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COMPARISON OF ASPIRIN AND INDOMETHACIN PRE-TREATMENTS ON THE RESPONSES TO REDUCED RENAL ARTERY PRESSURE IN CONSCIOUS DOGS

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SUMMARY

1. To examine the role of prostaglandins in physiologically induced renin release, we reduced renal artery pressure within the autoregulatory range in chronically instrumented conscious dogs with aspirin, indomethacin or no pre-treatment.

2. In untreated dogs, reduction of renal artery pressure to 60 mmHg for 90 min produced rises in plasma renin activity (+5.4 ± 1.0 ng ml⁻¹ hr⁻¹) and mean arterial pressure (+17 ± 2 mmHg) without significant effect on renal blood flow (n = 13).

3. Aspirin pre-treatment (2 × 25-40 mg kg⁻¹ orally) had no effect on the renin, arterial pressure or renal blood flow responses to renal artery pressure reduction (n = 7). In contrast, indomethacin pre-treatment (2 × 2-3 mg kg⁻¹ orally) significantly lessened the increase in plasma renin activity during reduced renal artery pressure (+2.0 ± 0.3 ng ml⁻¹ hr⁻¹, n = 11).

4. The relative effectiveness of aspirin and indomethacin in inhibiting prostaglandin production in the kidney was then tested in separate experiments by measuring the renal blood flow responses to renal artery injections of arachidonate (5–200 μg kg⁻¹). In the doses used above, aspirin markedly attenuated the blood flow response to arachidonate but indomethacin had almost no effect. Both aspirin and indomethacin abolished the hypotensive effect of intravenous arachidonate (0.5 mg kg⁻¹).

5. These results tentatively suggest that indomethacin may not effectively inhibit renal prostaglandin production in conscious dogs at the doses used in these experiments. Thus the reduced renin release in response to lowered renal artery pressure in indomethacin pre-treated dogs may have been due to another, non-prostaglandin action of indomethacin.

6. The results from the aspirin pre-treated dogs suggest that prostaglandins are not involved in the release of renin in response to reduced renal artery pressure in conscious dogs.

INTRODUCTION

Arachidonic acid, the prostaglandin precursor, and various individual prostaglandins stimulate the release of renin from the kidney in vivo and in vitro (see Dunn & Zambraski, 1980; Dunn & Hood, 1977 and Dusting, Moncada & Vane, 1979 for

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reviews of this literature). In addition, the prostaglandin synthase inhibitor indomethacin has been reported to reduce the renin response to a number of stimuli, particularly in anaesthetized animals and in vitro renal preparations (Dunn & Zambraski, 1980; Dunn & Hood, 1977; Dusting et al. 1979). This and other evidence has led to the suggestion that prostaglandins may be the obligatory endogenous mediators of renin release from the kidney (Dusting et al. 1979; Moncada & Vane, 1980), although Dunn & Zambraski (1980) note that there is conflicting evidence for a role of prostaglandins in some circumstances. Since there is evidence that prostaglandin production may be augmented by surgical procedures in anaesthetized animals (Terragno, Terragno & McGiff, 1977; Swain, Heyndrickx, Boettcher & Vatner, 1975), we have examined the importance of prostaglandins in physiologically induced renin release in conscious, chronically instrumented dogs. We reduced renal artery pressure within the autoregulatory range in conscious dogs and compared the effects of two inhibitors of prostaglandin production (indomethacin and aspirin) on the response.

METHODS

Preparation of dogs

Trained chronically instrumented dogs were prepared as previously described (Anderson, Johnston & Korner, 1979; Anderson & Korner, 1980; Anderson, Korner, Angus & Johnston, 1981). In brief, male mongrel dogs (average weight 24 kg) were trained to lie quietly on a low padded table in a quiet laboratory. The dogs were then instrumented under halothane/nitrous oxide anaesthesia, after initial induction with thiopentone. The left renal artery was exposed via a flank incision, and an inflatable silastic cuff and a Doppler flowmeter were placed around the artery. A thin catheter (9-8 mm external diameter) was inserted into the renal artery distal to the cuff and two further catheters were placed in the abdominal aorta. Another catheter was placed in the inferior vena cava. The right kidney was removed through a right flank incision. In about one out of five dogs, double renal arteries to the left kidney necessitated its removal and preparation of the right renal artery. The catheters were exteriorized on the chest wall and protected by a canvas jacket. The dogs were given pethidine at the end of the operation, and penicillin (250 mg day⁻¹) and streptomycin (250 mg day⁻¹) for 5 days. They had free access to water and were fed a diet of raw beef and biscuits which gave them a daily Na⁺ intake of about 60 m-moles. At least 2 weeks were allowed between surgery and the experiments. By this time, the dogs were thoroughly accustomed to the laboratory by daily visits to the laboratory for catheter flushing.

