PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 166, 57–63 (1981)

The Renin–Angiotensin System and Renal Prostaglandin E_2 Release in Dogs (41024)

TAKESHI OKAHARA, MONOHAR R. MANCHANDIA, ANDREW M. MICHELAKIS AND KENJIRO YAMAMOTO

Clinical Pharmacology Program, Departments of Pharmacology and Toxicology and Medicine, Michigan State University, East Lansing, Michigan 48824

Abstract. The relationship between renin and renal prostaglandin E_2 (PGE_2) release was investigated in anesthetized dogs using a highly specific radioimmunoassay for PGE_2 measurement. There was a dissociation between the acute inhibition of renin release with intrarenal infusion of angiotension II (AII) or angiotensin III (AIII) and renal PGE_2 release. Intrarenal infusion of norepinephrine resulted in a significant increase both in renin and renal PGE_2 release. Intrarenal infusion of bradykinin increased renal PGE_2 but not renin release, and infusion of isoproterenol increased renin release but not renal PGE_2 release. Renal pressure reduction from 134 to 71 mm Hg increased renin release while the renal PGE_2 release was unaltered. In addition, renal vasoconstriction was observed with an infusion of norepinephrine, AII, and AIII, while renal vasodilation was observed with an infusion of isoproterenol and bradykinin, and renal pressure reduction. Neither renal vasoconstriction nor vasodilation, however, correlated with renal PGE_2 release. These results suggest that the renin–angiotensin system probably does not play a regulatory role in the control of renal PGE_2 release, and that the change of renal vascular tone does not accompany renal PGE_2 release.

Prostaglandin E_2 (PGE_2) and the renin–angiotensin system have been postulated to play an important role in the regulation of renal hemodynamics and systemic blood pressure (1–3). Although the release of such humoral factors has been extensively investigated (1, 4), the release of these factors seems to depend on concomitant conditions of administration of furosemide (5), hemorrhagic hypotension (6), reduced renal perfusion pressure (7–9), and intrarenal administration of calcium ionophore, A23187 (10). Recent reports suggest that PGE_2 and PGI_2, and PG's intermediate synthetic products may influence renin release (11), and that indomethacin, an inhibitor of PGs synthesis, may decrease renin release from the rabbit kidney (12). However, little is known of the role of the renin–angiotensin system on the release of renal PGs.

In the present experiments, we used a highly specific radioimmunoassay procedure for the measurement of PGE_2 and investigated the effects of AII, AIII, adrenergic agents, bradykinin, and changes in renal perfusion pressure on renin and PGE_2 release from the dog kidney, in an attempt to determine a possible correlation between the control of renal PGE_2 release and that of renin secretion.

Methods. *Animal experiments.* Adult mongrel dogs, of either sex with an average body weight of 21 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv), and supplemental doses were given as required. An endotracheal tube was inserted, and the respiration was regulated with a respirator. The left kidney was exposed through a retroperitoneal flank incision. The renal nerve fibers were carefully preserved. The renal blood flow (RBF) was measured by an electromagnetic flow meter (Carolina Medical Electronics, Model 501). Systemic blood pressure was monitored from the right femoral artery. Arterial and renal venous blood samples were collected from catheters introduced into the axillary artery and renal vein through the left spermatic or ovarian vein. A 23-gauge needle inserted into the left renal artery proximal to the flow probe served for intrarenal drug infusion or monitoring of renal BP.

Twelve dogs were divided into two sub-

0037-9727/81/010057-07$01.00/0

Copyright © 1981 by the Society for Experimental Biology and Medicine.
All rights reserved.

groups, seven were given AII (Beckman) and five were given AIII (Beckman). After two 10-min control observations, AII or AIII was infused into the left renal artery at a rate of 120 ng/min for 90 min. Both arterial and renal venous blood samples were taken at 3, 30, 60, and 90 min during the time of infusion.

