

Effect of Prostaglandin E₂ on Reflex Adrenal Catecholamine Secretion

Seung Keun Oh* and Timothy S. Harrison

Department of Surgery, College of Medicine, Seoul National University, Seoul 110, Korea
and Department of Surgery, Pennsylvania State University College of Medicine*

= Abstract = Prostaglandin E₂ was administered peripherally and centrally to experimental dogs in order to demonstrate the effect of prostaglandin E₂ on reflex adrenal secretion of catecholamines following hemorrhage in acutely anephric conditions.

Diminished adrenal catecholamine secretion in anephric dogs was restored by peripheral infusion of prostaglandin E₂ dose-dependently. Almost an identical response of adrenal secretion was observed by the peripheral and central infusions of prostaglandin E₂, suggesting its effect is not selectively mediated by the central nervous system in contrast to angiotensin II. The action of prostaglandin E₂ on the adrenal medulla in relation to the renin-angiotensin system appears to be systemic.

Key Words: *Prostaglandin E₂, Catecholamine, Renin-angiotensin system*

INTRODUCTION

Adrenal catecholamine secretion is stimulated by acute hemorrhage and the renin-angiotensin system is involved in this reaction. Elimination of the main source of renin by bilateral nephrectomy diminishes reflex catecholamine secretion from the adrenal medulla after hemorrhage (Harrison *et al.* 1973). This diminished adrenal catecholamine secretion has been shown to be restored by intravenous (IV) infusion of angiotensin II dose-dependently or intraventricular (IVT) infusion of sub-systemic threshold quantities of angiotensin II (Corwin *et al.* 1985), and by IV infusion of supraphysiologic quantities of prostaglandin E₂ (PGE-2) (Badder *et al.* 1978).

The response of adrenal medulla to PGE-2 in relation to the renin-angiotensin system has not been completely understood. This study was undertaken to demonstrate the effect of PGE-2 on the adrenal medulla, the systemic dose-responsiveness of PGE-2's effect in restoring catechola-

mine secretion following hemorrhage in acutely anephric conditions, and whether the PGE-2's effect is centrally or peripherally mediated.

MATERIALS AND METHODS

1. Materials and Grouping

Healthy male mongrel dogs (15 to 18 kg body weight) were prepared and divided into 7 groups for this study. Each group consisted of 5 dogs as follows.

Group A: Normal controls without treatment.

Group B: Anephric controls without IV or IVT infusion of PGE-2.

Group C: Animals with IVT infusion of artificial cerebrospinal fluid (CSF) at 1.0 ml/min.

Group D: Animals with IV infusion of PGE-2 at 1.0 ng/kg/min with concurrent IVT infusion of artificial CSF at 1.0 ml/min.

Group E: Animals with IV PGE-2 at 10.0 ng/kg/min and IVT CSF at 1.0 ml/min.

Group F: Animals with IV PGE-2 at 100.0 ng/kg/min and IVT CSF at 1.0 ml/min.

Group G: Animals with IVT infusion of PGE-2 at 10.0 ng/kg/min.

* Author for correspondence.

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2. Surgical Preparation

Each animal was lightly anesthetized (sodium pentobarbital, 20 mg/kg IV), mechanically ventilated (98%O₂/2%CO₂) through an endotracheal tube, and heparinized (150 units/kg IV bolus, with 75 units/kg IV hourly).

The right femoral artery was cannulated for hemorrhage during the experimental period, and the right femoral vein for IV infusion of PGE-2. The left femoral artery was also cannulated for blood pressure monitoring and blood from it continuously withdrawn throughout the experimental period at 0.3 ml/min for catecholamine measurement.

A shunt was placed between the left adrenal-lumbar vein and femoral vein to divert all adrenal venous blood flow to the femoral vein, ligating the left adrenal vein to the inferior vena cava. Adrenal venous blood was also withdrawn continuously from a side arm of the cannula at 0.3 ml/min.

A needle was inserted into the left lateral cerebral ventricle for infusion of artificial CSF or PGE-2, and the cisterna magna was punctured at the base of the skull for CSF drainage. This ventriculo-cisternal procedure was not performed in normal and anephric control group animals.

The diagram of our experiment was simply illustrated in Fig. 1.

3. Experimental Procedure

Baseline-1 samples for catecholamines were obtained from the femoral artery and adrenal vein after surgical preparation, measuring adrenal venous flow rates simultaneously.

