Prostaglandins and Renin Release

The Effect of PGI₂, PGE₂, and 13,14-Dihydro PGE₂ on the Baroreceptor Mechanism of Renin Release in the Dog

JOHN G. GERBER, ROBERT T. KELLER, AND ALAN S. NIES

SUMMARY We compared the ability of the vasodilator prostaglandins PGI₂, PGE₂, and 13,14-dihydro PGE₂ to release renin when infused into the denervated, nonfiltering canine kidney in vivo. Papaverine was used as a nonprostaglandin vasodilator. All the prostaglandins tested were capable of stimulating renin secretion, with the scale of potency being 13,14-dihydro PGE₂ > PGI₂ > PGE₂; papaverine had no effect on renin secretion. These results indicate that both PGE₂ and PGI₂ can stimulate renin secretion but that vasodilation per se is not a stimulus. 13,14-Dihydro PGE₂ was included because it is a poorer substrate than PGE₂, both for transport into cells and catabolism to inactive products, but has comparable potency to PGE₂ when tested in systems with limited ability to catabolize PGE₂. The fact that 13,14-dihydro PGE₂ was the most potent prostaglandin tested suggests that the effects of PGE₂ in our system are reduced by the kidneys' recognized ability to extract and catabolize PGE₂. Since PGI₂ is less avidly metabolized than PGE₂ by the kidney, the differences in observed potency between PGE₂ and PGI₂ could be largely the result of differences in renal catabolism of the two prostaglandins rather than differences in intrinsic potency. Therefore, both PGE₂ and PGI₂ are candidates for the endogenous prostaglandin responsible for stimulating renin secretion.


WE HAVE recently shown that prostaglandins play a significant role in the intrarenal baroreceptor control of renin release (Data et al, 1978). However, neither the products of arachidonate metabolism responsible for renin release nor the mechanism by which prostaglandins implement renin release have been clarified. There are disagreements regarding which prostaglandin might be important in renin release. Bolger et al. (1978) found that an infusion of prostaglandin E₂ (PGE₂) into the canine renal artery in vivo released renin but that prostaglandin I₂ (PGI₂) did not, whereas Gerber et al. (1978a) reported that PGE₂ and PGI₂ were equipotent in their capacity to release renin in the dog. In vitro, rabbit renal cortical slices responded to PGI₂ by releasing renin into the medium (Wharton et al., 1977); however, PGE₂ was inactive even in high concentrations (Weber et al., 1976).

There are potential explanations for these discrepancies which we felt needed to be examined. Since all the vasodilatory prostaglandins result in significant natriuresis (Tannenbaum et al., 1975; Friesinger et al., 1978; Gerber et al., 1978b), the increased sodium chloride delivery to the macula densa could modulate the renin secretory capacity of these prostaglandins at the juxtaglomerular apparatus. In addition, the rates of renal uptake and/or metabolism of PGE₂ and PGI₂ are different, and this potentially could affect the apparent activity of these prostaglandins (Gerkens et al., 1978).

To clarify which of the prostaglandins have the ability to release renin, we infused PGE₂ and PGI₂ intrarenally into canine nonfiltering kidneys; this procedure eliminates the macula densa component of renin release. In addition, we determined the ability of 13,14-dihydro PGE₂ to release renin, to evaluate the importance of renal uptake and/or metabolism of PGE₂ in determining its activity in vivo. 13,14-Dihydro PGE₂ is a poor substrate for both the catabolic enzyme, prostaglandin 15-hydroxydehydrogenase, and the organic acid transport system for PGE₂, but it still retains the biological activity of the parent prostaglandin (Ånggård and Larsson, 1971; Eling et al., 1977; Ånggård, 1966). Finally, since all three prostaglandins studied result in renal vasodilation, we examined the effect of a nonprostaglandin vasodilator on renin release to assess the importance of renal vasodilation per se on renin release.