Nineteen dogs were separated into three subgroups. In the first seven dogs, norepinephrine was infused into the renal artery at a rate of 2.0 μg/min for 90 min. The blood samples were taken before, and at 3, 30, 60, and 90 min during the infusion. In another six dogs, isoproterenol was infused into the left renal artery at a rate of 1.7 μg/min for 90 min. Blood samples were taken at the same intervals as in the first subgroup. In the remaining six dogs, renal arterial pressure was reduced by a partial occlusion of the left renal artery. In this series, all visible nerve fibers were cut off, and 5% xylocaine was applied to the surrounding tissue. Renal arterial pressure was reduced to 70−75 mm Hg by direct partial occlusion of the renal artery and was monitored throughout the experiment via a 23-gauge needle inserted into the renal artery. Blood samples were taken before and at 3, 30, and 60 min during the pressure reduction. After a 40-min recovery period, further experiments were performed using the same animals. Bradykinin (Sigma Co., St. Louis, Mo.) was infused into the renal artery at a rate of 500 ng/min for 15 min. Additional blood specimens were taken before and at 3 and 15 min during the infusion.

Laboratory procedures. Measurement of prostaglandin E_2. PGE_2 was measured by the method described by Jaffe *et al.* (13). Briefly, blood samples were collected in plastic syringes, transferred to heparanized and siliconized tubes, and blood cells were immediately separated by centrifuging twice at 10,000*g* for 10 min.

Extraction was started without storage of the plasma in a freezer. Tritium-labeled PGE_2 (1000 cpm) was added to 3.0 ml of plasma to determine the recovery using this procedure. The mixture was initially extracted with petroleum ether (9 ml) to remove neutral lipids, followed by extraction with a solvent (9 ml) consisting of ethyl acetate, isopropanol, and 0.1 *N* HCl, 3:3:1 by volume. The obtained organic phase was dried, and silicic acid column chromatography (0.6 g, 100 mesh, Mallinckrodt, Mo.) was carried out to separate the prostaglandins. We used benzene, ethyl acetate, and methanol as the developing solution; however, PGE_2 could not be separated from PGE_1. The separation profiles of other PG's are illustrated in Fig. 1. To achieve the specific measurement of PGE_2, a highly specific antibody for PGE_2 (Pasteur Institute, Paris) was employed for the radioimmunoassay. The cross-reactivity to PGE_1 was approximately 3% and that to other PGs was less than 1%.

After the separation, the dried PGE fraction was resuspended in 0.1 ml of absolute ethanol and 0.9 ml of 0.15-*M* phosphate buffer (pH 7.4). Half of the solution was added to a 15-ml scintillation mixture and counted in a liquid scintillation counter for the recovery of initially added ^{3}H-labeled PGE_2. Two 0.1-ml fractions of the solution were added to tubes containing 0.1 ml of antibody for PGE_2, 0.1 ml of ^{3}H-labeled PGE_2 (10,000 cpm), and incubation was carried out for 3 hr. At the end of incubation, 1 ml of charcoal suspension (activated NoritA, Fisher Scientific (2.5 mg/ml), Dextran T70, Pharmacia Fine Chemical, (0.25 mg/ml) was added to each tube, and the preparation was centrifuged at 5000*g* for 10 min. The supernatant was immediately decanted into the scintillation vial and counted for 10 min. The standard curve was read from 5 to 250 pg of PGE_2 per test tube. Final recovery for PGE_2 was 61.4 ± 0.4 (n = 240) when the initially added ^{3}H-labeled PGE_2 was calculated. The recovery of 200 and 500 pg of PGE_2 added to 3 ml of plasma was 199 ± 2 and 494 ± 10 pg (n = 4), respectively, after the corrections for recovery rate. In the plasma treated with alkaline (pH 9.5) before the start of extraction, there was a negligible PGE_2 concentration. PGE_2 secretion rate was calculated as follows: (PGE_2 conc. in renal venous plasma − PGE_2 conc. in arterial plasma) × renal plasma flow.

