The Role of Epinephrine in Essential Hypertension

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The effects of epinephrine (E) on plasma norepinephrine (NE) concentrations and cardiovascular responses before and after β -blockade were studied in 36 patients with essential hypertension and 10 age-matched normal controls. The resting plasma NE and E were significantly higher in the borderline hypertensives (251 ± 21 (SE) pg/ml, $p < 0.005$; 57 ± 5 , $p < 0.05$) than in normal controls (127 ± 18 ; 38 ± 7). An immediate rise in plasma E and NE was observed after one bolus intravenous administration of glucagon (1 mg). Then, plasma E fell rapidly to the baseline, whereas plasma NE declined much slowly. Propranolol did not affect the plasma E response to glucagon, but eliminated a prolonged rise of plasma NE. Exogenous E infusion (1.25 – 1.50 $\mu\text{g}/\text{min}$) for 30 min caused a definite rise in both plasma NE and blood pressures and lasted more than 30 min after termination of the infusion. Propranolol did not alter the time course of plasma E, but again inhibited a prolonged rise in both plasma NE and blood pressures. These findings support the view that plasma E can act physiologically as a sustained stimulator to the presynaptic β -adrenoceptors, leading to an enhancement of NE release and a rise in blood pressure in man.

RECENT studies have demonstrated that the release of norepinephrine (NE) from sympathetic nerve endings is influenced by feedback mechanisms operating through both presynaptic α - and β -adrenoceptors.^{1,2} Activation of the presynaptic α -adrenoceptors by NE triggers a negative feedback mechanism, through which transmitter released into the synaptic cleft is inhibited. Experiments on isolated tissues have shown that activation of presynaptic β -adrenoceptors possesses an opposite effect; these receptors facilitate the release of transmitter

during nerve stimulation. According to the recent hypothesis,³ plasma epinephrine (E) is taken up into the peripheral transmitter stores and subsequently released as a co-transmitter to activate presynaptic β -adrenoceptors. These mechanisms may be important not only in the physiological control of sympathetic activity, but also in the pathogenesis of hypertension. In fact, sustained hypertension has been successfully induced in rats by prolonged administration of E at the physiological plasma concentrations.⁴

This preliminary report aimed to test the hypothesis that presynaptic β -adrenoceptors may play a role in the physiological regulation of NE release in man. For this purpose, we examined the effects of intravenously infused exogenous E and glucagon-induced endogenous E on plasma

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NE concentrations and cardiovascular responses before and after β -blockade. The present results appear to lend support to the current hypothesis.

SUBJECTS AND METHODS

Subjects in this study consisted of 36 patients with essential hypertension (19 men and 17 women) aged 14–57 years with a mean age of 36.9 ± 2.0 (SEM) and 10 normotensive healthy volunteers (8 men and 2 women) aged 23–50 years with a mean age of 34.5 ± 2.9 . Informed consent was obtained from each subject. All of the patients had complete diagnostic examinations to exclude secondary forms of hypertension. All subjects were on a free diet and any medication was discontinued for at least 4 weeks before the studies. These patients were then subclassified according to whether they had borderline or sustained hypertension. The former (18 cases, mean age of 31.9 ± 2.6) had an intermittent hypertension of 140/90 mmHg or greater with intervening periods of normal blood pressure (BP), and the latter (18 cases, mean age of 41.9 ± 2.5) showed constantly the diastolic blood pressure (DBP) of 95 mmHg or greater.

Every study was started at 9:00 AM to minimize diurnal variations. Subjects were allowed to have a light breakfast without coffee and asked to refrain from smoking since getting up in the morning.

Subjects remained in supine position throughout the study. BP and heart rate (HR) were serially measured with the automatic sphygmomanometer (Nippon Colin BP 203x). After 60-min observation, blood specimen for the measurement of plasma catecholamines (CA) was taken through an indwelling catheter previously placed in an antecubital vein and one mg of glucagon was intravenously injected through the same catheter. BP, HR and plasma CA were serially measured 1, 2, 3, 5 and 20 min after the glucagon injection. A week later, the same procedure was repeated in 4 subjects (2 normal subjects and 2 borderline hypertensives) under the premedication with propranolol which was given in a single oral dose of 20 mg 120 min prior to the study.