Experiments

Reduction of renal artery pressure. All experiments were conducted with the dogs quietly recumbent. After a 30 min control period, the silastic cuff around the renal artery was inflated to lower distal pressure to 60 mmHg. This pressure was then maintained at 60 mmHg for 90 min by frequent adjustments of the degree of cuff inflation. After 90 min the cuff was deflated and the changes followed for another 30 min.

Prior to the experiment, the dogs were given indomethacin, aspirin or no drug. Indomethacin was given at 2–3 mg kg⁻¹ orally in two doses 2 hr apart and aspirin was given at 25–40 mg kg⁻¹ in two doses 3 hr apart. Renal artery stenosis was induced approximately 45 min after the second doses of indomethacin or aspirin.

As far as possible each dog was studied three times; i.e. with indomethacin, aspirin and no pre-treatment in random order. This was however not possible in all dogs due to technical failures, usually rupture of the wall of the renal artery beneath the hard shells of the Doppler flow probes between experiments. At least 10 days were allowed between experiments. All successfully completed experiments have been included in the results (n = 11, 7 and 13 for indomethacin, aspirin and no pre-treatment respectively), with separate analysis of the results from dogs in which paired experiments were performed, comparing no pre-treatment with either indomethacin (n = 7) or aspirin (n = 5) pre-treatments.
**Test of inhibition of renal prostaglandin synthesis.** In a separate group of dogs the degree of functional blockade of prostaglandin synthesis in the kidney by indomethacin and aspirin was tested by measuring the renal blood flow response to injections of the prostaglandin precursor, arachidonate. Na\(^+\) arachidonate (Nuchex) was injected in bolus doses of 5–200 \(\mu\)g kg\(^{-1}\) into the renal artery. Indomethacin \((n = 6)\) and aspirin \((n = 7)\) were given at the doses used for the main series of experiments described above. The effect of a third drug, phenylbutazone \((10–12 \text{ mg kg}^{-1} \text{ orally})\), on the renal blood flow response to arachidonate was also studied.

The arterial blood pressure response to intravenous Na\(^+\) arachidonate injections \((0.5–1 \text{ mg kg}^{-1})\) were also studied before and after indomethacin \((n = 7)\) and aspirin \((n = 5)\).

**Measurements**

Aortic and renal artery pressures were measured via the implanted catheters, using Statham P23Dc transducers and a Devices recorder. Renal blood flow was measured in kHz Doppler shift and converted to millilitres per minute using a calibration factor of 84 ml. min\(^{-1}\) kHz\(^{-1}\). We have previously published details of the Doppler flowmetry technique (Anderson et al. 1979, 1981; Anderson & Korner, 1980). Renal vascular resistance was calculated as distal renal artery pressure divided by renal blood flow. Plasma renin activity was measured by radioimmunoassay from arterial blood sampled through one of the aortic catheters (Anderson et al. 1979). Plasma salicylate concentrations were measured by the technique of Trinder (1957). Plasma indomethacin levels were measured by high pressure liquid chromatography (Skellern & Salole, 1975).

**Statistics**

Responses to stenosis were compared by Student's \(t\) test of the difference between resting values and average values after 60–90 min of renal artery pressure reduction and by analysis of variance, with appropriate partitions of the 'between times' sums of squares to allow testing the significant changes within groups and comparison of changes between groups. Regression lines were compared by analysis of covariance.

**RESULTS**

**Response to renal artery pressure reduction**

Renal artery pressure was reduced to 60 mmHg by partial inflation of the cuff around the renal artery, and then maintained at this pressure for 90 min. The volumes of saline needed to inflate the cuff to achieve this pressure are given in Table 1. The responses in the dogs pre-treated with aspirin or indomethacin were compared to those in dogs with no pre-treatment. In all, thirteen dogs were studied without pre-treatment, eleven dogs with indomethacin pre-treatment and seven dogs with aspirin pre-treatment. The results from these dogs are shown in Fig. 1. Of these, paired indomethacin and no pre-treatment experiments were performed in seven dogs and paired experiments of aspirin and no pre-treatment were performed in five dogs. These results are given in Fig. 2A, B (respectively).

