Role of Prostaglandins in the Control of Renin Secretion in the Dog

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SUMMARY Infusion of indomethacin into anesthetized, salt-depleted dogs caused an increase in mean arterial blood pressure (MABP), and decreases in heart rate (HR), urine flow rate (V), renal plasma flow (RPF), and renin secretion rate. MABP was 112.1 ± 5.4 mm Hg (P < 0.005) 80 minutes after the infusion of indomethacin. V was 0.38 ± 0.06 ml/min during control periods and was 0.08 ± 0.01 ml/min (P < 0.005) 80 minutes after the infusion of indomethacin. RPF was 126.3 ± 13.3 ml/min and 41.5 ± 7.5 ml/min, respectively (P < 0.005), before and after 80 minutes of infusion. Renin secretion rate decreased from 1,194.1 ± 383.9 U/min during control periods to reach 384.0 ± 125.8 U/min (P < 0.025) by 80 minutes of infusion of indomethacin. Subsequent infusion of prostaglandin E1 (PGE1) into the renal artery for 80 minutes caused increases of V to 0.53 ± 0.13 ml/min (P < 0.01), of RPF to 102.4 ± 23.1 ml/min (P < 0.01), and of renin secretion rate to 2,582.6 ± 786.4 U/min (P < 0.005). The decrease in renin secretion rate during the infusion of indomethacin persisted when renal perfusion pressure (RPP) was maintained relatively constant before and during the infusion of indomethacin. Furthermore, we found that infusion of prostaglandin E1 (PGE1) into the kidney gave the same pattern of response as PGE2. The data suggest that PGE1 and PGE2 play a role in the control of renin secretion.

Prostaglandins have been found in a variety of animal tissues and appear to possess some biological activities in the preparations in which they have been studied.1-3 It has been reported that synthesis of prostaglandins of the E and F series takes place in the kidney and that those of the E series are released following many types of stimulus. Although much work has been done on the role of prostaglandins in renal function, relatively little has been done to examine the role of prostaglandins in the control of renin secretion.4-6 The present investigation was made to examine this role. It appeared that if prostaglandins play a role in the control of renin secretion, infusion of a prostaglandin synthetase inhibitor into the kidney should cause a decrease in renin release. Furthermore, infusion of prostaglandins into the kidney should lead to an increase in renin release.

Methods

Female mongrel dogs (body weight, 14-21 kg) were used in the experiments. Except for the dogs used in protocol 3, they were maintained for 1-2 weeks on a diet containing 4 mEq of sodium each day. The dogs used in protocol 3 were anesthetized with sodium pentobarbital (30 mg/kg, iv) and ventilated with a respirator. Anesthesia was maintained by intermittent administration of pentobarbital. A Tygon catheter [Surprenant, outside diameter (o.d.) 2.5 mm] was placed in a femoral artery for collection of arterial blood samples and measurement of arterial blood pressure. Arterial blood pressure was determined with Statham transducers (P23Ia) and recorded on a Brush 440 recorder. Heart rate (HR) was determined from the arterial blood pressure recordings. Tygon catheters were also placed in a jugular vein and a femoral vein for infusions. A midline abdominal incision was made and the left ureter catheterized. In some experiments, the right ureter was also catheterized. The left renal artery was isolated and a 20-gauge needle was inserted for infusions into the left kidney. A small Tygon catheter was inserted through the left ovarian vein and advanced into the left renal vein for the collection of blood samples.

Dextrose (2.5%) in water was infused through the catheter in the jugular vein at a rate of 0.60 ml/min. Inulin and sodium p-aminohippurate (PAH), dissolved in saline, were given at 30 mg/kg and 15 mg/kg, respectively. This was followed by a sustaining infusion of both at 0.58 ml/min to maintain plasma concentrations of about 20 and 2 mg/100 ml, respectively. Urine was collected at 20-minute periods. Arterial (15 ml) and left renal vein (5 ml) blood samples were collected at the midpoint of each urine collection. After each blood sample collection, an equal amount of blood from donor dogs was given back to the experimental animal. Indomethacin (Merck Sharp & Dohme) was dissolved in 0.05 M phosphate buffer (pH 7.4) and centrifuged at 2,500 rpm to remove "carrier." The supernatant fluid was used for infusion. The small amount of indomethacin (if any) lost during centrifugation was not taken into account in the calculation of dosage. Prostaglandins E1 and E2 (PGE1 and PGE2) (Upjohn) were dissolved in 95% ethanol (1 mg/ml) and stored in a freezer as stock solutions. Dilutions were made subsequently in 0.05 M phosphate buffer (pH 7.4) to produce an infusion rate of 4.12 μg/min when given through the left renal artery at 0.103 ml/min.