In 4 patients with essential hypertension, intravenous catheters for E infusion and blood sampling were inserted into antecubital veins of the right and the left arm, respectively. After 60-min observation, a continuous infusion of L-epinephrine was started and maintained for 30

min at a rate of 1.25–1.5 $\mu\text{g}/\text{min}$. BP and HR were continuously monitored at 3-min intervals before, during and after the termination of E infusion. Blood samples for measurements of plasma CA concentration were obtained before, at the last minute of infusion, and 5 and 30 min after the termination of E infusion. A week later, propranolol was prescribed in a single oral dose of 20 mg and the same procedure was repeated 90 min after the medication.

Plasma NE and E concentrations were determined with a sensitive fluorimetric method.⁵ As soon as blood specimen was taken, blood was transferred into an ice-chilled polyethylene tube and plasma was separated in a refrigerated centrifuge. Plasma specimen was then stored with 1.0% sodium metabisulfite at -20°C until assayed.

Statistical significance was tested with Student's two-tailed paired *t*-test and analysis of variance. Values are expressed as the mean $\pm$ SEM.

RESULTS

The basal levels of plasma NE concentrations in normal subjects, borderline and sustained hypertensives were 127 ± 18 , 251 ± 21 and 176 ± 18 pg/ml, respectively. Plasma NE was significantly higher in the borderline hypertensives ($p < 0.005$) and tended to increase but not significantly ($p < 0.1$) in the sustained hypertensives, when compared with those of normal subjects. On the other hand, the basal levels of plasma E concentrations in normal subjects, borderline and sustained hypertensives were 38 ± 7 , 57 ± 5 and 40 ± 6 pg/ml, respectively. Plasma E was also significantly higher in the borderline hypertensives than in control subjects ($p < 0.05$). Although the mean values of plasma E in the sustained hypertensives were similar to those of normal subjects, 17% of them showed an increased plasma E concentration, which exceeded the sum of the mean value plus 2 standard deviations in normal controls.

An apparent increase in plasma CA was observed immediately after one bolus injection of glucagon in every case studied. However, there were some differences in the time course between plasma E and NE concentrations. Plasma E reached a peak concentration 2 to 3 min after intravenous glucagon and declined rapidly to the baselines thereafter, while plasma NE concentrations were maximal 2 to 5 min

TABLE I THE RESPONSES OF PLASMA CATECHOLAMINES AND HEMODYNAMIC PARAMETERS TO INTRAVENOUS GLUCAGON BEFORE AND AFTER TREATMENT WITH PROPRANOLOL

		% change after intravenous glucagon					
	Baseline	0	1	2	3	5	20 (min)
Norepinephrine							
	pg/ml	%					
before	149 ± 33	100	105 ± 2	122 ± 3 ^{††}	120 ± 13	136 ± 10 [†]	123 ± 6 ^{*†}
after	203 ± 35	100	114 ± 5	117 ± 5 [†]	100 ± 3	91 ± 11	98 ± 6
Epinephrine							
	pg/ml						
before	37 ± 17	100	149 ± 32	341 ± 78 [†]	399 ± 127	211 ± 39	152 ± 41
after	38 ± 12	100	94 ± 17	228 ± 36 [†]	324 ± 72 [†]	177 ± 26	104 ± 10
Mean blood pressure							
	mmHg						
before	78 ± 2	100	113 ± 6	109 ± 7	110 ± 6	106 ± 4	108 ± 4
after	78 ± 3	100	115 ± 2 ^{††}	114 ± 6	118 ± 5 [†]	104 ± 3	97 ± 2
Heart rate							
	beats/min						
before	60 ± 2	100	121 ± 4 [†]	134 ± 6 ^{††}	111 ± 2 [†]	110 ± 4	109 ± 2
after	57 ± 1	100	114 ± 3 [†]	107 ± 6	107 ± 5	108 ± 3	102 ± 3

Results are expressed as mean ± SEM.

