Modulation by Prostaglandins of Adrenergic Transmission in the Isolated Perfused Rabbit and Rat Kidney

By Kafait U. Malik and John C. McGiff

ABSTRACT

In the isolated perfused rabbit kidney prostaglandins (PGs) E1, (0.02-0.1 ng/ml), E2 (0.02-0.1 ng/ml), and A2 (1-5 ng/ml) inhibited the vasoconstrictor responses to sympathetic nerve stimulation by 21-44%, 31-39%, and 20-23%, respectively, without altering those to injected norepinephrine. In contrast, in the rat kidney PGE1, (0.5 ng/ml), PGE2 (0.5 ng/ml), and PGA2 (5 ng/ml) enhanced the vasoconstrictor responses to sympathetic nerve stimulation by 41%, 27%, and 11%, respectively; the equiconstrictor responses to injected norepinephrine remained unaltered. Higher concentrations of these agents produced vasodilation in the rabbit kidney and vasoconstriction in the rat kidney. In both species PGF2α produced vasoconstriction and enhanced the responses to both adrenergic stimuli. In the rabbit kidney inhibitors of PG synthesis augmented the responses to sympathetic nerve stimulation without altering those to injected norepinephrine, whereas in the rat kidney inhibition of the responses to both adrenergic stimuli occurred. Arachidonic acid inhibited the vasoconstrictor responses to sympathetic nerve stimulation in the rabbit kidney, but in the rat kidney it caused augmentation of these responses. Since these effects of arachidonic acid were reduced by indomethacin, they appear to be mediated through the acid's conversion to PGs. We conclude that PGs of the E series modulate adrenergic transmission in the kidney and that their modulatory actions are species dependent.

KEY WORDS

sympathetic stimulation
adrenergic transmitter
indomethacin
renal vasculature
vasoconstrictor responses
norepinephrine release mechanism
inhibition of prostaglandin synthesis
meclofenamate
arachidonic acid

Prostaglandins (PGs), particularly those of the E series, have been shown to modulate adrenergic transmission in several tissues (1-3). PGE1 and PGE2 reduce the response to sympathetic nerve stimulation by inhibiting the release of the adrenergic transmitter. After inhibition of PG synthesis, the response to nerve stimulation is enhanced as a result of an increased release of norepinephrine (2, 4). PG-adrenergic interactions also occur in the kidney where PGs may constitute an important regulatory system (5). Thus, in addition to having potent renal vasodilator-diuretic actions, PGE2 and to a lesser extent PGA2 antagonize the renal vasoconstrictor and antiuretic actions of sympathetic nerve stimulation. These observations taken together with the high PG biosynthetic capacity of the kidney (6) and the ability of both norepinephrine and sympathetic nerve stimulation to release a PGE-like material (7-9) suggest that PGs may modulate the activity of the adrenergic nervous system within the kidney. The present study was undertaken to explore the role of PGs in the regulation of sympathetic activity in the rabbit and rat renal vascular beds. The effect of PGs of the E and A series on vascular tone and adrenergic transmission is species dependent. In the rabbit kidney PGE1, PGE2, and PGA2 dilate the vascular bed and inhibit adrenergic transmission, whereas in the rat kidney these agents constrict the vasculature and facilitate adrenergic transmission.

Methods

Experiments were performed on albino rabbits of both sexes weighing 2-3 kg and male Sprague-Dawley rats weighing 300-350 g. Rabbits were anesthetized with sodium pentobarbital (30 mg/kg, iv) and rats with ether. The abdomen was opened by a midline incision, and the kidney, the renal artery, and the abdominal aorta were exposed. The renal artery was separated from its surrounding tissue, and the aorta was ligated below and above the renal artery. A polyethylene cannula was inserted into the renal artery and flushed with heparinized saline (100 units/ml). The kidney was isolated with the renal vein and the ureter intact and immediately transferred to a thermostatically controlled Plexiglas box where it was covered with a cotton gauze moistened with...
Tyrode’s solution. The fluid perfusing the kidney flowed from the cut end of the renal vein and the ureter. The rabbit and rat kidneys were perfused at constant rates, 15 and 6 ml/min, respectively, using a Harvard peristaltic pump (model 1210). Tyrode’s solution of the following millimolar composition was used: NaCl 137, KCl 2.7, CaCl₂ 1.8, MgCl₂ 1.1, NaHCO₃ 12, NaH₂PO₄ 0.42, and d(-)+glucose 5.6. The perfusion fluid was maintained at a temperature of 37°C and aerated with a 95% O₂-5% CO₂ mixture. Changes of perfusion pressure in the rabbit kidney were measured with a manometer and recorded on a kymograph using an isotonic frontal-writing lever. The position of the lever was kept at an angle of either 100° or 70°. In the rat kidney, changes in perfusion pressure were measured with a Statham strain-gauge pressure transducer and recorded on an Esterline Angus physiograph. Before cannulation of the renal artery, in the rabbit the pressure in the cannula was 50 mm Hg at a flow rate of 15 ml/min, whereas in the rat it was 16 mm Hg at a flow rate of 6 ml/min. During perfusion of the kidney of either species, the average pressure in the cannula was 85 mm Hg (range 75 to 100 mm Hg).