Measurement of PRA. PRA was mea-

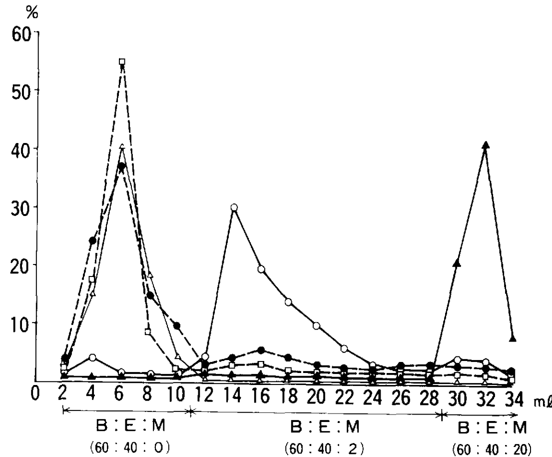

FIG. 1. A typical separation of prostaglandin E_2 from other prostaglandins on a silicic acid column chromatograph. ^{3}H-labeled PGA_2 (solid circles), E_2 (open circles), $F_{2\alpha}$ (solid triangles), 15-keto-PGE_2 (open squares), and 13,14-dihydro-15-keto-PGE_2 (open triangles) were added to 3 ml of plasma (each radioactivity 10,000 cpm). The extraction and separation were performed as described under Methods. The ordinate is percentage recovery of radioactivity, and the abscissa is elution volume and its composition of benzene (b), ethyl acetate (E), and methanol (M) by volume.

sured by radioimmunoassay as previously described (14) and expressed as the amount of AI generated per milliliter of plasma during 1-hr incubation. Renin secretion rate was calculated as described in PGE_2 secretion rate.

Renal vascular resistance was calculated as the ratio of the systemic or the renal arterial BP to RBF and expressed as mm Hg·g·min/ml.

Statistical significance was determined by Student's paired t test.

The radioactive chemicals used were obtained from the following sources: PGA_2, PGE_1, $PGF_{2\alpha}$ (New England Nuclear); 13,14-dihydro-15-keto-PGE_2 (Amersham); and the 15-keto-PGE_2 (the product from PGE_2) as described previously (15).

Results. *Effect of intrarenal infusion of AII and AIII on the release of PGE_2 and renin.* Intrarenal infusion of AII resulted in a decrease in the rate of renin secretion. This inhibitory effect was also observed with AIII infusion. The hemodynamic effects of both angiotensins were similar; the RBF was decreased significantly, while the systemic blood pressure remained unchanged. Calculated renal vascular resistance was 38.6 ± 3.0 in the preinfusion period and increased to 57.2 ± 4.6, 54.1 ± 5.8, 51.9 ± 6.9, and 53.4 ± 6.8 mm Hg·g·min/ml at 3, 30, 60, and 90 min of AII infusion. PGE_2 concentrations in renal venous and arterial plasma in the preinfusion period of AII infusion were 376 ± 61 pg/ml (ranging from 154 to 671 pg/ml) and 334 ± 84 (ranging from 86 to 740 pg/ml), respectively. The PGE_2 levels in both plasma samples did not change significantly throughout the infusion period. PGE_2 secretion rates before AII and AIII infusion were 99 ± 71 and 148 ± 75 pg/g·min, respectively, and these values remained unchanged during the infusion (Table I).

Effect of adrenergic agents of the release of PGE_2 and renin. As shown in Table II, intrarenal infusion of norepinephrine at a rate of 2.0 μg/min resulted in a decrease of RBF and an elevation of systemic BP. Renal vascular resistance increased from 42.1 ± 3.0 to 62.3 ± 4.6, 59.1 ± 3.2, 51.7 ± 3.1, and 48.3 ± 2.8 mm Hg·g·min/ml at 3, 30, 60, and 90 min of the infusion period. PGE_2 concentration in renal venous plasma increased significantly 30 min after the start of infusion and was accompanied by an increase in renin release (Table II). It seems that the release of PGE_2 and renin was re-