In dogs with no drug pre-treatment, reduction of distal renal artery pressure produced a rapid rise in plasma renin activity which reached steady-state levels at 60 and 90 min \((+5.4\pm1.0 \text{ ng ml}^{-1} \text{ hr}^{-1} \text{ above control})\), (Fig. 1). Arterial blood pressure also began to increase almost immediately and reached steady-state levels which were 17±2 mmHg above resting levels (Fig. 1). Reduction of renal artery pressure to 60 mmHg had no significant effect on renal blood flow, either initially \((16\pm8.5\% \text{ above resting values})\) or after 60–90 min \((46\pm8.4\% \text{ below resting})\) (Fig. 1).

In dogs with indomethacin pre-treatment, there was a smaller rise in plasma renin activity in response to renal artery pressure reduction than in the untreated dogs.
The average rise in plasma renin activity at 60 and 90 min was 2.0±0.3 ng ml\(^{-1}\) hr\(^{-1}\) \((n=11)\) compared to 5.4±1.0 ng ml\(^{-1}\) hr\(^{-1}\) \((n=13)\) in untreated dogs \(P<0.05\) unpaired Student's \(t\) test, (Fig. 1). For the seven dogs with paired experiments, the rises in plasma renin activity were 1.8±0.2 and 4.4±1.5 ng ml\(^{-1}\) hr\(^{-1}\) with and without indomethacin pre-treatment respectively \(P<0.05\),

### Table 1. Renal artery pressure reduction

<table>
<thead>
<tr>
<th>Cuff inflation volume (ml. saline)</th>
<th>Pre-treatment</th>
<th>Initially</th>
<th>After 30 min</th>
<th>After 90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.20±0.02</td>
<td>0.25±0.02</td>
<td>0.28±0.03</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.19±0.03</td>
<td>0.25±0.04</td>
<td>0.28±0.04</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.19±0.02</td>
<td>0.23±0.02</td>
<td>0.25±0.01</td>
<td></td>
</tr>
</tbody>
</table>

Degree of inflation of the cuff around the renal artery required to initially reduce distal pressure to 60 mmHg and to maintain it at 60 mmHg for 30 and 90 min.

![Fig. 1. Responses to renal artery stenosis to reduce distal pressure to 60 mmHg for 90 min (between vertical arrows). Conscious dogs were studied after no pre-treatment with cyclo-oxygenase inhibitors \(A, n=13\) and after indomethacin pre-treatment \(B, n=11\) and aspirin pre-treatment \(C, n=7\). Blood pressures and renal blood flow are depicted as means of values averaged over 5 min periods in each dog, ± S.E. of the mean. Plasma renin activity is shown as means of samples taken at the times indicated ± S.E. of the mean.](image)

(Fig. 2A). Fig. 3 shows the rise in plasma renin activity in paired experiments in individual dogs. The rise in arterial pressure was also less in indomethacin pre-treated dogs \(7.8\) mmHg compared to \(15.3\) mmHg without indomethacin, \(0.05 < P < 0.1\), by analysis of variance), (Fig. 2A). The renal blood flow response to renal artery pressure reduction was not however altered by indomethacin (Fig. 2A).

In contrast to indomethacin, aspirin pre-treatment of these conscious dogs did
Indomethacin versus No pre-treatment

A

<table>
<thead>
<tr>
<th>Mean arterial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
</tbody>
</table>

\( P < 0.05 \)

\[ \Delta \text{Renal blood flow} \]

Aspirin versus No pre-treatment

B

<table>
<thead>
<tr>
<th>Mean arterial pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
</tbody>
</table>

\[ \Delta \text{Renal blood flow} \]

Fig. 2. Average effects of renal artery pressure reductions to 60 mmHg for 90 min. Values between 60 and 90 min were averaged and expressed as change (\( \Delta \)) from resting values in each dog. The plotted bars represent the mean values (±s.e.m.) of seven dogs which received indomethacin and no pre-treatment in separate paired experiments (Fig. 2A), and five dogs which received aspirin and no pre-treatment in separate paired experiments (Fig. 2B). \( P < 0.05 \) denotes a significant difference between the response in the dogs pre-treated with indomethacin or aspirin compared to that when the dogs were untreated; where no \( P \) value is given, aspirin or indomethacin had no significant effect on the response.