A bipolar platinum electrode was placed on the periarterial nerve plexus about 3 mm distal to the cannula. The nerves were stimulated at 2 Hz using supramaximal biphasic rectangular pulses 1 msec in duration for 22 seconds at 4-minute intervals. Equivalent vasoconstrictor responses to exogenous norepinephrine were obtained by infusing norepinephrine (50–75 ng) at 4-minute intervals directly into the cannula leading to the renal artery for 15–22 seconds with a Braun-Melsungen infusion pump. The following drugs were used: norepinephrine bitartrate (Levophed, Winthrop Labs), prostaglandins E₁, E₂, A₁, and F₂₀ (Upjohn Co.),¹ indomethacin (Merck, Sharp & Dohme), sodium meclofenamate (Parke, Davis & Co.), hexamethonium bromide (K & K Labs), dl-isoproterenol hydrochloride (Aldrich Chemical Co.), propranolol (Ayerst Labs), guanethidine (CIBA), and arachidonic acid (99% pure), acetylcholine chloride, atropine sulfate, and 6-hydroxydopamine (Sigma Chemicals).

Prostaglandins and arachidonic acid were initially dissolved in ethanol (1 mg/ml), but further dilutions were made with Tyrode’s solution. The small amounts of ethanol present in these solutions did not affect the vascular tone or the vasoconstrictor responses to nerve stimulation and injected norepinephrine. All other drugs were dissolved in Tyrode’s solution. Norepinephrine was injected into the arterial cannula, and the other agents were added to the perfusion fluid to obtain the final concentration.

Paired and unpaired t-tests were performed according to the methods described by Steel and Torrie (10).

**Results**

**EFFECT OF PERIARTERIAL NERVE STIMULATION ON PERFUSION PRESSURE IN THE ISOLATED RABBIT AND RAT KIDNEY**

The isolated rabbit and rat kidney perfused with Tyrode’s solution maintained a steady basal perfusion pressure even after prolonged periods of perfusion for up to 4 hours. The weights of the rabbit and rat kidneys, which averaged 13.5 g (range 9 to 20 g) and 1.6 g (range 1.5 to 1.8 g), respectively, did not change after perfusion for 4 hours. Stimulation of periarterial nerves at frequencies of 1–2 Hz or infusion of norepinephrine directly into the arterial cannula constricted the renal blood vessels and raised the perfusion pressure. Responses to nerve stimulation or injected norepinephrine at 4-minute intervals remained stable for 4 hours. The vasoconstrictor responses to nerve stimulation in both the rabbit and the rat kidney were abolished after pretreatment with 6-hydroxydopamine (10 mg/kg twice in 48 hours), which produces selective degeneration of adrenergic nerve terminals (11). Since the responses to nerve stimulation in both species were blocked by the adrenergic neuron blocking agent guanethidine (0.5 µg/ml) (12) and slightly potentiated by hexamethonium (100 µg/ml), a ganglionic blocking agent (13), the periarterial nerves are primarily postganglionic adrenergic nerves.

**EFFECT OF PROSTAGLANDINS E₁, E₂, A₁, AND F₂₀ ON THE PERFUSION PRESSURE IN THE RABBIT AND RAT KIDNEY**

**Rabbit Kidney.**—Infusion of either PGE₁ (0.1 ng/ml) (11 experiments), PGE₂ (0.1 ng/ml) (11 experiments), PGA₂ (5 ng/ml) (12 experiments), or PGF₂₀ (5 ng/ml) (12 experiments), did not alter the basal perfusion pressure. In an additional 34 experiments, PGE₁ (0.5 ng/ml), PGE₂ (0.5 ng/ml), and PGA₂ (25 ng/ml) were either ineffective or produced a fall of 2–2.5 mm Hg (average 2.3 mm Hg) in 4 of 11, 3 of 11, and 5 of 12 experiments, respectively. In contrast, PGF₂₀ (25 ng/ml) caused an increase of 1.5–2 mm Hg in 6 of 11 experiments. Higher concentrations of PGE₁ or PGE₂ (5 ng/ml) and of PGA₂ (50 ng/ml) invariably produced a fall in perfusion pressure, whereas higher concentrations of PGF₂₀ (50 ng/ml) increased perfusion pressure (P < 0.001) (Fig. 1, Table 1).