TABLE I. EFFECTS OF ANGIOTENSIN II AND III ON PROSTAGLANDIN E_2 RELEASE FROM THE DOG KIDNEY

Time (min)	BP (mm Hg)	RBF ml/g·min	Renal PRA (ng/ml)	Renin secretion rate (ng/g·min)	Renal venous PGE_2 concentration (pg/ml)	PGE_2 secretion rate (pg/g·min)
0	136 ± 4	3.60 ± 0.21	3.6 ± 1.3	2.3 ± 1.0	376 ± 61	99 ± 71
Angiotensin II was infused into the renal artery at a rate of 120 ng/min						
3	137 ± 2	2.47 ± 0.20*	3.7 ± 1.4	2.9 ± 1.0	364 ± 73	97 ± 33
30	138 ± 5	2.76 ± 0.35*	2.7 ± 1.0	1.4 ± 0.9	360 ± 47	101 ± 51
60	136 ± 4	2.89 ± 0.35*	2.6 ± 1.1	1.6 ± 0.8	324 ± 49	48 ± 84
90	137 ± 5	2.79 ± 0.35	2.3 ± 1.0*	1.4 ± 0.4*	359 ± 55	39 ± 75
0	135 ± 3	3.78 ± 0.20	4.5 ± 0.9	3.0 ± 1.1	287 ± 67	148 ± 75
Angiotensin III was infused into the renal artery at a rate of 120 ng/min						
3	135 ± 3	2.78 ± 0.20*	3.6 ± 0.7	2.3 ± 0.6	271 ± 58	11 ± 65
30	135 ± 3	2.58 ± 0.08*	2.0 ± 0.7*	1.0 ± 0.4	263 ± 49	67 ± 53
60	136 ± 4	2.73 ± 0.18	1.6 ± 0.6*	0.1 ± 0.9*	289 ± 59	43 ± 24
90	136 ± 4	2.80 ± 0.21	1.7 ± 0.6*	0.6 ± 0.4*	302 ± 63	118 ± 70

Note. All values are mean ± SE. Angiotensin II infusion ($n = 7$), Angiotensin III ($n = 5$).
* Significantly different from corresponding value observed prior to angiotensin II or angiotensin III infusion.

lated in this particular group. However, a dissociation between PGE_2 and renin release was observed during isoproterenol infusion. Intrarenal infusion of isoproterenol at a rate of 1.7 μg/min resulted in a tendency towards increase in RBF with a decrease in systemic BP. Renal vascular resistance decreased from 36.3 ± 4.3 to 30.6 ± 7.0, 27.5 ± 2.4, 25.6 ± 2.4, and 24.2 ± 2.4 mm Hg·g·min/ml at 3, 30, 60, and 90 min of the infusion. The PGE_2 secretion rate was not influenced while the renin secretion rate was increased during the infusion (Table III).

Effect of renal pressure reduction on the release of PGE_2 and renin. Renal arterial pressure was reduced to 71 mm Hg by a partial occlusion of the left renal artery. This pressure was the lower limit of autoregulation so that the RBF maintained a fairly constant level. Renal vascular resistance decreased from 37.9 ± 2.2 to 18.4 ± 0.7, 21.9 ± 1.4, and 20.4 ± 1.0 mm Hg·g·min/ml at 3, 30, and 60 min during partial occlusion of the renal artery. The renin secretion rate increased at the initial phase of the manipulation and returned to the preclamping level. However, the PGE_2 secretion rate did not change significantly during the period of pressure reduction (Table IV).

TABLE II. EFFECTS OF NOREPINEPHRINE ON PROSTAGLANDIN E_2 RELEASE FROM THE DOG KIDNEY

Time (min)	BP (mm Hg)	RBF (ml/g·min)	Renal PRA (ng/ml)	Renin secretion rate (ng/g·min)	Renal venous PGE_2 concentration (pg/ml)	PGE_2 secretion rate (pg/g·min)
0	141 ± 4	3.43 ± 0.23	2.4 ± 1.0	6.1 ± 1.9	205 ± 69	79 ± 35
Norepinephrine was infused into the renal artery at a rate of 2.0 μg/min						
3	148 ± 3*	2.41 ± 0.12*	8.8 ± 1.7	9.8 ± 1.9	221 ± 98	248 ± 125
30	155 ± 2*	2.66 ± 0.11*	10.6 ± 1.6	10.4 ± 1.4*	341 ± 98*	252 ± 119
60	161 ± 4*	3.15 ± 0.16	12.2 ± 1.8*	11.8 ± 1.2*	395 ± 106*	297 ± 103
90	161 ± 5*	3.38 ± 0.14	13.0 ± 2.3*	12.8 ± 2.5*	420 ± 87*	448 ± 154*

Note. All values are mean ± SE ($n = 7$).
* Significantly different from corresponding value observed prior to administration of norepinephrine ($P < 0.05$).