not affect the response to reduction of renal artery pressure to 60 mmHg (Figs. 1 and 2B). In the five dogs in which paired experiments were performed with aspirin and no pre-treatment, plasma renin activity rose 3.9±0.7 and 4.8±2.1 ng ml\(^{-1}\) hr\(^{-1}\) respectively, arterial pressure rose 15.9±4.5 and 13.3±3.0 mmHg respectively, and renal blood flow fell 9±21 and 11±15% respectively (Fig. 2B). These are the changes from control averaged from 60–90 min post-stenosis and there is no significant difference between the responses in the two groups for any variable. This is also the case if the results for all seven aspirin pre-treated and thirteen untreated dogs are
compared (Fig. 1). Fig. 3 shows the rises in plasma renin activity in individual dogs; in four out of five dogs the rise was greater after aspirin pre-treatment than without pre-treatment.

Neither aspirin nor indomethacin significantly affected resting arterial pressure, renal blood flow or plasma renin activity.

In indomethacin pre-treated dogs, plasma indomethacin concentrations were $3.1 \pm 0.6 \, \mu g \, ml^{-1}$ immediately prior to reduction of renal artery pressure to $60 \, mmHg$ and $1.1 \pm 0.2 \, \mu g \, ml^{-1}$ 90 min later. Plasma salicylate values were $97.7 \pm 7.6$ and $90.8 \pm 7.9 \, \mu g \, ml^{-1}$ at these times in aspirin pre-treated dogs.

**Arachidonate injections**

Injections of arachidonate into the renal artery produced dose-related increases in renal blood flow in the absence of aspirin or indomethacin (Fig. 4). Doses from $5 \, \mu g \, kg^{-1}$ to $200 \, \mu g \, kg^{-1}$ increased renal blood flow without effects on systemic arterial pressure. Doses of $400 \, \mu g \, kg^{-1}$ or greater tended to lower arterial pressure and were therefore not used.

Aspirin markedly reduced the renal blood flow response to renal artery arachidonate injections (Fig. 4 A). For example, $50 \, \mu g \, kg^{-1}$ arachidonate increased renal blood flow by $24 \pm 5 \%$ before aspirin and by only $8 \pm 2 \%$ after aspirin. In contrast, indomethacin had virtually no effect on the magnitude of the renal blood flow response to arachidonate (Fig. 4 B). Analysis of covariance revealed that the slightly reduced slope of the regression of flow on arachidonate dose after indomethacin was not significant (Fig. 4 B). The duration of the renal blood flow responses to arachidonate
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were also not altered by indomethacin. Phenylbutazone gave similar results to those of aspirin, markedly reducing the renal blood flow response to arachidonate; e.g. 50 µg kg\(^{-1}\) arachidonate increased renal blood flow by 27.1 ± 7.1% before and by 11.8 ± 1.0% after phenylbutazone, and 100 µg kg\(^{-1}\) arachidonate increase flow by 39.0 ± 8.5% before and 16.8 ± 3.7% after phenylbutazone (n = 4).

![Graph A](image1)

Arachidonate (µg kg\(^{-1}\), i.r.a.)

![Graph B](image2)

Arachidonate (µg kg\(^{-1}\), i.r.a.)

Fig. 4. Effect of bolus injections of arachidonate into the renal artery on renal blood flow (peak changes), before and after aspirin (top, n = 7) or indomethacin (lower, n = 6). Histograms on the right of each graph show the average resting values before and after aspirin or indomethacin treatment (not significantly different in either case).

Intravenous injections of arachidonate (0.5 mg kg\(^{-1}\)) produced marked falls in arterial pressure (Fig. 5), lasting 3-5 min. The peak reduction in arterial pressure occurred 0.5-2 min after injection and was associated with tachycardia (+ 26 ± 8 Hz). Indomethacin and aspirin pre-treatment both completely abolished this response to 0.5 mg kg\(^{-1}\) arachidonate i.v. (Fig. 5). Indomethacin also reduced the hypotensive response to 1 mg kg\(^{-1}\) arachidonate i.v., from 35.5 ± 6.0 mmHg to 6.0 ± 2.5 mmHg.