IV or IVT infusions were begun with bilateral

nephrectomy as scheduled, and baseline-2 samples with simultaneous adrenal venous flow rates obtained 15 minutes after infusions.

Animals were acutely hemorrhaged at 25 ml/kg via the cannula placed in the right femoral artery to approximately 50 mmHg mean arterial pressure. Continuous systemic arterial and adrenal venous samples with adrenal venous flow rates were obtained 15, 30 and 60 minutes after hemorrhage.

During the procedure, arterial pH was monitored and IV boluses of sodium bicarbonate were infused when required to maintain arterial pH between 7.38 to 7.42.

4. Catecholamine Analysis and Statistics

Plasma epinephrine(EP), norepinephrine(NE) and dopamine(DM) were measured using the single isotope radioenzymatic assay of Peuler and Johnson(1977). Adrenal medullary secretion rates were calculated by relating the difference between simultaneous adrenal venous and systemic arterial catecholamine concentrations to the average adrenal venous flow rates during sampling periods.

Results obtained were analyzed and compared to determine statistical significance by Student's "t" test.

RESULTS

Mean adrenal secretion rates (μ g/min) of EP, NE and DM were increased in response to hemorrhage from 0.039 ± 0.016 to 0.716 ± 0.393 , from 0.004 ± 0.002 to 0.084 ± 0.056 and from 0.001 ± 0.001 to 0.006 ± 0.004 respectively in normal control animals. In anephric control animals, adrenal secretion rates of all three catecholamines after hemorrhage (EP, 0.365 ± 0.265 to 0.711 ± 0.319 ; NE, 0.080 ± 0.061 to 0.210 ± 0.111 ; DM, 0.008 ± 0.007 to 0.018 ± 0.030) were significantly diminished when compared with those in normal control animals ($P < 0.01$) (Table 1).

The response to hemorrhage of group C animals given IVT infusion of artificial CSF during the experiment was not statistically different from that observed in anephric control animals ($P > 0.05$), demonstrating IVT infusion of artificial CSF did not affect reflex adrenal catecholamine secretion after hemorrhage (Table 2).

IV infusions of PGE-2 at 1.0, 10.0, and 100.0 ng/kg/min in combination with IVT infusions of artificial CSF in group D, E and F significantly supported reflex adrenal catecholamine secretions when compared with those in anephric control animals ($p < 0.01$) (Table 3). These infusions sup-

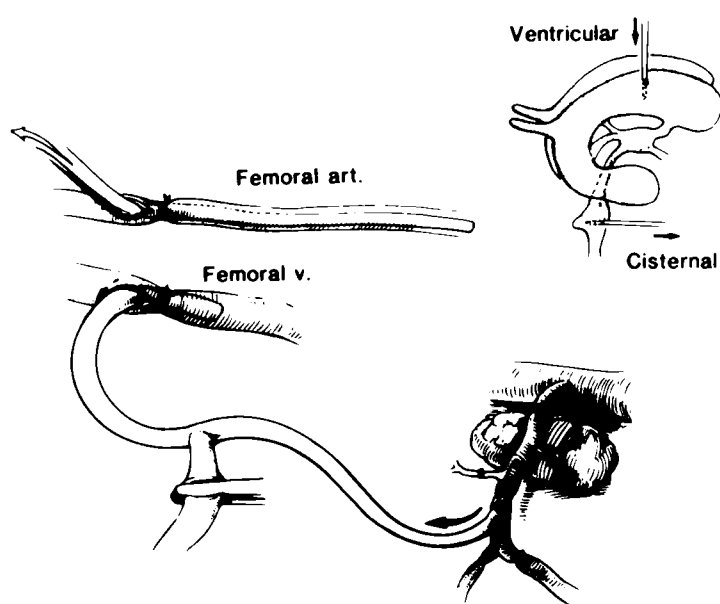


Fig. 1. Diagram of the experiment.