TABLE III. EFFECTS OF ISOPROTERENOL ON PROSTAGLANDIN E_2 RELEASE FROM THE DOG KIDNEY

Time (min)	BP (mm Hg)	RBF (ml/g·min)	Renal PRA (ng/ml)	Renin secretion rate (ng/g·min)	Renal venous PGE_2 concentration (pg/ml)	PGE_2 secretion rate (pg/g·min)
0	131 ± 7	3.74 ± 0.29	3.3 ± 0.8	2.9 ± 0.5	246 ± 84	161 ± 169
Isoproterenol was infused into the renal artery at a rate of 1.7 μg/min						
3	117 ± 6	3.91 ± 0.24	5.1 ± 0.6*	7.2 ± 1.1*	232 ± 66	188 ± 157
30	113 ± 4	4.25 ± 0.34	6.3 ± 0.8*	8.9 ± 1.7*	227 ± 69	72 ± 88
60	112 ± 3	4.50 ± 0.40	7.8 ± 0.6*	7.2 ± 1.6*	235 ± 103	84 ± 154
90	108 ± 4	4.63 ± 0.40	7.7 ± 0.6*	8.0 ± 2.0*	247 ± 92	95 ± 88

Note. All values are mean ± SE (n = 6).
* Significantly different from corresponding value observed prior to administration of isoproterenol infusion ($P < 0.05$).

Effect of intrarenal bradykinin infusion on the release of PGE_2 and renin. After complete recovery from the pressure reduction experiment, bradykinin was infused into the renal artery (500 ng/min) to determine whether the kidneys were capable of synthesizing PGE_2. This infusion of bradykinin resulted in an increase of RBF with no change in systemic BP. PGE_2 concentration in the renal venous plasma was increased more than double, and PGE_2 secretion rate was also significantly increased in all dogs. However, the response of renin release showed a wide variation. Renin secretion rate was increased in three out of six dogs, but remained unchanged in the other animals. Thus, there was a dissociation between PGE_2 and renin release, even in this group.

Discussion. In the present work we attempted to separate main metabolites of PGE_2, 15-keto-PGE_2, and 13,14-dihydro-15-keto-PGE_2, as well as other PG's, PGA_2 and $PGF_{2\alpha}$, before the assay, and both arterial and renal venous levels of PGE_2 were determined in anesthetized dogs. The secretory rate of PGE_2 from the kidney was also calculated. This value may be an un-

TABLE IV. EFFECTS OF REDUCED RENAL PERFUSION PRESSURE AND INTRARENAL INFUSION OF BRADYKININ ON PROSTAGLANDIN E_2 RELEASE FROM THE DOG KIDNEY

Time (min)	Systemic BP (mm Hg)	Renal BP (mm Hg)	RBF (ml/g·min)	Renal PRA (ng/ml)	Renin secretion rate (ng/g·min)	Renal venous PGE_2 concentration (pg/ml)	PGE_2 secretion rate (pg/g·min)
0	137 ± 4	134 ± 4	3.65 ± 0.20	1.7 ± 0.6	0.7 ± 0.3	361 ± 85	195 ± 107
Partial renal artery occlusion was started							
3	142 ± 3	71 ± 2	3.90 ± 0.13	9.2 ± 3.7*	18.8 ± 7.1*	399 ± 95	234 ± 107
30	144 ± 4	77 ± 2	3.69 ± 0.14	3.1 ± 1.0	3.2 ± 1.7	327 ± 100	115 ± 149
60	146 ± 4	72 ± 2	3.60 ± 0.22	3.3 ± 1.0	1.7 ± 0.6	397 ± 93	65 ± 114
Partial renal artery occlusion eliminated							
100	138 ± 5		3.51 ± 0.20	2.4 ± 1.3	0.3 ± 0.3	375 ± 80	171 ± 102
Bradykinin was infused into the renal artery at a rate of 500 ng/ml							
103	138 ± 5		5.66 ± 0.50**	4.8 ± 3.2	7.0 ± 6.0	638 ± 86**	754 ± 199**
115	139 ± 5		4.13 ± 0.44**	4.2 ± 2.9	4.1 ± 4.0	619 ± 112**	423 ± 192**

Note. All values are mean ± SE (n = 6).
* Significantly different from corresponding value observed prior to partial renal artery occlusion.
** Significantly different from corresponding value observed prior to bradykinin infusion.

derestimation of the true PGE_2 secretory rate from the kidney, since PGE_2 also degradates within the kidney and escapes into the urine (16). However, it does reflect the rate of PGE_2 synthesis within the kidney (8, 17).