**DISCUSSION**

The results of this study do not support the claim that prostaglandins are 'obligatory endogenous mediators' of renin release from the kidney (Dusting *et al.* 1979; Moncada & Vane, 1979). Neither aspirin nor indomethacin completely blocked
the rise in plasma renin levels in response to prolonged reduction of renal artery pressure. In fact aspirin pre-treatment had no effect on the renin response to reduced renal artery pressure. In contrast indomethacin did reduce, but not abolish, the renin response to reduced renal artery pressure. However this effect of indomethacin may not have been due to its inhibition of prostaglandin production as explained below.

Fig. 5. The effect of intravenous bolus arachidonate (0.5 mg kg\(^{-1}\)) on mean arterial pressure before and after indomethacin (top) or aspirin (bottom). The Figure shows average resting values immediately prior to arachidonate injection (\(A\), resting) and peak reduction in pressure after arachidonate injection (\(B\), arachidonate).

We decided to use two chemically dissimilar non-steroidal anti-inflammatory drugs in this study because such drugs are known to have a diversity of activities on biological mechanisms apart from inhibition of prostaglandin synthesis (Flower, Moncada & Vane, 1980). We administered the drugs aspirin and indomethacin in doses commonly used by other workers, but we also assessed the inhibitory effects of the two drugs on prostaglandin synthesis. We did this by measuring the cardiovascular effects of the prostaglandin precursor substance arachidonate, injected into the renal artery or intravenously before and after aspirin and indomethacin. Arachidonate injected into the renal artery produced dose-related increases in renal blood flow and intravenous arachidonate produced hypotension. Both aspirin and indomethacin blocked the hypotensive response to intravenously injected arachidonate, but only aspirin blocked the renal vasodilatatory response to intrarenal arachidonate. That is, indomethacin did not block metabolism of arachidonate to vasodilatory substances after intrarenal injections, but did block this metabolism after intravenous injection. This suggests that indomethacin did not effectively
inhibit prostaglandin production from arachidonate in the kidney, whereas aspirin
did, and that both drugs inhibited prostaglandin production elsewhere in the body.
A third drug, phenylbutazone, produced similar results to aspirin. Confirmation of
the results of this functional test, suggesting that indomethacin did not inhibit renal
prostaglandin synthase, will require more direct measurements of prostaglandin
production and the present results should therefore be interpreted cautiously. For
example, arachidonate is a substrate for other enzymes such as lipoxygenase. It is
therefore possible that a drug which inhibits cyclo-oxygenase might divert arachi-
donate metabolism into vasodilatory leukotrienes, although the results with aspirin
and phenylbutazone argue against this possibility. Another potential problem with
this functional assay is that indomethacin can inhibit the catabolism of prostaglandins
as well as the synthesis at some doses (Pace-Asciak & Cole, 1975), but the duration
of effect of arachidonate on renal blood flow was not affected by indomethacin in the
present experiments. Furthermore, the effects of arachidonate metabolism on renal
blood flow, rather than on renin release, were assessed by this assay. On the other
hand, an advantage of this functional test of inhibition of renal prostaglandin
production is that it was performed in situ in the experimental setting used in the
main set of experiments. We have no explanation for the apparent failure of
indomethacin to inhibit renal prostaglandin produced in these unanaesthetized dogs.
However, the effectiveness of this hydrophobic drug depends on its concentration in
the particular target tissue and it may be noteworthy in this regard that very little
indomethacin is excreted in urine in dogs in contrast to other species (Hucker, Zacchei, Cox, Brodie & Cantwell, 1966). Higher doses of indomethacin may be
required to inhibit renal prostaglandin production but the dose used here is commonly
employed and the blood levels of indomethacin achieved were high compared to those
reported for therapeutic use in man (e.g. Alvan, Orme, Bertilsson, Ekstrand &
Palmer, 1975; Watkins, Abbot, Hensby, Webster & Dollery, 1980). It is commonly
assumed that an effect of indomethacin is synonymous with an action of prosta-
glandins although it is rarely specifically tested whether indomethacin has inhibited
prostaglandin production. The results from our experiments do not constitute
conclusive proof that indomethacin failed to inhibit renal prostaglandin production,
but it would seem prudent not to necessarily equate an effect of indomethacin on the
kidney with a role for prostaglandins.