PROTOCOL 1

After the completion of all surgical procedures, 0.05 M phosphate buffer (pH 7.4) was infused into the left renal artery at 0.388 ml/min. Ninety minutes later, urine was...
This is a scientific research document from Circulation Research, Volume 40, No. 5, May 1977. The content discusses the effects of indomethacin and PGE2 on mean arterial blood pressure (MABP), heart rate (HR), urine flow rate (V) from the left kidney, and left renal vein plasma renin activity (Rv PRA) in salt-depleted dogs. Indomethacin and PGE2 were infused through the left renal artery. CONT = control (for all figures).

Protocol 1

This series of experiments was essentially the same as in protocol 1 except that an aortic choker was placed above the renal arteries to control renal perfusion pressure (RPP) so that RPP could be maintained relatively constant before and during the infusion of indomethacin. This could be achieved with an accuracy of ±3 mm Hg.

Protocol 2

After the completion of all surgical procedures, 0.05 M phosphate buffer (pH 7.4) was infused into the left renal artery (0.103 ml/min). Ninety minutes later collection of urine was begun. This was followed by the infusion of PGE2 into the left renal artery at 4.12 μg/min for 60 minutes.

Results

Infusion of indomethacin into salt-depleted dogs caused an increase in mean arterial blood pressure (MABP), and decreases in HR, V, RPF, and renin secretion rate (Figs. 1 and 2). Mean MABP was 112.1 ± 5.4 mm Hg during control periods and was 147.7 ± 5.6 mm Hg after 80 minutes of infusion of indomethacin (P < 0.005). HR was collected for three consecutive 20-minute periods. Indomethacin was then given through the left renal artery at 0.5 mg/kg followed by a sustaining infusion of 388 μg/min for 80 minutes. This was followed by the infusion of PGE2 into the left renal artery at 4.12 μg/min for 60 minutes.

The statistical analysis was done with Student's t-test for paired data.
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20 40 60 20 40 60 80 20 40 60

MABP
mmHg

V
ml/min

RPF
ml/min

RENIN
SECRETION
RATE
U/min

120 100 80 60 40 20 0

1200 1000 800 600 400 200 0

120 100 80 60 40 20 0

1200 1000 800 600 400 200 0

FIGURE 3 Effect of indomethacin and PGE2 on mean arterial blood pressure (MABP), urine flow rate (V), renal plasma flow (RPF), and renin secretion rate in salt-depleted dogs when renal perfusion pressure (RPP) was maintained relatively constant. Indomethacin and PGE2 were infused through the left renal artery. 149.0 ± 7.9 beats/min during control periods and was 107.0 ± 10.9 beats/min after 80 minutes of infusion of indomethacin (P < 0.005). V from the left kidney was 0.38 ± 0.06 ml/min during control periods and had decreased to 0.08 ± 0.01 ml/min (P < 0.005) by 80 minutes of infusion of indomethacin. RPF and renin secretion rate had both decreased from 126.3 ± 13.3 ml/min and 1194.1 ± 353.9 U/min during control periods to 41.5 ± 7.5 ml/min (P < 0.005) and 384.0 ± 125.8 U/min (P < 0.025), respectively, by the end of the 80-minute infusions. Left kidney GFR decreased from 20.7 ± 2.8 ml/min during control periods to 12.1 ± 3.2 ml/min (P < 0.005) after 80 minutes of infusion. Plasma sodium concentration showed no significant change during the infusion of indomethacin, whereas plasma potassium concentration showed a small but statistically significant (P < 0.025) rise.