Intrarenal infusion of AII and AIII inhibited renin release, while it had no significant effect on PGE_2 release from the kidney. These inhibitory effects of renin release are similar to findings of Freeman *et al.* (18). However, other investigators found that intrarenal infusion of AII increased the PG-like material in the venous effluent in the dog (19,20) and recently Dunn *et al.* also observed a slight increase of PGE_2 release from dog kidney (8). Although this may be a direct effect, in other tissue the effect of AII on PGE release seems to be secondary to the release of catecholamines (21). Under the conditions we used, neither AII nor AIII affected renal PGE_2 release.

Although infusion of β-adrenergic agents and pressure reduction increased the release of renin, there was no significant effect on renal PGE_2 release. In contrast, the effect of norepinephrine may be due to mechanisms other than those regulating renin release. However, the mechanisms involved in the release of PGE_2 by norepinephrine is unknown (22). Previous studies suggested that the release of a renal PGE-like substance could be induced by changes in size of the renal vasculature such as vasoconstriction or vasodilation (23). Thus, the renal vasoconstriction induced by norepinephrine, which leads to changes in renal hemodynamics and possibly alterations in medullary blood flow, may trigger the release of a PGE-like substance from the kidney. We also did experiments in which the effect of norepinephrine on PGE_2 release was compared to that of AII and AIII at dose levels which had equivalent renal vascular effects. Stimulation of PGE_2 release was observed only in cases of the norepinephrine infusion. These results suggest that there is no correlation between drug-induced renal vasoconstriction and PGE_2 release.

The dissociation between renin and PGE_2 release was further clearly observed. It was reported by other investigators that pressure reduction to 100 mm Hg did not affect the PGE release while pressure reduction to 50 mm Hg below the autoregulatory limit increased the PGE release in the pump-perfused dog kidney (24). Similar findings were also reported by Satoh and Zimmerman (7) and Dunn *et al.* (8). However, since in latter experiments, RBF was markedly reduced below the autoregulatory limit, it is difficult to eliminate the effect of renal hemodynamics changes on PGE release. We have already reported that pressure reduction within the autoregulatory range increased renin release in the dog (9). In the present experiment, RBF was well maintained during 60 min of clamping of the renal artery. At an early stage of this manipulation, increase in the release of renin was observed with hyperregulation of RBF, while renal PGE_2 release did not occur with this hemodynamic change. Thus, our findings suggest that renal PGE_2 does not contribute to the maintenance of RBF against the reduced perfusion pressure, at the lower limit of the autoregulation. These findings are also supported by the data of Anderson *et al.* (25).

The relationship between bradykinin and PGE release has been reported (26). The mechanism seems to involve an increase of availability of arachidonic acid through activation of phospholipase A_2 (27). However, this increase of PGE_2 release from the kidney seems to be independent of the renal vascular effect, since a similar magnitude of renal vasodilation was observed with isoproterenol infusion and pressure reduction, these treatments having no significant effect on PGE_2 release. In the present experiment, we examined the interrelationship between renal PGE_2 and renin release, under various conditions. Another PG, PGI_2, is also one of the important factors which contribute to renin release (11) and studies are underway in an attempt to assess the contribution. The present experiment does suggest, however, that the control of PGE_2 release from the kidney may be independent of the renin–angiotensin system. In addition, the increase of PGE_2 release, as induced by norepineph-

rine and bradykinin, could hardly be explained by the hemodynamic effects of these agents.