Indomethacin did reduce the amount of renin released in response to reduction of
renal artery pressure. This occurred in spite of the drug’s apparent failure to inhibit
renal prostaglandin production and is in contrast to the effect of aspirin. This effect
of indomethacin may therefore be via another action of this drug. Indomethacin has
been reported to have several actions in the body apart from the inhibition of
prostaglandin production (Dunn & Zambraski, 1980), including, inhibition of phos-
phodiesterase (Newcombe, Thanassi & Ciosek, 1974), protein kinase (Kantor &

The results from the experiments using aspirin argue against a role for prosta-
glandins in the release of renin during reduction of renal perfusion pressure within the
autoregulatory range. The dose of aspirin used achieved high plasma levels (cf. Data,
Chang & Nies, 1976), was shown to alter renal arachidonate metabolism in dogs in
this study, and was greater than that previously shown to inhibit renal prostaglandin
synthase in vitro (Caterson, Duggin, Horvath, Mohandas & Tiller, 1978). Despite this, pre-treatment of dogs with aspirin did not alter the renin response to reduction of renal artery pressure to 60 mmHg for 90 min. This suggests either that prostaglandin production was not stimulated by reduction of renal artery pressure within the autoregulatory range in conscious dogs, or that prostaglandins were produced but had no effect on renin release. The latter is unlikely because it is well proven that exogenously applied prostaglandins or arachidonic acid stimulate renin release in vivo and in vitro (e.g. Gerber, Keller & Nies, 1979; Seymour & Zehr, 1979; Weber, Larsson, Anggard, Hamberg, Corey, Nicolaou & Samuelsson, 1976). Thus these aspirin results suggest that prostaglandin production was not stimulated by reduction of renal artery pressure within the autoregulatory range in conscious dogs and oppose the hypothesis that prostaglandins necessarily mediate renin release (Dusting et al. 1979; Moncada & Vane, 1979). Other investigators have also recently shown that renin release may occur independently of prostaglandins in a variety of circumstances (e.g. Dietz, Davis, DeForrest, Freeman, Echtenkamp & Seymour, 1981; Dietz, Davis, Freeman, Echtenkamp & Villarreal, 1981; Seymour, Davis, Echtenkamp, Dietz & Freeman, 1981). It has also recently been shown that prostaglandins do not apparently mediate renin release during even severe reductions in renal blood flow in conscious dogs (Anderson, 1982).

Greater renal vasoconstriction might have been expected in the aspirin pre-treated dogs compared to untreated dogs in response to reduced renal artery pressure. Angiotensin II can be shown to liberate arachidonic acid and increase renal prostaglandin production in some in vitro kidney preparations and in anaesthetized animals (Aiken & Vane, 1973; Needleman, Kauffman, Douglas, Johnston & Marshall, 1973, Schlondorff, Roczniak, Satriano & Folkert, 1980; Zusman & Keiser, 1977) and prostaglandins modify the renal blood flow response to infusions of angiotensin II in conscious dogs (Swain et al. 1975). Thus as angiotensin II levels increased in parallel with the increasing plasma renin levels during the 90 min period of reduced renal artery pressure, renal vascular resistance might have been higher in the dogs with inhibition of prostaglandin production and renal blood flow may have fallen more. However, neither indomethacin nor aspirin altered the response of renal blood flow or renal vascular resistance to reduction of renal artery pressure, in agreement with previously published results (e.g. Anderson, Taher, Cronin, McDonald & Schrier, 1975; Bell, Sinclair & Parry, 1975).

In summary, prostaglandins were not apparently involved in the renin or renal blood flow responses to reduced renal artery pressure in conscious dogs. This conclusion is based on findings that aspirin was without effect during reduction of renal artery pressure to 60 mmHg, despite its apparent inhibition of renal prostaglandin production. The results therefore suggest that prostaglandins may not be obligatory mediators of the physiologically induced release of renin. The results also tentatively suggest that indomethacin, in the doses used here, may not effectively inhibit renal prostaglandin production in dogs but may inhibit renin release by another mechanism.
Preliminary poster presentations of parts of this work have been presented to symposia on Prostaglandins and the Kidney, Stuttgart, 1980, and Arachidonic Acid Metabolites and the Kidney, Rome, 1981.

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