Table 1. Adrenal catecholamine secretion rates(μ g/min) after hemorrhage

Group		Baseline-1	Baseline-2	Posthemorrhage time		
				15 min	30 min	60 min
A	EP	0.039 \pm 0.016	0.286 \pm 0.282	0.590 \pm 0.411	0.700 \pm 0.525	0.716 \pm 0.393
	NE	0.004 \pm 0.002	0.027 \pm 0.030	0.056 \pm 0.053	0.068 \pm 0.065	0.084 \pm 0.056
	DM	0.001 \pm 0.001	0.002 \pm 0.002	0.005 \pm 0.003	0.006 \pm 0.005	0.006 \pm 0.004
		(T)	(H)	P<0.01		
B	EP	0.365 \pm 0.265	0.209 \pm 0.115	0.460 \pm 0.361	0.604 \pm 0.592	0.711 \pm 0.319
	NE	0.080 \pm 0.061	0.052 \pm 0.036	0.111 \pm 0.088	0.129 \pm 0.126	0.201 \pm 0.111
	DM	0.008 \pm 0.007	0.007 \pm 0.007	0.010 \pm 0.012	0.012 \pm 0.007	0.018 \pm 0.030

T: No treatment in group A and nephrectomy in group B, H: hemorrhage at 25m/kg

Table 2. Adrenal catecholamine secretion rates(μ g/min) in anephric hemorrhaged dogs

Group		Baseline-1	Baseline-2	Posthemorrhage time		
				15 min	30 min	60 min
B	EP	0.365 \pm 0.265	0.209 \pm 0.115	0.460 \pm 0.361	0.604 \pm 0.592	0.711 \pm 0.319
	NE	0.080 \pm 0.061	0.052 \pm 0.036	0.112 \pm 0.088	0.129 \pm 0.126	0.201 \pm 0.111
	DM	0.008 \pm 0.007	0.007 \pm 0.007	0.010 \pm 0.012	0.012 \pm 0.007	0.018 \pm 0.030
		(T)	(H)	P>0.05		
C	EP	0.162 \pm 0.092	0.131 \pm 0.049	0.325 \pm 0.083	0.433 \pm 0.116	0.444 \pm 0.102
	NE	0.028 \pm 0.015	0.018 \pm 0.007	0.047 \pm 0.013	0.076 \pm 0.026	0.086 \pm 0.022
	DM	0.004 \pm 0.002	0.002 \pm 0.001	0.005 \pm 0.002	0.007 \pm 0.003	0.007 \pm 0.002

T: Nephrectomy in group B and nephrectomy with IVT CSF in group C, H: Hemorrhage at 25 ml/kg

Table 3. Effect of IV PGE-2 on adrenal catecholamine secretion in anephric hemorrhaged dogs

Group		Baseline-1	Baseline-2	Posthemorrhage time		
				15 min	30 min	60 min
D	EP	0.199 \pm 0.142	0.159 \pm 0.092	0.247 \pm 0.095	0.500 \pm 0.291	0.758 \pm 0.544
	NE	0.058 \pm 0.056	0.041 \pm 0.025	0.057 \pm 0.016	0.138 \pm 0.044	0.172 \pm 0.089
	DM	0.004 \pm 0.002	0.003 \pm 0.004	0.003 \pm 0.001	0.007 \pm 0.006	0.012 \pm 0.011
E	EP	0.383 \pm 0.527	0.406 \pm 0.466	0.691 \pm 0.398	1.317 \pm 0.674	1.429 \pm 0.450
	NE	0.082 \pm 0.104	0.220 \pm 0.356	0.172 \pm 0.137	0.241 \pm 0.137	0.278 \pm 0.101
	DM	0.007 \pm 0.010	0.007 \pm 0.008	0.009 \pm 0.006	0.021 \pm 0.019	0.021 \pm 0.013
F	EP	0.376 \pm 0.271	0.282 \pm 0.307	1.147 \pm 1.240	1.171 \pm 1.421	1.047 \pm 1.291
	NE	0.056 \pm 0.032	0.055 \pm 0.053	0.214 \pm 0.309	0.498 \pm 0.795	0.823 \pm 1.530
	DM	0.005 \pm 0.005	0.006 \pm 0.007	0.019 \pm 0.032	0.054 \pm 0.102	0.042 \pm 0.077

T: Nephrectomy, IV PGE-2 at 1.0 ng/kg/min and IVT CSF in group D
Nephrectomy, IV PGE-2 at 10.0 ng/kg/min and IVT CSF in group E
Nephrectomy, IV PGE-2 at 100.0 ng/kg/min and IVT CSF in group F
H: Hemorrhage at 25ml/kg

ported adrenal EP secretion in a log-log relationship ($r=0.563$)($p<0.05$). Adrenal secretions of NE and DM also increased with increasing doses of IV PGE-2, but the increase did not have a log-log

relationship (Fig. 2).
IVT infusion of PGE-2 at 10.0 ng/kg/min in group G animals also supported reflex adrenal secretions of all three catecholamines (EP, $0.368\pm$