Methods

Twelve mongrel dogs of either sex weighing 15-30 kg were used for the intrarenal infusions of the various prostaglandins. The dogs were prepared aseptically under pentobarbital anesthesia (25 mg/kg, iv). Through a left flank incision the left ureter was ligated, and the left renal artery was occluded for 2 hours, as in the procedure described by Blaine....
et al., (1970), to make that kidney nonfiltering. Two days later the dogs were anesthetized with pentobarbital and ventilated through an endotracheal tube with a Harvard respirator. Catheters were inserted into a femoral artery for blood pressure monitoring and into a femoral vein for drug administration.

Through an abdominal incision the right kidney was excised, an electromagnetic flow probe was placed in the left renal artery, and the left kidney was denervated by severing all visible renal nerves and applying a 5% phenol solution to the vessels. The left renal vein was cannulated through the gonadal vein for blood withdrawal to determine plasma renin activity (PRA), and the renal artery was punctured with a curved 25-gauge needle for infusion of the various prostaglandins. The incision was closed and the dog was allowed to stabilize for 30 minutes. All the dogs received propranolol, 0.5 mg/kg, as an intravenous bolus followed by a continuous infusion of 6 µg/kg per min for the remainder of the experiment. Propranolol was administered to effect a β-blockade against circulating catecholamines. In addition, the dogs were treated with indomethacin (8 mg/kg, iv) 30 minutes prior to the experiment to reduce the endogenous production of prostaglandins. The prostaglandins infused intrarenally were PGE2 (3 x 10^-10 and 10^-9 g/kg per min), PGE2 (10^-9 and 10^-8 g/kg per min), and 13,14-dihydro PGE2 (3 x 10^-10 and 3 x 10^-9 g/kg per min). Four of the dogs received an intrarenal infusion of papaverine of 1, 2, and 4 mg/min. The intrarenal infusions were arranged in a balanced cross-over design, each dog receiving only two sets of infusions with a waiting period of at least 1.5 hours between the sets. The compounds were infused in increasing concentrations for a total of 12 minutes at each concentration, with arterial and renal venous samples for PRA taken at 10 minutes after the start of the infusions. Five minutes prior to the start of all sets of infusions, control arterial and renal venous PRA were obtained. Renal blood flows and arterial blood pressures were continuously recorded. PRA was measured by radioimmunoassay, as previously described (Haber et al., 1969). Renin secretory rates were calculated by multiplying the arterial-venous differences in PRA by renal plasma flow. Prior to killing the dogs, we infused a 1% lissamine green solution intrarenally to confirm that the kidneys were indeed nonfiltering.

Statistics on renin secretory rates were done using an adaptation of the signed rank test described by Wilcoxon and Wilcox (1964) for comparing each of several treatments to its own control (two-way classification). Although this test is rather insensitive to the changes of the first dose effect, the non-Gaussian distribution of the renin secretory rates lends to this nonparametric statistical analysis. The renal blood flow changes after the various doses of the prostaglandins were analyzed by Dunn's t-test for multiple comparisons to a control.

## Results

All the compounds infused into the renal artery resulted in significant renal vasodilation, but only the prostaglandins resulted in stimulation of renin secretion (Table 1). The baseline renin secretory rates prior to the prostaglandin infusions were similar in all the groups, allowing for valid comparisons of changes in renin secretion. Of the three prostaglandins, 13,14-dihydro PGE2 appeared to be the most potent stimulator of renin secretion, because it was the only prostaglandin that produced a consistent increase in renin secretory rate at 3 x 10^-10 g/kg per min. PGI2 was the next most potent prostaglandin in this model; it was able to stimulate

