accelerate their own clearance through a β-adrenergic mechanism, while β-blockade may reduce the clearance of plasma CA. An elevation of plasma NE levels induced by transiently raised plasma E between normotensive and hypertensive subjects. Either raised plasma CA levels or enhanced sympathoadrenal activity has been indicated in some of the borderline or sustained hypertensive subjects, but these findings were not observed in the majority of patients studied. Therefore, the pathogenic importance of these pressor mechanisms remains unclear.

Conclusion

The present study suggests that both endogenous (glucagon-stimulated) and exogenous (infused) E at the physiological plasma concentration can act as a sustained stimulator of the presynaptic β-adrenergic receptors to enhance NE release from peripheral sympathetic nerve terminals in humans. The present results thus support the hypothesis that increased plasma E is incorporated into the transmitter stores in sympathetic nerve terminals and subsequently released as a cotransmitter to activate the presynaptic β-adrenergic receptors, which leads to an enhancement of NE release and a rise in BP.

An apparent difference could not be proved in the efficiency of both cardiovascular and plasma NE responses to transiently raised plasma E between normotensive and hypertensive subjects. Either raised plasma CA levels or enhanced sympathoadrenal activity has been indicated in some of the borderline or sustained hypertensive subjects, but these findings were not observed in the majority of patients studied. Therefore, the pathogenic importance of these pressor mechanisms remains unclear.

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The effects of epinephrine on norepinephrine release in essential hypertension.
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