To determine if the vasodilator actions of PGE₁, PGE₂, and PGA₂ were related to stimulation of either muscarinic or β-adrenergic receptors, we studied possible modification by atropine and propranolol of the effects of prostaglandins on basal pressure. Atropine and propranolol in doses of 10 ng/ml completely abolished the vasodilator action of 10 ng/ml of acetylcholine and 10 ng/ml of isoproterenol, but they did not alter the fall in basal perfusion pressure produced by PGE₁ and PGE₂ (5 ng/ml) or by PGA₂ (50 ng/ml) (four experiments). To determine if the vasoconstriction produced by PGF₂₀ (50 ng/ml) was due to its effect...
on vascular smooth muscle or to liberation of norepinephrine from the sympathetic fibers, we examined the effect of an adrenergic blocking agent, phentolamine (14). Phentolamine (100 ng/ml) completely abolished the renal vasoconstrictor response to injected norepinephrine (50-75 ng) but it did not affect the response produced by PGF$_{2\alpha}$ (50 ng/ml).

**Rat Kidney.**—Infusion of either PGE$_1$ (0.5 ng/ml), PGE$_2$ (0.5 ng/ml), PGF$_{2\alpha}$ (5.0 ng/ml), or PGA$_2$ (5.0 ng/ml) (6 experiments with each PG) did not alter the basal perfusion pressure. PGE$_1$ or PGE$_2$ at 2.5 ng/ml and PGA$_2$ or PGF$_{2\alpha}$ at 25 ng/ml were either ineffective or increased perfusion pressure 5-20 mm Hg (average 11 mm Hg) in 7 of 10, 7 of 9, 6 of 11, and 7 of 10 experiments, respectively. Higher

<table>
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<th>Substance</th>
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<th>Rat kidney</th>
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<td>PGE$_1$ (5 ng/ml)</td>
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<td>PGA$_2$ (50 ng/ml)</td>
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<td>PGF$_{2\alpha}$ (50 ng/ml)</td>
<td>$+3.6 \pm 0.3$</td>
<td>$&lt; 0.001$</td>
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<td>Indomethacin (5 µg/ml)</td>
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<td>Meclofenamate (5 µg/ml)</td>
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All values for changes in perfusion pressure are means ± SE. N = number of experiments.

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concentrations of PGE₁ (5 ng/ml), PGE₂ (5 ng/ml), PGA₂ (50 ng/ml), or PGF₂α (50 ng/ml) usually decreased perfusion pressure 2–3 mm Hg transiently; an invariable increase in perfusion pressure then followed (Fig. 1, Table 1). Phentolamine (100 ng/ml), which completely abolished the renal vasoconstrictor responses to injected norepinephrine (50–75 ng), did not alter the renal vasoconstriction produced by PGE₁ (5 ng/ml), PGE₂ (5 ng/ml), PGA₂ (50 ng/ml), or PGF₂α (50 ng/ml) (3 experiments with each PG). Moreover, the vasoconstrictor response to these agents was not altered in the kidneys of rats pretreated with 6-hydroxydopamine (11) (3 experiments).

**Effect of Prostaglandins E₁, E₂, A₁, and F₂α on the Vasoconstrictor Responses of Rabbit and Rat Kidneys to Sympathetic Nerve Stimulation and Injected Norepinephrine**

**Rabbit Kidney.**—Infusions of PGE₁ (0.02 ng/ml), PGE₂ (0.02 ng/ml), or PGA₂ (1 ng/ml) for 16–20 minutes did not alter the basal perfusion pressure and were either ineffective or reduced the vasoconstrictor responses to nerve stimulation; an equiconstrictor response to injected norepinephrine remained unaltered (Table 2). PGE₁ (0.1 ng/ml), PGE₂ (0.1 ng/ml), or PGA₂ (5 ng/ml) invariably reduced the vasoconstrictor responses to nerve stimulation without altering an equiconstrictor response to injected norepinephrine (Figs. 2 and 3, Table 2). Higher concentrations of PGE₁ (5 ng/ml), PGE₂ (5 ng/ml), and PGA₂ (25 ng/ml) usually produced a fall in the basal perfusion pressure and reduced the vasoconstrictor responses to nerve stimulation to a greater degree than they did an equiconstrictor response to injected norepinephrine (Table 2).

