EFFECTS OF PHENYLEPHRINE ON RENIN AND PROSTAGLANDIN E2 RELEASE IN ANESTHETIZED DOGS

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It has been noted that sympathetically induced renin release is mediated by a beta-adrenoceptor mechanism (1). Concerning a role of alpha-adrenoceptor mechanism in renin release, Vandongen et al. (2) demonstrated that an alpha-agonist inhibits renin response to isoproterenol in perfused rat kidney. It has been suggested that adrenergic stimulation causes prostaglandin (PG) release, and this response is blocked by an alpha-antagonist (3). It has also been demonstrated that the renal PG system modulates renin release induced by several types of stimuli (4, 5). Therefore, it may be conceivable that an alpha-adrenoceptor mechanism participates in renin release by the activation of the renal PG system. We investigated the effects of an alpha-agonist, phenylephrine, on renin and PG release in anesthetized dogs.

Mongrel dogs of either sex weighing 12 to 23 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.), paralyzed with decamethonium bromide (0.25 mg/kg, i.v.), and artificially ventilated. The left kidney was exposed via a retroperitoneal approach. Renal blood flow was measured with an electromagnetic flow probe (2.5-3.5 mm in diameter) placed at the renal artery. Systemic blood pressure was monitored with a pressure transducer through a catheter inserted into the right brachial artery, and this catheter was also used to collect arterial blood samples. A fish-hooked 25-gauge needle connected to a polyethylene tube was inserted into the renal artery for the drug infusion. The renal vein was cannulated through the gonadal vein to collect renal venous blood samples. Phenylephrine (L-phenylephrine, Sigma) was infused intrarenally with an infusion pump (Harvard Apparatus, 975) at the dose which caused reduction in renal blood flow to approximately half of the control level within 1 min after the start of the infusion. This dose was variable among the dogs employed and ranged between 3-20 μg/min. Experimental values were obtained during the control period, 10 min during the infusion of phenylephrine, and during the recovery period 20 min after the infusion was stopped.

Arterial and renal venous blood samples (4 ml) were withdrawn simultaneously, transferred into chilled tubes containing EDTA, and centrifuged. Plasma renin activity (PRA) and plasma PGE2 concentration were measured by radioimmunoassay according to the methods of Fyhrquist et al. (6) and Green et al. (7), respectively. Secretion rate was calculated by multiplying the difference between the renal venous and arterial PRA or plasma PGE2 concentration by renal plasma flow.

All values are expressed as mean±S.E. The statistical test employed was the Student's t-test, and significance was taken as P<0.05.

The effects of phenylephrine on renal
Table 1. Effects of phenylephrine on renal blood flow and systemic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PE</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Blood Flow (ml/min)</td>
<td>195±35</td>
<td>114±18*</td>
<td>192±38</td>
</tr>
<tr>
<td>Systemic Blood Pressure (mmHg)</td>
<td>141±4</td>
<td>140±2</td>
<td>142±3</td>
</tr>
</tbody>
</table>

Values are mean±S.E. (n=6). PE=Phenylephrine *P<0.05 as compared to the Control. See details in the text.

blood flow and systemic blood pressure are summarized in Table 1. Renal blood flow was significantly reduced with intrarenal phenylephrine. Patterns of the response in renal blood flow during the infusion of phenylephrine were different among the dogs. Initially reduced blood flow was partially recovered in two dogs, maintained in two dogs, and gradually decreased in the other dogs. Systemic blood pressure was slightly increased, but this change was not significant. When the infusion was stopped, renal blood flow was immediately recovered, and transient hyperemia response was observed in 5 out of 6 dogs.

The effects of phenylephrine on renin and PGE2 release are shown in Fig. 1. Phenylephrine markedly increased renin secretion rate from 451±143 ng Angiotensin I (Al)/min (Venous and Arterial PRA: 14.8±4.4 ng Al/ml·hr and 9.7±2.4 ng Al/ml·hr, respectively) to 1733±512 ng Al/min (P<0.05. Venous and Arterial PRA: 43.2±11.9 ng Al/ml·hr and 12.9±3.0 ng Al/ml·hr, respectively). Two out of 6 dogs employed in this study had high renin secretion rate (rather than 800 ng Al/min) during the control period, which contributed to the relatively higher mean control value. PGE2 secretion rate was also increased from 299±208 pg/min to 2864±560 pg/min (P<0.02). After the infusion was stopped, renin and PGE2 secretion rate returned to 315±87 ng Al/min and 618±564 pg/min, respectively, and they were not different from the respective control values.

These results suggest that an alpha-adrenoceptor mechanism is involved in renin release and that alpha-stimulation activates renal PG synthesis. Therefore, it is possible that PGs modulate the renin release mediated by alpha-adrenoceptors. To examine this possibility, we tried to compare the renin response to phenylephrine before and after the treatment of a PG synthesis inhibitor, indomethacin (5 mg/kg, i.v.). Twenty minutes after the treatment of indomethacin, the infusion of phenylephrine at the same dose as used before indomethacin decreased renal blood flow nearly to zero. Consequently, we failed to obtain renal venous blood samples.

Blair (8) demonstrated that phenoxybenzamine infused into the renal artery reduced renin release in dogs. Our present results also give evidence for the participation of an alpha-mechanism in sympathetically mediated renin release.

In the present study, it was clearly shown that alpha-adrenergic stimulation increased...
PG production. It was also demonstrated that PG release was caused by renal nerve stimulation (3, 9) and by norepinephrine (3), which was blocked with phenoxybenzamine (3).

The present study does not rule out the possibility that renin and PG release in response to phenylephrine might result from the reduction in renal blood flow with phenylephrine. Under this condition, the renal baroreceptor mechanism might be stimulated and cause renin release, and partial ischemia of the kidney might stimulate the PG system.

However, in our preliminary experiment, when non-vasoconstrictor dose of phenylephrine (1 ng/min) was infused into the renal artery in 3 dogs, all of the dogs showed increase in both renin and PGE2 secretion rate (from 112±48 ng Al/min to 212±33 ng Al/min, and from 237±194 pg/min to 948±290 pg/min, respectively). Therefore, it may be possible that phenylephrine-induced renin and PGE2 release involve other mechanisms which are independent of the change in renal blood flow. Blair also showed renin release with non-vasoconstrictor dose of phenylephrine in a recent session abstract (10).

DiBona (11) suggested that renal tubular sodium reabsorption was enhanced by adrenergic stimulation through alpha-adrenoceptors. The macula densa mechanism might also be activated by reduction in sodium delivery to the macula densa during phenylephrine infusion.

Branchevsky (12) demonstrated that phenylephrine has a beta-agonistic effect on the heart. The cardiac beta-receptors are beta-1 type, and it is said that adrenergically induced renin release is mediated by beta-1 receptors (13). Therefore, the effect of an alpha- and/or beta-antagonist on phenylephrine-induced renin release should be examined in further studies.

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REFERENCES