In contrast to indomethacin, subsequent infusion of PGE2 into the left renal artery caused increases in V, RPF, and renin secretion rate (Figs. 1 and 2). U1V also increased from 4.8 ± 1.0 µEq/min to reach 18.7 ± 5.7 µEq/min by 60 minutes of infusion of PGE2 (P < 0.025). There was also an increase in U1V after the infusion of PGE2. U2V increased from 8.9 ± 1.1 µEq/min to reach 19.8 ± 2.2 µEq/min after 60 minutes of infusion of PGE2 (P < 0.005). Plasma potassium increased further (P < 0.005) with PGE2 infusion.

Since there was an increase in MABP during the infusion of indomethacin, the observed decrease in renin secretion rate might result from the increase in MABP. We therefore performed another series of experiments in which we controlled RPP by an aortic choker so that RPP could be maintained relatively constant before and during the infusion of indomethacin. The results are shown in Figure 3. It can be seen that infusion of indomethacin caused significant decreases in renin secretion rate even when RPP was maintained relatively the same before and during the infusion of indomethacin. In these experiments, plasma sodium and potassium concentration showed no significant change following the infusion of indomethacin.

Infusion of PGE1 into the left kidney of the dog caused significant increases in renin secretion rate (P < 0.005). RPF (P < 0.025), V (P < 0.005), and U1NaV (P < 0.005) without significant change in MABP (Figs. 4 and 5). Mean plasma potassium concentration increased from 3.2 ± 0.08 mEq/liter during control periods to 3.4 ± 0.08 mEq/liter 120 minutes after the infusion of PGE1 (P < 0.05). Sodium and potassium excretion also increased from 32.4 ± 5.9 µEq/min and 13.8 ± 0.7 µEq/min, respectively, during control periods to reach 151.2 ± 20.3 µEq/min (P < 0.005) and 28.3 ± 1.9 µEq/min (P < 0.005), respectively, by 120 minutes of the infusion of PGE1.

Discussion

This series of experiments demonstrated that infusion of indomethacin into the kidney caused decreases in V and

FIGURE 4 Effect of PGE1 on mean arterial blood pressure (MABP), heart rate (HR), urine flow rate (V), and left renal vein plasma renin activity (Rv PRA). PGE1 was infused through the left renal artery.
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fenamic acid into the kidney of the dog causes suppression of renin secretion. Meclofenamic acid has been shown to decrease in renin secretion rate when RPP was maintained relatively constant (Fig. 3). A similar effect of oral indomethacin into the kidney caused significant decreases in renin secretion rate (Fig. 2). This is probably the result of the suppression of prostaglandin synthesis in the kidney. The observed decrease in renin secretion rate in the experiments of protocol 1 could result from the increase in MABP during the infusion of indomethacin (Fig. 1). Such an effect cannot explain the results from the experiments of protocol 2. In some experiments, infusion of indomethacin caused significant decreases in renin secretion rate when RPP was maintained relatively constant (Fig. 3). A similar effect of oral indomethacin on PRA in man has been reported. Furthermore, it has been reported that infusion of meclofenamic acid into the kidney of the dog causes suppression of renin secretion. Meclofenamic acid has been shown to be an inhibitor of prostaglandin synthetase. Thus indomethacin and meclofenamic acid, two structurally unrelated compounds that inhibit prostaglandin synthesis, both suppress renin secretion. Probably through the inhibition of prostaglandin synthesis. This is further strongly supported by our observations that direct infusion of PGE2 or PGE1 into the renal artery caused significant increases in renin secretion rate (Figs. 2 and 5) within 20 minutes. When no PGE was given following the course of indomethacin, no significant rise in renin secretion occurred for at least 60 minutes (unpublished observations). Werning et al. also reported that infusion of PGE1 into the renal artery of the dog caused an increase in renin release. Although Vander reported that infusion of PGE1 into the aorta of the dog caused a decrease in renin secretion, the dose used in Vander's experiments (0.2-0.5 μg/min) was lower than that in Werning's or in our own.