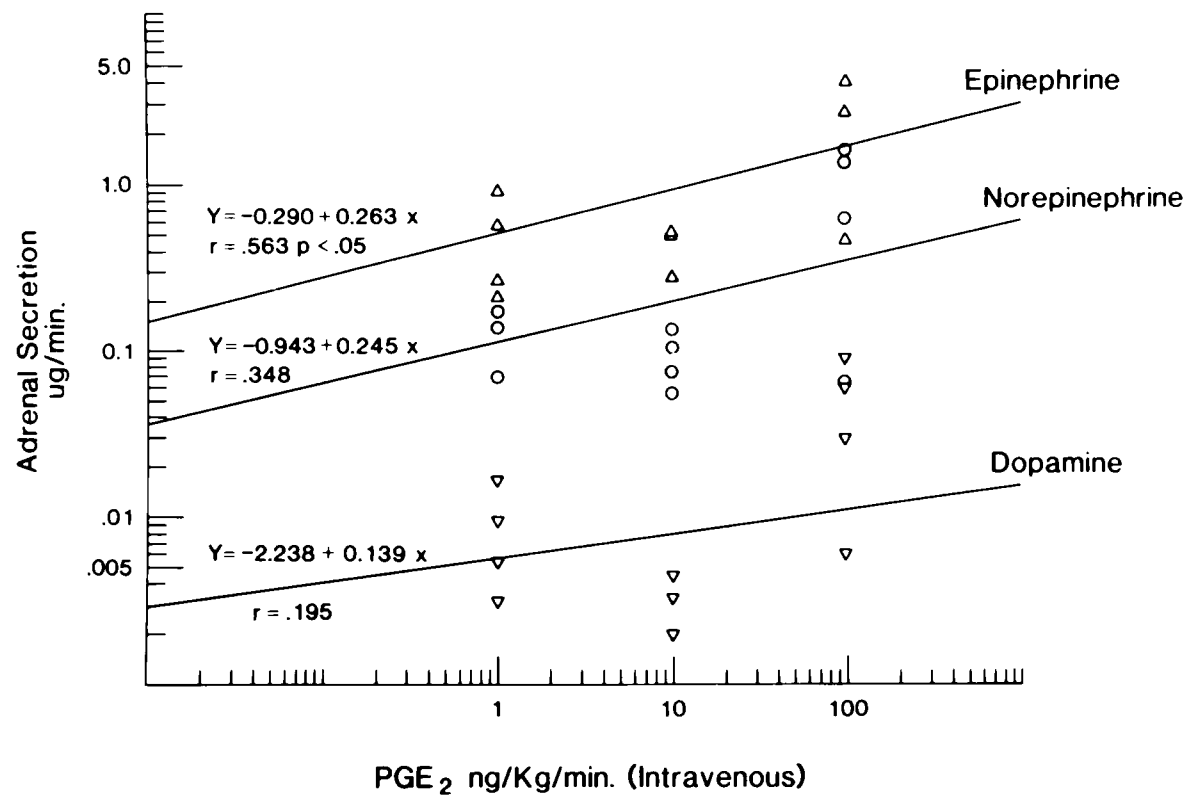


Fig. 2. Dose-response curves of PGE₂.

Table 4. Effect of IVT PGE-2 on adrenal catecholamine secretion in anephric hemorrhaged dogs

Group		Baseline-1	Baseline-2	Posthemorrhage time		
				15 min	30 min	60 min
C	EP	0.162±0.092	0.131±0.049	0.325±0.083	0.433±0.116	0.444±0.102
	NE	0.028±0.015	0.018±0.007	0.047±0.013	0.076±0.026	0.086±0.022
	DM	0.004±0.002	0.002±0.001	0.005±0.002	0.007±0.003	0.007±0.002
		(T)	(H)	P<0.01		
G	EP	0.368±0.273	0.516±0.460	0.821±0.397	1.327±0.368	2.006±0.956
	NE	0.131±0.143	0.151±0.147	0.258±0.195	1.440±0.193	2.775±0.419
	DM	0.006±0.002	0.009±0.007	0.019±0.012	0.030±0.014	0.051±0.035