We thank Dr. John Pike of Upjohn Pharmaceutical Co. for provision of the prostaglandins, Yoko Kunitake for clerical assistance, and M. Ohara, Kyoto University, for criticism of the manuscript. This work was supported in part by U.S. Public Health Service Grant HL 25995 and a grant from the American Heart Association. The technical assistance of Paul Susan is also appreciated.

---

1. Dunn, M. J., and Hood, V. L., Amer. J. Physiol. **233**, F169 (1977).
2. Johannsen, J., Omvik, P., Jr., and Kill, F., Amer. J. Physiol. **230**, 1042 (1976).
3. Osborn, E. C., Tildesley, G., Leach, K. G., and Rigby, G. V., Amer. J. Physiol. **226**, 518 (1974).
4. Davis, J. O., and Freeman, R. H., Physiol. Rev. **1**, 1 (1976).
5. Weber, P. C., Scherer, B., and Larsson, C., Eur. J. Pharmacol. **41**, 329 (1977).
6. Selkurt, E. E., Circ. Shock **1**, 89 (1973).
7. Satoh, S., and Zimmerman, B. G., Circ. Res. (Suppl. I) **36** and **37**, 89 (1975).
8. Dunn, M. J., Liard, J. F., and Dray, F., Kidney Intern. **13**, 136 (1978).
9. Abe, Y., Okahara, T., Kishimoto, T., Yamamoto, K., and Ueda, J., Amer. J. Physiol. **225**, 319 (1975).
10. Okahara, T., Abe, Y., Imanishi, M., Miura, K., and Yamamoto, K., Jap. Circul. J. **44**, 394 (1980).
11. Gerber, J. G., Branch, R. A., Nies, A. S., Gerkens, J. F., Shand, D. G., Hollifield, J., and Oates, J. A., Prostaglandins **15**, 81 (1978).
12. Larsson, C., Weber, P., and Änggård, E., European J. Pharmacol. **28**, 391 (1974).
13. Jaffe, B. M., Behrman, H. R., and Parker, C. W., J. Clin. Invest. **52**, 398 (1973).
14. Haber, E., Koerner, T., Page, L., Kliman, B., and Purnode, A., J. Clin. Endocrinol. Met. **29**, 1349 (1969).
15. Okahara, T., Boye, G. L., Michelakis, A. M., and Hung, C. T., Pharmacologist (Abstract) **19**, 183 (1977).
16. Larsson, C., and Änggård, E., Eur. J. Pharmacol. **21**, 30 (1973).
17. Zambraski, E. J., and Dunn, M. J., Amer. J. Physiol. **236**, F552 (1979).
18. Freeman, R. H., Davis, J. O., Lohmeier, T. E., and Spielman, W. S., Circ. Res. (Suppl. II) **38**, 99 (1976).
19. McGiff, J. C., Crowshaw, K., Terragno, N. A., and Lonigro, A. J., Circulation Res. (Suppl. I) **26** and **27**, 121 (1970).
20. Aiken, J. W., and Vane, J. R., J. Pharmacol. Exp. Ther. **184**, 678 (1973).
21. Limas, C. J., Biochim. Biophys. Acta **337**, 417 (1974).
22. Terashima, R., Anderson, F. L., Jobiz, W., Tsagaris, T. J., and Kuida, H., Proc. Soc. Exp. Biol. Med. **147**, 449 (1974).
23. Needleman, P., Douglas, J. R., Jr., Jakshik, B., Stoecklein, P. B., and Johnson, E. M., Jr., J. Pharmacol. Exp. Therap. **188**, 453 (1974).
24. Dighe, K. K., Hall, J. C., Smith, G. W., and Ungar, A., Brit. J. Pharmacol. **59**, 571 (1977).
25. Anderson, R. J., Taher, M. S., Cronin, R. E., McDonald, K. M., and Schrier, R. W., Amer. J. Physiol. **229**, 731 (1975).
26. McGiff, J. C., Terragno, N. A., Malik, K. U., Lonigro, A. J., Circ. Res. **31**, 36 (1972).
27. Juan, H., Naunyn-Schmiedeberg's Arch. Pharmacol. **300**, 77 (1977).

Received January 31, 1980. P.S.E.B.M. 1981, Vol. 166.