Infusion of PGF₂α (1 ng/ml) slightly potentiated the vasoconstrictor response to nerve stimulation in two of seven experiments, whereas the equiconstrictor response to injected norepinephrine and the basal perfusion pressure remained unaltered (Table 2). PGF₂α (5 ng/ml) invariably potentiated the vasoconstrictor responses to nerve stimulation more than it did an equiconstrictor response to injected norepinephrine (Table 2). Higher concentrations of PGF₂α (25 ng/ml) usually increased perfusion pressure 1.5–2 mm Hg and potentiated the vasoconstrictor responses to both nerve stimulation and injected norepinephrine; the degree of potentiation of responses to nerve stimulation was greater than that of responses to injected norepinephrine (Table 2).

**Rat Kidney.**—Infusion of PGE₁ (0.1 ng/ml), PGE₂ (0.1 ng/ml), PGA₂ (1 ng/ml), or PGF₂α (1 ng/ml) usually decreased perfusion pressure 2–3 mm Hg transiently; an invariable increase in perfusion pressure then followed (Fig. 1, Table 1). Phentolamine (100 ng/ml), which completely abolished the renal vasoconstrictor responses to injected norepinephrine (50–75 ng), did not alter the renal vasoconstriction produced by PGE₁ (5 ng/ml), PGE₂ (5 ng/ml), PGA₂ (50 ng/ml), or PGF₂α (50 ng/ml) (3 experiments with each PG). Moreover, the vasoconstrictor response to these agents was not altered in the kidneys of rats pretreated with 6-hydroxydopamine (11) (3 experiments).

**Table 2**

Effect of Prostaglandins, Arachidonic Acid, and Inhibitors of Prostaglandin Synthesis on Equiconstrictor Responses to Sympathetic Nerve Stimulation and Injected Norepinephrine in the Rabbit Kidney

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<th>Substance</th>
<th>Dose (ng/ml)</th>
<th>N</th>
<th>Response to NS (% change)</th>
<th>N</th>
<th>Response to NE (% change)</th>
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<td>-44 ± 4†</td>
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<tr>
<td></td>
<td>0.5†</td>
<td>7</td>
<td>-60 ± 6†</td>
<td>4</td>
<td>-47 ± 5†</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PGE₂</td>
<td>0.02</td>
<td>2</td>
<td>-31 ± 2†</td>
<td>5</td>
<td>0</td>
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<tr>
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<td>0.1</td>
<td>6</td>
<td>-39 ± 3†</td>
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<tr>
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<td>0.5†</td>
<td>6</td>
<td>-47 ± 5†</td>
<td>5</td>
<td>-28 ± 5*</td>
<td>&lt; 0.01</td>
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<td>PGA₂</td>
<td>1.0</td>
<td>6</td>
<td>-20 ± 4*</td>
<td>3</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>1.0†</td>
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<td>-23 ± 2†</td>
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<td></td>
<td>5.0</td>
<td>6</td>
<td>-25 ± 2†</td>
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<tr>
<td></td>
<td>25.0†</td>
<td>5</td>
<td>-65 ± 8†</td>
<td>6</td>
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<tr>
<td>PGF₂α</td>
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<td>4</td>
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<tr>
<td></td>
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Response values are means ± se. NS = nerve stimulation and NE = norepinephrine; N = number of experiments.

* P < 0.01.
† P < 0.001.
‡ Dose which usually produced a fall in basal pressure (average 2.3 mm Hg).
§ P < 0.1.
‖ Dose which raised basal pressure (average 1.7 mm Hg).
MODULATION OF SYMPATHETIC TRANSMISSION

Effect of PGE₁ and PGE₂ on the vasoconstrictor responses of isolated perfused rabbit (top) and rat (bottom) kidneys to sympathetic nerve stimulation (NS) and on the equiconstrictor responses to injected norepinephrine (NE). Sympathetic nerves to the renal vessels were stimulated for 22 seconds at 4-minute intervals. Norepinephrine (30-75 ng) was injected directly into the arterial cannula at 4-minute intervals.