Newcombe and associates reported that indomethacin inhibits cyclic nucleotide phosphodiesterase in chicken epiphyseal cartilage. If this occurs also in the juxtaglomerular apparatus, intracellular cyclic AMP should have increased. An increase in cyclic AMP in the medium has been shown to increase release of renin from kidney cell suspensions in vitro.

Since it has been reported that synthesis of prostaglandins of both the E and F series takes place in the kidney, infusion of indomethacin into the kidney would be expected to suppress prostaglandin synthesis of both the E and the F series. Recent observations in our laboratory suggest that it is the suppression of the synthesis of prostaglandin E series which is responsible for the decrease in renin secretion during the infusion of indomethacin. This is borne out by the fact that infusion of PGF2α into the renal artery caused little or no renin release (unpublished observations), whereas infusion of PGE1 or PGE2 into the renal artery caused consistent increases in renin release.

The mechanism(s) by which PGE1 and PGE2 cause increases in renin secretion were not examined in the present study. There was no significant change in MABP or in plasma sodium concentration during the infusion of PGE2 and PGE1. It is unlikely that the increase in renin secretion is due to increases in plasma potassium concentration. If changes in plasma potassium concentration were responsible for the increase in renin release during the infusion of PGE2, the observed increase in plasma potassium concentration would be expected to lead to a decrease instead of an increase in renin release.

In some experiments, it may be that the increase in renin secretion during the infusion of PGE2 or PGE1 was due to plasma volume contraction. Since there was a sodium diuresis following the infusion of PGE1, plasma volume contraction would lead to an increase in the sympathetic discharge to the kidney and in release of catecholamines from the adrenal medulla. Both of which have been shown to cause renin release. This explanation is unlikely in the present experiments, since the response of renin secretion to the infusion of PGE2 or PGE1 was rapid, within 10 minutes after the start of infusion, at a time...
when only some 200 μEq of sodium had been excreted. Furthermore, the dogs received more fluid by infusion than they lost through diuresis. That the natriuresis by PGE1, or PGE2 may activate macula densa cells and thereby lead to an increase in renin secretion8 and 21 can also be ruled out, since recent observations in our laboratory show that infusion of PGE1, into nonfiltrating kidneys also causes increases in renin release (unpublished observations).

Since there was an increase in renal plasma flow (RPF) during the infusion of PGE1, and PGE2, (Figs. 2 and 5),5,8 it could be that the observed increase in renin release is due to vasodilation induced by PGE1, and PGE2. It has been suggested that one of the mechanisms for the increase in renin release is vasodilatation.26 At present, we cannot differentiate whether the increase in renin release by prostaglandin E1 is a direct effect of the PGE's on the renin-secreting granular cells or is secondary to its vasodilatory effect.

It must be pointed out that in the present series of experiments, the dogs had been subjected to anesthesia and surgical procedures prior to the infusion of indomethacin and PGE2, and had been fed low salt diets. Therefore prostaglandin synthesis may have been increased by the experimental conditions. Recently it has been reported that synthesis of prostaglandins is increased in animals under anesthesia and subjected to surgical operations.27

The physiological role of prostaglandins in the control of renin secretion is still uncertain. It is recognized that the dose of prostaglandins used was high. It has, however, been demonstrated that excessive synthesis of prostaglandins in the kidney is probably involved in the abnormally high renin secretion in patients with Bartter's syndrome. It has been reported that treatment with indomethacin in these patients leads to decreases in V rate and PRA, which corresponded to a decrease in urinary prostaglandins.28