T: Nephrectomy and IVT CSF in group C and nephrectomy and IVT PGE-2 in group G, H: Hemorrhage at 25 ml/kg

0.273 to 2.006±0.956; NE, 0.131±0.143 to 0.775±0.419; DM, 0.006±0.002 to 0.051±0.035) when compared with those (EP, 0.162±0.092 to 0.444±0.102; NE, 0.028±0.015 to 0.086±0.022; DM; 0.004±0.002 to 0.007±0.002) observed in group C animals given IVT infusion of artificial CSF (p<0.01) (Table 4). This support of adrenal catecholamine secretions was not statistically different from that observed in group E animals given IV infusion of PGE-2 at 10.0 ng/kg/min with IVT infusion of artificial CSF (p>0.05), and reflex EP secretion rates (0.383±0.527 to 1.425±0.450 in group E animals vs. 0.368±

0.273 to 2.006±0.956 in group G animals) were almost identical between two group (Fig. 3).

DISCUSSION

Acute hemorrhage or hypovolemic shock initiates the cascade of reactions in the renin-angiotensin system, stimulating renin secretion from the renal juxtaglomerular cells. The renin acts on circulating angiotensinogen, hydrolyzing a leucine-leucine bond to yield angiotensin I which is converted to angiotensin II(A-II), the active component of the renin-angiotensin system. The A-II stimulates catecholamine secretion in response to the hemor-

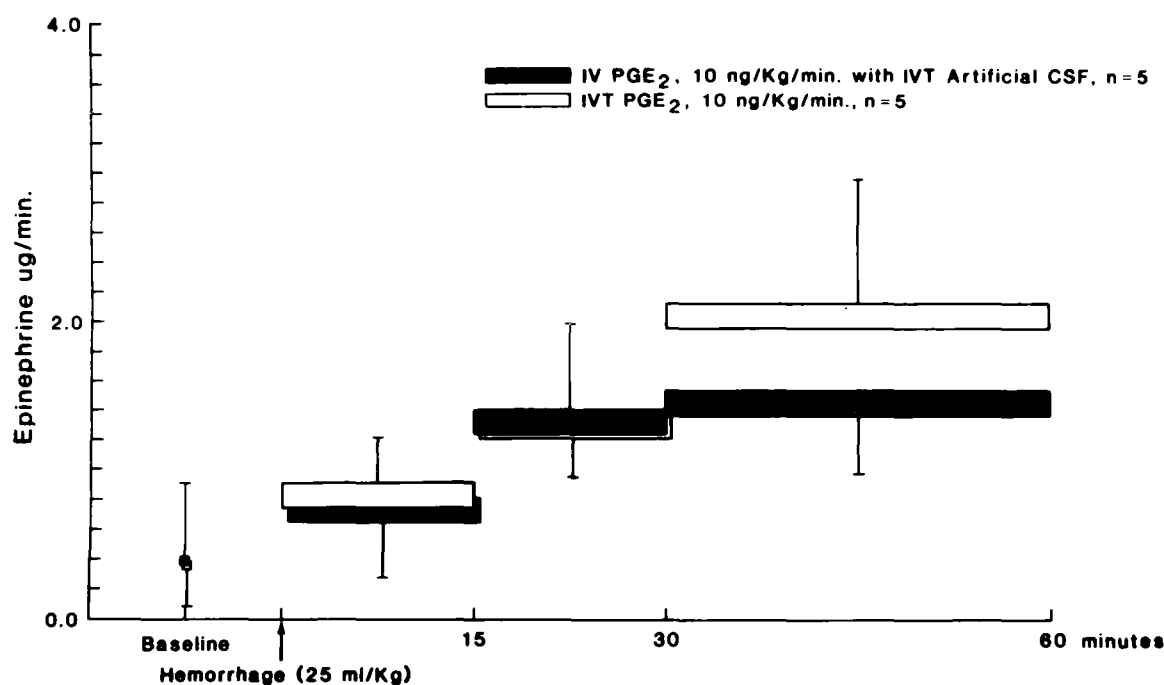


Fig. 3. Adrenal epinephrine secretion rates in anephric hemorrhaged dogs after IV or IVT infusion of PGE₂.

rhage. We observed a marked increase of adrenal catecholamine secretion after hemorrhage in normal control group animals and blunted secretion in anephric controls, suggesting that the renin-angiotensin system was definitely involved in this reaction.