<table>
<thead>
<tr>
<th>Infusion rate (per min)</th>
<th>Renin secretory rates (ng angiotensin I/hr per min)</th>
<th>Renal blood flow (ml/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE2</td>
<td>0</td>
<td>10 ± 4.5</td>
<td>89 ± 15</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>10^-9 g/kg</td>
<td>23 ± 9.0</td>
<td>144 ± 26 (P &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>10^-8 g/kg</td>
<td>103 ± 25.7 (P &lt; 0.01)</td>
<td>176 ± 30 (P &lt; 0.01)</td>
</tr>
<tr>
<td>PGI2</td>
<td>0</td>
<td>12 ± 2.4</td>
<td>106 ± 13</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>3 x 10^-10 g/kg</td>
<td>26 ± 7.7</td>
<td>126 ± 13 (P &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>10^-9 g/kg</td>
<td>46 ± 9.0 (P &lt; 0.05)</td>
<td>140 ± 13 (P &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>3 x 10^-8 g/kg</td>
<td>72 ± 15.0 (P &lt; 0.01)</td>
<td>150 ± 17 (P &lt; 0.01)</td>
</tr>
<tr>
<td>H3PGE2</td>
<td>0</td>
<td>12 ± 6.2</td>
<td>92 ± 16</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>3 x 10^-10 g/kg</td>
<td>35 ± 9.3</td>
<td>127 ± 29 (P &lt;0.02)</td>
</tr>
<tr>
<td></td>
<td>3 x 10^-9 g/kg</td>
<td>92 ± 23.7 (P &lt; 0.01)</td>
<td>157 ± 31 (P &lt; 0.01)</td>
</tr>
<tr>
<td>Papaverine</td>
<td>0</td>
<td>25 ± 9</td>
<td>112 ± 42</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>1 mg</td>
<td>19 ± 5</td>
<td>122 ± 46</td>
</tr>
<tr>
<td></td>
<td>2 mg</td>
<td>16 ± 5</td>
<td>140 ± 47 (P &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>4 mg</td>
<td>28 ± 14</td>
<td>157 ± 49 (P &lt; 0.01)</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. H3PGE2 = 13,14-dihydro PGE2.
Significance tested with Dunnett's t-test for multiple comparisons to a control for the renal blood flow, and with modified signed rank test for multiple comparisons for the renin secretory rates.
renin secretion significantly at $10^{-9}$ g/kg per min, whereas PGE$_2$ was inconsistent at this infusion rate, augmenting renin release in only three of seven dogs (Fig. 1).

All the baseline renin values were very low, probably because of the combination of a nonfiltering kidney, renal denervation, $\beta$-adrenergic blockade, and indomethacin pretreatment. The control arterial-venous differences in renin were $0.24 \pm 0.1$ ng of angiotensin $1/\text{hr per ml}$ for PGE$_5$, $0.28 \pm 0.1$ for PG$_{I_2}$, and $0.26 \pm 0.15$ for 13,14-dihydro PGE$_2$. In none of the dogs was there an alteration in systemic arterial pressure with any of the infusions.

**Discussion**

There is increasing evidence that prostaglandins have an important role in renal renin release. Enhanced prostaglandin production by intrarenal infusion of arachidonic acid stimulates renin release, and inhibition of prostaglandin synthesis by indomethacin reduces renin release in many animal species (Larsson et al., 1974; Bolger et al., 1976; Fröligh et al., 1976). Furthermore, we have demonstrated that at least the renal baroreceptor stimulus to renin release is prostaglandin mediated (Data et al., 1978). However, there still remains the question of which renal cortical prostaglandin mediates renin release. Renal cortical microsomes produce mainly PGE$_5$, PGF$_{2\alpha}$, and PG$_{I_2}$ from $[^{14}C]$arachidonic acid (Wharton et al., 1978). Of those three, PGE$_5$ and PG$_{I_2}$ are the most likely candidates. PGF$_{2\alpha}$ has no effect on renal hemodynamics in vivo and inhibits renin release from renal cortical slices in vitro (Weber et al., 1976; Tannenbaum et al., 1975).

Our data indicate that in the denervated, nonfiltering dog kidney model, which isolates the baroreceptors from other stimuli of renin release, PG$_{I_2}$ is more potent in stimulating renin release than PGE$_5$. However, 13,14-dihydro PGE$_2$, a metabolite of PGE$_5$, was slightly more potent than PG$_{I_2}$ and considerably more potent than PGE$_5$. The denervated nonfiltering kidney model we used offers advantages over the intact kidney model. Effects of infusion of prostaglandins into innervated, filtering kidneys must be interpreted with caution, because prostaglandins can produce effects on the macula densa and sympathetic nervous system that may obscure the direct effects on renin release. Thus the ability of infused prostaglandin to release renin may be masked by an increased sodium chloride delivery to the macula densa, which decreases renin secretion. In addition, the effects of prostaglandins to stimulate renin secretion may be diminished by the ability of prostaglandins to decrease norepinephrine release from sympathetic nerves (Hedqvist, 1970). Our model eliminates the other components and focuses on the baroreceptor mechanism of renin release, which is the only mechanism thus far shown to be mediated by prostaglandins (Data et al., 1978).