*p < 0.05 before vs after propranolol; †p < 0.05 baseline vs after intravenous glucagon;

††p < 0.01 baseline vs after intravenous glucagon

TABLE II THE RESPONSES OF PLASMA CATECHOLAMINES AND HEMODYNAMIC PARAMETERS TO L-EPINEPHRINE INFUSION BEFORE AND AFTER TREATMENT WITH PROPRANOLOL

		After infusion			
	Baseline	0	5	30	60 (min)
Norepinephrine (pg/ml)					
before	114 ± 7	196 ± 44	189 ± 29 ^{*†}	157 ± 20 [*]	
after	139 ± 18	133 ± 31	121 ± 22	119 ± 19	
Epinephrine (pg/ml)					
before	44 ± 5	322 ± 35 ^{††}	69 ± 9 ^{††}	51 ± 7 [†]	
after	37 ± 4	286 ± 40 ^{††}	78 ± 14 ^{††}	50 ± 14	
Systolic blood pressure (mmHg)					
before	124 ± 2	130 ± 2 ^{††}	123 ± 2	140 ± 3 ^{**†}	139 ± 6 ^{*†}
after	125 ± 4	137 ± 8	120 ± 6	127 ± 5	129 ± 5
Diastolic blood pressure (mmHg)					
before	83 ± 3	73 ± 4 ^{***††}	74 ± 4 ^{*†}	93 ± 2 ^{*†}	93 ± 3 ^{***†}
after	84 ± 3	86 ± 3	82 ± 3	83 ± 3	83 ± 2
Heart rate (beats/min)					
before	59 ± 5	70 ± 4 ^{†††}	65 ± 5 ^{*††}	59 ± 5	62 ± 5 [†]
after	58 ± 3	56 ± 3	59 ± 3	58 ± 4	58 ± 5

Results are expressed as mean ± SEM.

*p < 0.05 before vs after propranolol; **p < 0.01 before vs after propranolol; ***p < 0.005 before vs after propranolol; †p < 0.05 baseline vs after epinephrine infusion; ††p < 0.01 baseline vs after epinephrine infusion

after intravenous glucagon and then followed a course of very slow descent. The peak values of the percent increments of plasma NE in normal subjects, borderline and sustained hypertensives

were 148 ± 10, 123 ± 4 and 143 ± 11%, respectively. The value of borderline hypertensives was significantly smaller than that of normal subjects (p < 0.01). On the other hand, those

values of plasma E in normal subjects, borderline and sustained hypertensives were 404 ± 59 , 204 ± 31 and 216 ± 21 , respectively. Plasma E showed also smaller responses to glucagon in both the borderline and sustained hypertensives than in normal subjects ($p < 0.05$ and $p < 0.005$, respectively). The maximal increments (% changes) of plasma NE and E concentrations in all subjects were inversely correlated with their baseline levels, respectively ($r = -0.49$, $p < 0.001$; $r = -0.53$, $p < 0.001$, respectively). Table I shows the effects of β -blockade by propranolol on glucagon-induced changes of both plasma CA and cardiovascular responses. Propranolol did not affect significantly the response of plasma E to intravenous glucagon, whereas this premedication resulted in a remarkable change in the time course of plasma NE response to intravenous glucagon. The delayed and prolonged elevation of plasma NE induced by intravenous glucagon was completely eliminated after the administration of propranolol. The cardiovascular response to intravenous glucagon also tended to diminish after β -blockade.

The changes of both plasma CA concentrations and cardiovascular responses during and after E infusion are summarized in Table II. Plasma E concentrations were increased from 44 ± 5 to 322 ± 35 pg/ml at the end of 30-min infusion of E. Five min after stopping the infusion, plasma E concentrations promptly declined to 69 ± 9 pg/ml. Interestingly, an exogenous E infusion brought about a concomitant rise in plasma NE concentrations in every subject studied. Plasma NE concentrations were increased from 114 ± 7 to 196 ± 44 pg/ml at the end of E infusion. Definite increase in plasma NE lasted more than 30 min after stopping of the E infusion. A premedication with propranolol did not alter the time course of plasma E concentrations during and after exogenous E infusion. On the other hand, a striking difference was observed in the time course of plasma NE concentrations before and after β -blockade. A β -blockade completely inhibited an increase in plasma NE concentration induced by exogenous E infusion. During E infusion, both systolic blood pressures (SBP) and HR increased from 124 ± 2 mmHg and 59 ± 5 /min to 130 ± 2 mmHg and 70 ± 4 /min, respectively, whereas diastolic blood pressure (DBP) decreased from 83 ± 3 to 73 ± 4 mmHg. After the stopping of E infusion, both SBP and DBP showed a gradual and sustained rise for 60 min or longer. A premedication with

propranolol altered clearly their cardiovascular responses to E infusion as observed in plasma NE concentration. On β -blockade, both SBP and DBP tended to rise during the E infusion and returned to the baseline levels promptly after stopping of the E infusion, whereas HR showed only a slight fluctuation during and after E infusion. Thus, a considerable difference was proved in the time course of BP and HR before and after β -blockade.