ng/ml) in the rat kidney did not alter the basal perfusion pressure or the vasoconstrictor responses to nerve stimulation or injected norepinephrine. PGE₁ (0.5 ng/ml), PGE₂ (0.5 ng/ml), PGA₂ (5 ng/ml), or PGF₂α (5 ng/ml) infused for 16-20 minutes potentiated the vasoconstrictor responses to nerve stimulation; the equiconstrictor responses to injected norepinephrine were increased only transiently by PGE₁, and unaffected by PGE₂, PGA₂, and PGF₂α (Figs. 2-4, Table 3). Higher concentrations of PGE₁ (2.5 ng/ml), PGE₂ (2.5 ng/ml), PGA₂ (25 ng/ml), and PGF₂α (25 ng/ml) usually increased the basal perfusion pressure by an average of 11 mm Hg and consistently potentiated the vasoconstrictor responses to both nerve stimulation and injected norepinephrine; the augmentation of the responses to nerve stimulation was greater than that of the responses to injected norepinephrine (Table 3).

Ng/ml in the rabbit kidney did not alter the basal perfusion pressure or the vasoconstrictor responses to nerve stimulation or injected norepinephrine. PGE₁ (0.5 ng/ml), PGE₂ (0.5 ng/ml), PGA₂ (5 ng/ml), or PGF₂α (5 ng/ml) infused for 16-20 minutes potentiated the vasoconstrictor responses to nerve stimulation; the equiconstrictor responses to injected norepinephrine were increased only transiently by PGE₁, and unaffected by PGE₂, PGA₂, and PGF₂α (Figs. 2-4, Table 3). Higher concentrations of PGE₁ (2.5 ng/ml), PGE₂ (2.5 ng/ml), PGA₂ (25 ng/ml), and PGF₂α (25 ng/ml) usually increased the basal perfusion pressure by an average of 11 mm Hg and consistently potentiated the vasoconstrictor responses to both nerve stimulation and injected norepinephrine; the augmentation of the responses to nerve stimulation was greater than that of the responses to injected norepinephrine (Table 3).

MODIFICATION BY INDOMETHACIN AND MECLOFENAMATE OF THE EFFECTS OF PROSTAGLANDINS E₁, E₂, A₂, AND F₂α ON PERFUSION PRESSURE AND VASOCONSTRICTOR RESPONSES TO SYMPATHETIC NERVE STIMULATION AND INJECTED NOREPINEPHRINE IN THE RABBIT AND RAT KIDNEY

Rabbit Kidney.—To determine whether the fall in basal perfusion pressure produced by infusion of exogenous PGE and PGA compounds and the increase in perfusion pressure produced by PGF₂α in the rabbit kidney (Fig. 1) are modified by inhibition of endogenous PG synthesis, we examined the effect of indomethacin and meclofenamate on these actions of exogenous PGs (15). Neither anti-inflammatory agent in concentrations of 0.1-1 μg/ml in the rabbit kidney affected the basal perfusion pressure, the vasodilator actions of PGE₁ (5 ng/ml), PGE₂ (5 ng/ml), PGA₂ (50 ng/ml), acetylcholine (10 ng/ml), or isoproterenol (10 ng/ml), or the vasoconstrictor effect of PGF₂α (50 ng/ml). However, in higher concentrations, indomethacin (5 μg/ml) and meclofenamate (5 μg/ml) had significant direct but opposite effects on renal vascular resistance: indomethacin increased and meclofenamate decreased perfusion pressure (Table 1). We, therefore, used the lower concentrations of these agents to determine the effects of inhibition of PG synthesis on the renal vasoconstrictor responses to adrenergic stimuli. Infusion of indomethacin or meclofenamate (0.1-1 μg/ml) for 16-30 minutes augmented (P < 0.001) the vasoconstrictor responses to nerve stimulation; the equiconstrictor responses to injected norepinephrine remained unaltered (Figs. 5 and 6, Table 2). Potentiation of the vasoconstrictor response to
nerve stimulation produced by indomethacin or meclofenamate in the rabbit kidney was abolished by the simultaneous infusion of either PGE₁ (100 pg/ml), PGE₂ (100 pg/ml) or PGA₂ (5 ng/ml) (three experiments).