The differences between our data and those reported by others may be explained by the differences in experimental models. Bolger et al. (1978) demonstrated that PGE$_2$ increased renin secretion in the dog but that PG$_{I_2}$ was inactive. Since in their dogs the kidneys were innervated and filtering, an interaction of the prostaglandins at either the renal sympathetics or at the macula densa might have obscured the primary effects of PG$_{I_2}$ on renin release. However, Gerber et al. (1978a) used dogs with denervated and filtering kidneys and found PGE$_2$ and PG$_{I_2}$ to be equipotent in stimulating renin release. The dogs used by Gerber et al. (1978a) also were pretreated with indomethacin, as were the dogs in the present study, whereas those used by Bolger et al. (1978) were not. This difference suggests that endogenous prostaglandins may alter the renin secretory response to infused prostaglandins. A working hypothesis is that endogenous PG$_{I_2}$ is the important prostaglandin for renin release mediated by the intrarenal baroreceptor, and in the anesthetized laparotomized dog the baroreceptors are activated to stimulate endogenous PG$_{I_2}$. Under these circumstances endogenous PG$_{I_2}$ would occupy the receptors on the juxtaglomerular apparatus and compete with exogenously infused PG$_{I_2}$ resulting in a decrease in apparent potency of exogenous PG$_{I_2}$. However, regardless of the explanation for the discrepancies between published studies, our data clearly indicate that both PG$_{I_2}$ and PGE$_5$ can produce renin release in vivo when exogenous influences on renin secretion are eliminated.

Why doesn’t PGE$_2$ also stimulate renin release from cortical slices in vitro? Clearly, renal vasodilation by itself is not responsible for renin release in vivo, since papaverine vasodilated the renal vasculature without affecting renin release. Although papaverine has been shown by Witty et al. (1971) to inhibit renin release to hemorrhage in the nonfiltering kidney preparation, in the filtering prepara-
tension papaverine had no inhibitory effect on renin release to hemorrhage, indicating that papaverine by itself does not interfere with renin release. Thus, papaverine is a model drug showing that vasodilation and renin release can be dissociated. This would suggest that the action of the prostaglandins on renin release is directly on the juxtaglomerular apparatus, rather than through alterations of arterial wall tension. Since PGE2 is more avidly metabolized by the kidney than PGI2 (Gerkens et al., 1978), it is possible that PGE2 exposed to renal cortical slices is quickly transported into cells and metabolized, whereas PGI2 remains intact and in contact with the cortical tissue for a longer period of time. Our data with 13,14-dihydro PGE2 is consistent with the hypothesis that the net activity observed with a prostaglandin is dependent not only on its intrinsic activity but also on the susceptibility of the prostaglandin to catabolism by an organ. Dihydro PGE2 does not have a greater intrinsic biological activity than PGE2 when tested on isolated tissue preparations with limited ability to catabolize prostaglandins (Ånggård, 1966). However, dihydro PGE2 differs from PGE2 in being a poorer substrate for both transport into cells and catabolism (Ånggård and Larsson, 1971; Eling et al., 1977). Therefore, when exposed to an organ such as the kidney, which is capable of quickly destroying PGE2, dihydro PGE2 would be predicted to have a greater net biological activity. Our data show this to be the case, in that dihydro PGE2 was considerably more potent than PGE2 in releasing renin. Whether these findings can be extrapolated to the differences between PGI2 and PGE2 in vitro will require additional data comparing the uptake and metabolism of these two prostaglandins by renal cortical slices.

From our data we cannot conclude which of the two prostaglandins, PGI2 or PGE2, is responsible for renin release, but PGI2 is more potent in the baroreceptor-isolated system. The final conclusions concerning the prostaglandins will depend on a very accurate and sensitive measurement of PGI2, PGE2, and their metabolites across the kidney. Such a measurement is not possible at this time.

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