It is believed that there is a close relationship between the renin-angiotensin system and PGE-2. PGE-2, a renal prostaglandin, is synthesized in the renal medulla (Lee *et al.* 1965). Its synthesis is stimulated by the pressor hormones including A-II (Zusman and Keiser 1977) and it stimulates renin secretion from the kidney (Dunn and Hood 1977).

The nature of PGE-2 is basically different from that of A-II. A-II enhances neurotransmission in the peripheral sympathetic system (McCubbin and Page 1963, Kaneko *et al.* 1966). On the other hand, PGE-2, as a potent vasodilator, definitely interferes with peripheral sympathetic neurotransmission by inhibiting NE release from adrenergic terminals (Hedqvist 1977). These two compounds, however, have similar effects on adrenal secretion. They both stimulate aldosterone secretion (Laragh *et al.* 1960, Ames *et al.* 1965, Saruta and Kaplan 1972) and increase resting catecholamine output (Peach 1971, Badder *et al.* 1978).

Of extreme interest is the ability of both PGE-2 and A-II to co-support reflex adrenal medullary catecholamine secretion during hemorrhagic shock in anephric animals (Harrison *et al.* 1973, Badder

et al. 1978). We observed that reflex secretion of catecholamines from the adrenal medulla in anephric animals was significantly increased after IV infusions of PGE-2. The adrenal secretion was stimulated even by the physiologic quantities. The effect of peripherally-infused A-II on the adrenal catecholamine secretion is known to be dose-dependent (Corwin *et al.* 1985), and the PGE-2's effect in relation to its amount has not been established. In our present study, PGE-2 stimulated the adrenal catecholamine secretion dose-dependently; the larger the PGE-2 amount, the greater the catecholamine secretion rate. Adrenal secretion rate of EP, the major catecholamine of the adrenal medulla, was especially proportional to the infused PGE-2 amount in a log-log relationship.

Corwin *et al.* (1985) reported that A-II was selectively more potent in restoring the adrenal medullary response when administered intraventricularly than when infused intravenously, suggesting the effect of A-II was mediated centrally, even if A-II was produced by the peripheral organs. However, PGE-2 was equally effective in its support of reflex adrenal catecholamine secretion regardless of whether it was infused peripherally or centrally according to our present study. These two findings suggest that the peripheral renin-angiotensin system acts by way of a central nervous system mechanism and PGE-2 plays a less specialized role in its interaction with A-II, even though PGE-2

is involved in the action of the renin-angiotensin system.

Definite roles of PGE-2 in the renin-angiotensin system have not been fully established. Some studies (Yamamoto *et al.* 1978, Fujimoto and Hisada 1978) just suggest that PGE-2 acts as a modulator or an arbitrating factor in this system. We believe that the action of PGE-2 in the centrally mediated relationship between the renin-angiotensin system and the adrenal medulla is systemic. Further investigations of this relationship including IVT infusion of PGE-2 synthetase inhibitor will delineate the definite roles of PGE-2 in this phenomenon of centrally-active A-II and the adrenal medullary secretion of catecholamines.

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= 국문초록 =

부신의 반사성 Catecholamine 분비에 대한 Prostaglandin E₂의 영향

서울대학교 의과대학 및 펜실바니아 주립대학교 의과대학 외과학교실

오승근 · Timothy S. Harrison

Prostaglandin E₂를 양측 신장을 적출한 실험 건의 정맥과 측뇌실에 주입한 후 prostaglandin E₂가 급성 출혈 상태에서 부신의 catecholamine 분비에 미치는 영향을 연구하였다.

무신 상태에서 감소되었던 부신의 catecholamine 분비량은 prostaglandin E₂를 정맥으로 주입한 후 현저하게 증가하였으며 그 증가는 주입된 양에 비례하였다.

Prostaglandin E₂가 부신의 catecholamine 분비에 미치는 영향은 정맥으로 주입하였거나 측뇌실로 주입하였거나 차이가 없었다.

Renin-angiotensin 제와 연관된 반사성 부신 catecholamine 분비에 대한 prostaglandin E₂의 영향은 중추신경계에 의하여 조절되는 것으로 알려진 angiotensin II와는 달리 말초성 작용으로 생각되었다.