If the decrease in renin secretion during the infusion of indomethacin results from the suppression of synthesis of prostaglandins in the kidney, the question arises as to how renal prostaglandins get access to the renin-secreting granular cells of the juxtaglomerular apparatus. The exogenous prostaglandins given into the renal artery could reach the renin-secreting granular cells through the renal arterial circulation. Since it has been reported that synthesis of prostaglandins takes place predominantly in the medulla, and not in the cortex,29 doubts have been raised as to how endogenous prostaglandins could get access to the cortex and thereby lead to an increase in renin secretion. In a recent report, Larson and Anggard29 showed that prostaglandin synthesis does take place in the cortex, although the rate is only 1/10 of that in the medulla. Furthermore, medullary prostaglandins could gain access to the juxtaglomerular apparatus via the ascending vasa recta, or via the ascending limbs of the loop of Henle. Recently it has been reported that synthesis of prostaglandins takes place in the mesenteric arteries.21 It is thus possible that the renal arteries also synthesize prostaglandins, and that these endogenous prostaglandins are released following some stimuli, and exert their actions on the renin-secreting granular cells. In summary, our data demonstrate that infusion of indomethacin into the renal artery of salt-depleted dogs causes decreases in renin release, and that infusion of PGE1, or PGE2, into the renal artery causes increases in renin release. Thus our data suggest that PGE1, and PGE2 play a role in the control of renin secretion.

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References

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Differences between Proximal Left and Right Bundle Branch Block Action Potential Durations and Refractoriness in the Dog Heart

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SUMMARY To date the electrophysiological mechanism responsible for aberrant intraventricular conduction of critically timed premature supraventricular impulses has not been documented. Microelectrode techniques were used to measure in vitro action potential and refractory period durations of the canine proximal right and left bundle branches equidistant from the distal bundle of His. Both measurements in the right bundle branch were statistically significantly longer than these parameters of the left bundle branch. Transection of the bundle branches immediately distal to the distalmost recording sites effected no change in the proximal right bundle action potential but caused marked prolongation of proximal left bundle branch action potential and refractory period durations. We conclude that functional right bundle branch aberrancy is most likely due to the longer proximal right bundle action potential duration and refractoriness. Our data also suggest that the shorter proximal left bundle branch action potential durations and refractory periods may be due to the proximity of the low ohmic resistance Purkinje fiber-muscle junctions on the left septal surface, effecting electrotonic shortening of these proximal left bundle branch parameters.

ALTHOUGH aberrancy of intraventricular conduction due to functional right bundle branch block is a well known phenomenon since first described by Sir Thomas Lewis, and in spite of the fact that a variety of explanations have been offered for the functional right bundle branch block, the responsible electrophysiological mechanism has not been documented. The purpose of this study was to record the behavior of the left and right bundle branches in vitro in an effort to determine whether electrotonic interactions between the bundle branches and septal muscle might account for the functional differences between the bundle branches.

Methods

Adult mongrel dogs of either sex, weighing 10-15 kg, were anesthetized with secobarbital (30 mg/kg, iv). Their hearts were removed rapidly through a lateral thoracotomy and immersed in cool oxygenated Tyrode’s solution. Initial experiments were performed on single bundle branch preparations. The right bundle branch preparation (Fig. 1, lower left) consisted of the right half of the interventricular septum containing the septal portion of the right bundle branch, the major Purkinje false tendon coursing from the lower interventricular septum to the anterior papillary muscle, and a portion of the right ventricular free wall containing most of the peripheral ramifications of the right bundle branch. The left bundle branch preparation (Fig. 1, right half) included the left half of the interventricular septum containing the common left bundle branch, its anterior, septal, and posterior divisions and their peripheral ramifications, and the anterior and posterior papillary muscles. The thickness of these preparations was approximately 8-10 mm. Either the right or left bundle of a particular dog was used. A total of seven right and seven left bundle branch preparations were studied. The preparation was pinned to the floor of a 60-ml Lucite chamber that was continuously superfused at a rate of 20 ml/min with Tyrode’s solution maintained at 37 ± 0.5°C and gassed with 95% O₂-5% CO₂. Composition of the Tyrode’s solution, in mmol/liter: Na⁺, 150; K⁺, 4.0; Cl⁻, 147; Ca²⁺, 2.7; HCO₃⁻, 12.0; H₂PO₄⁻, 0.9; Mg²⁺, 0.5; glucose, 5.5.

A bipolar, extracellular stimulating electrode was placed on the proximal portion of the bundle branch. Recording sites located 1 cm and 2 cm distal to the stimulating electrode were identified and marked with small stainless steel pins placed in the septal myocardium alongside the bundle branch. During constant stimulation at a
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