DISCUSSION

In the present study, the basal levels of plasma NE and E tended to be higher in some patients with essential hypertension. Mean concentrations of plasma E were significantly greater in the borderline hypertensives than those of age-matched normal subjects. These findings are in good accordance with the reports published recently^{6,7}. Furthermore, an attenuation in the response of plasma E to intravenous glucagon was observed in the hypertensive patients. An inverse correlation was also found between the basal levels and the responsiveness of plasma E to intravenous glucagon. An attenuated response of plasma E to glucagon in the hypertensives may be due to either diminished capacity of adrenal medulla to release E or the blunted sensitivity of glucagon receptor-mediated cascade reactions in the adrenal. However, the attenuation in the response of plasma E to glucagon was most evident in the sustained hypertensives, who showed normal response of plasma NE contrary to E. Such a non-parallelism could not be compatible with the view that blunted sensitivity of glucagon receptors accounts for the attenuated response of plasma CA in the hypertensives. An increased turnover of adrenal CA by enhanced sympathoadrenal activity could result in a reduction of releasable pool of E. An inverse correlation between basal levels and the responsiveness of plasma E to glucagon may support the latter possibility.

It must be noteworthy that the responses of plasma NE and E to glucagon showed quite different time courses to each other. Plasma E concentrations rose immediately after intravenous glucagon and returned promptly to basal levels. A concomitant rise in plasma NE concentrations was also observed after intravenous glucagon, but it tended to fall much slowly to the baseline. The rise was still observed 20 min or later after intravenous glucagon, suggesting the extrame-

dullary NE release rather than prolonged adrenomedullary response or delayed clearance of circulating NE. In fact, a parallel time course of NE and E response has been proved when glucagon-stimulated CA secretion was examined in the effluent of the isolated adrenal gland.⁹ Furthermore, the premedication with propranolol failed to affect the time course of plasma E after glucagon, but completely eliminated the prolonged response of plasma NE. This finding may clearly indicate that the prolonged rise of plasma NE observed after glucagon should be caused by the β -adrenoceptor-mediated extraadrenal NE release into the circulation.

An intravenous E infusion caused not only anticipated cardiovascular responses, but also an unexpected rise of plasma NE concentrations. Raised plasma NE concentration lasted for a prolonged period after termination of E infusion and accompanied with further elevation of both SBP and DBP. Baroreflex stimulation of peripheral sympathoadrenal activity triggered by depression of DBP during E infusion may have caused a rise in plasma NE concentrations.¹⁰ Changes of BP during E infusion, however, were more evident in the increase in pulse pressure ($+\Delta 16$ mmHg) than in the decrease in mean BP ($-\Delta 4$ mmHg). These changes may cause a suppression rather than a stimulation of baroreflex-mediated sympathetic activity.¹¹ Moreover, β -adrenergic blockade inhibited completely the rise in plasma NE during and after the termination of E infusion. An elevation of BP after E infusion also disappeared following β -blockade. Thus, β -blockade could prove clearly the influence of E not only on plasma NE concentrations but also on cardiovascular responses. The present results are consistent with some previous studies in experimental animals¹⁻⁴ and man.^{12,13}

From these observations, it is quite conceivable that both endogenous (glucagon-induced) and exogenous (infused) E at physiological plasma concentrations can act as a sustained stimulator to the presynaptic β -adrenoceptors to enhance the NE release in man. The present results are also consistent with the recent hypothesis that an increased plasma E in hypertensive subjects is incorporated into the transmitter stores in sympathetic nerve terminals and

subsequently released as a co-transmitter to activate the presynaptic β -adrenoceptors, leading to an enhancement of NE release and a rise in BP.³

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