**Rat Kidney.**—The rise in perfusion pressure (vasoconstriction) produced by PGE₁ (5 ng/ml), PGE₂ (5 ng/ml), PGA₂ (50 ng/ml), and PGF₂α (50 ng/ml) in the rat kidney (Fig. 1) was unaffected by the simultaneous infusion of indomethacin or meclofenamate (0.1 μg/ml) (three experiments with each agent). Higher concentrations (5 μg/ml) of these anti-inflammatory agents produced a fall in the basal perfusion pressure (Table 1).

Indomethacin and meclofenamate (1 μg/ml) reduced to a similar degree the vasoconstrictor responses to nerve stimulation and injected norepinephrine (Table 2). Lower concentrations (100 ng/ml) of these agents were ineffective or produced a decrease of 5–6 mm Hg in the responses to adrenergic stimuli (three experiments). The simultaneous infusion of PGE₁ (0.5 ng/ml), PGE₂ (0.5 ng/ml), PGA₂ (5.0 ng/ml), or PGF₂α (5.0 ng/ml) abolished the inhibitory effect of indomethacin or meclofenamate on the vasoconstrictor responses to nerve stimulation (four experiments with each agent). Higher concentrations of PGE₁ (1 ng/ml), PGE₂ (1 ng/ml), PGA₂ (10.0 ng/ml), and PGF₂α (10.0 ng/ml) also abolished the action of these anti-inflammatory agents on the vasoconstrictor responses to injected norepinephrine (three experiments with each drug).

**EFFECT OF ARACHIDONIC ACID ON PERFUSION PRESSURE AND VASOCONSTRICTOR RESPONSES TO SYMPATHETIC NERVE STIMULATION AND INJECTED NOREPINEPHRINE AND ITS MODIFICATION BY INDOMETHACIN IN RABBIT AND RAT KIDNEY**

To determine if increased endogenous formation of PGs affects vascular tone and adrenergic transmission, we examined the effect of a PG precursor, arachidonic acid (16), and the modification of its action by indomethacin in the rabbit and rat kidney.

**Rabbit Kidney.**—Infusion of arachidonic acid (100 ng/ml) for 4–12 minutes produced a fall (P < 0.001) in perfusion pressure (Fig. 7, Table 1); lower concentrations (10 ng/ml) were ineffective. The degree of fall in perfusion pressure produced by repeated infusions of arachidonic acid at 30–40-
### Table 3

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<tr>
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<th>Response to NE (% change)</th>
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<td>+73 ± 17§</td>
<td>+37 ± 7†</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>PGF₂0</td>
<td>1.0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>+25 ± 3*</td>
<td>6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>25.0†</td>
<td>+83 ± 17†</td>
<td>+39 ± 7†</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>10.0</td>
<td>+12 ± 2*</td>
<td>5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1000.0</td>
<td>-34 ± 4*</td>
<td>-25 ± 2*</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Meclomenate</td>
<td>1000.0</td>
<td>-31 ± 3*</td>
<td>-24 ± 3*</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

Response values are means ± SE. NS = nerve stimulation and NE = norepinephrine; N = number of experiments.

* P < 0.001.
† Dose which usually raised the perfusion pressure (average 11 mm Hg).
§ P < 0.01.
‡ P < 0.05.

![Figure 5](http://circres.ahajournals.org/)

**Figure 5**

Effect of indomethacin on the vasoconstrictor responses of isolated perfused rabbit (top) and rat (bottom) kidneys to sympathetic nerve stimulation (NS) and on the vasoconstrictor responses to injected norepinephrine (NE).

Minute intervals remained unaltered. However, during infusion of indomethacin for 40–60 minutes, the vasodilator effect of arachidonic acid in the rabbit kidney was reduced (P < 0.001) by 57 ± 5% (13 experiments). Perfusion with indomethacin-free Tyrode's solution for 30–60 minutes partially restored the effect of arachidonic acid (Fig. 7).

Arachidonic acid at a concentration (10 ng/ml) that did not alter the basal perfusion pressure reduced the vasoconstrictor responses to sympathetic nerve stimulation; the vasoconstrictor responses to injected norepinephrine remained unaltered (Fig. 7C, Table 2). The inhibition produced by arachidonic acid of the vasoconstrictor responses to nerve stimulation in the rabbit kidney was abolished by the simultaneous infusion of indomethacin (0.1–1 μg/ml), and the magnitude of the responses to nerve stimulation was increased above the height of control responses (five experiments) (Fig. 7).

**Rat Kidney.**—Arachidonic acid (100 ng/ml) infused for 4–12 minutes increased the perfusion pressure (Fig. 7, Table 1); lower concentrations (10 ng/ml) were ineffective. The repeated administration of arachidonic acid at 30-40-minute intervals produced a similar degree of increase in perfusion pressure. During infusion of indomethacin for 40–60 minutes, the effect of arachidonic acid in the rat kidney (vasoconstriction) was reduced (P < 0.001) by 76 ± 4% (eight experiments) (Fig. 7). Perfusion with indomethacin-free Tyrode's solution for 30–60 minutes partially restored the effect of arachidonic acid.

The vasoconstrictor responses to nerve stimula-
tion in the rat kidney were augmented by infusion of arachidonic acid (10 ng/ml); an equiconstrictor response to injected norepinephrine remained unaffected (Table 3). The augmentation in the vasoco- 

Discussion

Infusion of PGE₁, PGE₂, or PGA₂ dilated the rabbit renal vasculature. This effect was not due to stimulation of either muscarinic or β-adrenergic receptors, since atropine and propranolol did not alter the vasodilator action of these PGs. In contrast, PGE₁, PGE₂, and PGA₂ constricted the rat renal vasculature. PGF₂α produced renal vasoconstriction in both species. The vasoconstrictor effect of PGE₁, PGE₂, PGA₂ and PGF₂α in the rat kidney and that of PGF₂α in the rabbit kidney was not due to stimulation of α-adrenergic receptors or to release of catecholamines from sympathetic fibers, since phentolamine and chemical sympathectomy did not alter the vasoconstrictor actions of the PGs. These observations indicate major species differences in the response of renal vasculature to PGs of the E and A series. Although PGs of the E and A series have been shown to dilate some vascular beds, including the renal bed, of most animal species (5, 17-21), these agents have also been reported to constrict other vascular beds (22).

In addition to their actions on renal vascular
smooth muscle—dilation in the rabbit and constriction in the rat—PGEm, PGE2, and PGA2 affected adrenergic transmission differently in these two species. In the rabbit kidney PGs of the E and A series reduced the vasoconstrictor responses to nerve stimulation in concentrations lower than those required to decrease the vascular tone and the vasoconstrictor responses to injected norepinephrine. Higher concentrations, which usually produced a fall in the basal perfusion pressure, were either ineffective or reduced the vasoconstrictor responses to injected norepinephrine to a lesser degree than they did the responses to nerve stimulation (Table 2). Therefore, it appears that the attenuation of the vasoconstrictor responses to nerve stimulation by PGE1, PGE2, and PGA2 is due to diminished release of the adrenergic transmitter. Similar results have been reported by Frame et al (23) for PGE2 in the perfused rabbit kidney. These observations are supported by the demonstration that PGs of the E series inhibit release of the adrenergic transmitter as a result of sympathetic nerve stimulation in various tissues (1, 2).

The present results and the high PG synthetic capacity of the kidney (6) raise the possibility that endogenous PGs modulate adrenergic transmission in the renal vascular bed. This hypothesis is supported by our demonstration that either facilitation or inhibition of adrenergic transmission in the rabbit kidney can be achieved by either decreasing PG synthesis with anti-inflammatory agents or increasing PG synthesis with arachidonic acid, respectively. Indomethacin and meclofenamate augmented the vasoconstrictor responses to nerve stimulation in concentrations that neither altered the basal perfusion pressure, an index of vascular tone, nor affected the equiconstrictor responses to injected norepinephrine. This effect of PG inhibitors is most probably due to enhanced release of the adrenergic transmitter as a result of diminished PG synthesis (24–26). This view is further supported by the observation that exogenous PGE1 and PGE2 in low concentrations abolished potentiation of the vasoconstrictor responses to nerve stimulation produced by either indomethacin or meclofenamate in the rabbit kidney. Similar results have been reported in the dog spleen by Ferreira et al. (27). Moreover, in cat spleen, outflow of norepinephrine in response to nerve stimulation is reduced by PGE2 but is not altered by inhibition of PG synthesis (26). The proposed role of endogenous PGs as modulators of adrenergic transmission in the rabbit kidney is strengthened by our demonstration that a PG precursor, arachidonic acid (16), inhibited the vasoconstrictor response to nerve stimulation. This effect of arachidonic acid is presumably due to decreased release of the adrenergic transmitter, since it is produced by concentrations that do not affect either vascular tone or the equiconstrictor responses to injected norepinephrine. Higher concentrations of arachidonic acid decreased the vascular tone in the rabbit kidney. The inhibitory actions of arachidonic acid on vascular tone and the vasoconstrictor responses to nerve stimulation in the rabbit kidney are most likely mediated at least in part through its conversion to PGs, since these effects are reduced or prevented by indomethacin. These observations taken together with the effect of exogenous PGs support the hypothesis (1) that PGs of the E series may function as a physiological braking mechanism of release of the adrenergic transmitter in the rabbit kidney.

Our experiments, however, challenge the extension of this hypothesis (1) to all animal species. In the rat kidney, PGs of the E and A series (PGE1, PGE2, and PGA2) augmented the vasoconstrictor responses to sympathetic nerve stimulation. Since these effects were produced by concentrations that neither altered the vasoconstrictor responses to injected norepinephrine nor produced a degree of augmentation in the vasoconstrictor responses to nerve stimulation with that to injected norepinephrine, they are most likely due to enhanced release of the adrenergic transmitter. Facilitation of adrenergic transmission by PGs of the E and A series is not unique to the rat kidney; it occurs in other adrenergic tissues such as rat mesenteric arteries (28) and canine hindpaw vasculature (29). Since exogenous PGs of the E and A series facilitate adrenergic transmission in the rat kidney, the inhibition of PG synthesis should produce an opposite effect. Thus, in the rat kidney, indomethacin and meclofenamate reduced the vasoconstrictor responses to nerve stimulation without altering the basal pressure. Since the vascular responses to injected norepinephrine were also reduced, the inhibitory effect of these agents on the responses to nerve stimulation could be the result of decreased vascular reactivity to norepinephrine. A role of endogenously generated PGs in modulating adrenergic transmission in the rat kidney was also suggested by the effects of arachidonic acid, the precursor of PGE2 and PGF2α. Arachidonic acid augmented the vasoconstrictor responses to nerve stimulation without affecting those to injected norepinephrine. In higher concentrations arachidonic acid produced a direct constrictor effect on rat renal blood vessels. Since the latter effect as well as the former was diminished by indometha-
cin, these findings are consistent with the hypothesis that the effects of arachidonic acid on vascular tone and adrenergic transmission are at least in part mediated by its intrarenal conversion to PGs.

The results of this study taken together with the demonstration of the synthesis of PGs of the E, A, and F series in the rabbit and rat kidney (30, 31) strongly suggest their participation in the modulation of sympathetic nervous activity. Although the pattern of PG release in response to adrenergic nerve stimulation in the rat kidney has not been established, there is evidence supporting the augmented release of PGs of the E and F series and to a minor extent those of the A series from the rabbit kidney in response to nerve stimulation (9). Of the renal PGs that we have investigated, PGs of the E series are the most likely mediators of adrenergic transmission in the rabbit kidney. Thus, the effects of inhibition of PG synthesis by anti-inflammatory agents (facilitation of adrenergic transmission) and enhancement of PG synthesis by arachidonic acid (inhibition of adrenergic transmission) in the rabbit kidney are best explained on the basis of reduced and enhanced synthesis, respectively, of PGs of the E series. The intrarenal role of PGF2α, the second major prostaglandin in the kidney (30, 31) is uncertain. The failure of PG synthetase inhibitors to produce an effect on adrenergic transmission consistent with that expected as a result of diminished synthesis of PGF may be due to the relatively low synthesis of PGF compounds in the rabbit kidney compared with that of PGE compounds (30). Moreover, the concentration of PGF2α needed to affect adrenergic transmission in the rabbit and rat kidneys was 10–50 times greater than that of PGE1 and PGE2. Similarly, the involvement of renal PGA2 as a physiological modulator of adrenergic transmission is uncertain in view of the lack of conclusive evidence supporting its natural occurrence in the kidney (30). Moreover, PGA2 modified adrenergic transmission in the kidneys of both species in concentrations 10–50 times greater than those of PGE1 and PGE2. These observations and the demonstration in the rat kidney of the presence of PGE in concentrations greater than those of PGA and PGF (31) and the release of a PGE2-like substance in response to administration of isoproterenol (32) suggest that PGs of the E series are also the physiological modulators of adrenergic transmission in this species. The opposite effects in the rabbit and rat kidney of exogenous PGE1, PGE2, and PGA2 as well as endogenous PGs could be the result of major differences in PG receptors or the events resulting from PG-receptor interaction in these species. Finally, the present work suggests that, for those studies in which the definition of an antihypertensive role for PGs is the major objective, the use of the rat would not be suitable, since PGs of the E and A series may be prohypertensive in this species.

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