The Effect of Indomethacin and Other Anti-Inflammatory Drugs on the Renin-Angiotensin System

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ABSTRACT The administration of two different doses of indomethacin, 9 and 18 mg/kg, to two different groups of rabbits was followed 6 h later by a significant decrease in plasma renin activity, and these levels were not increased by hemorrhage. The administration of 2 mg/kg of indomethacin did not alter the basal levels of plasma renin activity, but it was effective in diminishing the peripheral increase of renin produced by hemorrhage. Similar effects were obtained in other groups of rabbits treated with 9 mg/kg of meclofenamate or 18 mg of aspirin. The lowering effect of indomethacin on plasma renin activity is not specifically related to hemorrhage because it also prevented the increase in plasma renin activity elicited by 5 mg/kg of furosemide.

Further studies showed that indomethacin did not exert any significant effect in vivo on the plasma level of renin substrate or on the generation of angiotensin from normal plasma by exogenous renin. And indomethacin did not interfere with the binding capacity of anti-angiotensin I for angiotensin I in the radioimmunoassay reaction or with the in vitro formation of angiotensin from hog renin-nephrectomized rabbit plasma reaction. The results thus indicate that the lowering effect of indomethacin on plasma renin activity is due to the interference with renal renin release. That this effect may be related to the blockade of prostaglandin synthesis is suggested by the similar effect exhibited by other blockers of prostaglandin synthesis.

INTRODUCTION

Our preliminary studies have shown that the administration of a large dose of indomethacin (18 mg/kg) to conscious normal rabbits or to rabbits with renovascular hypertension results in a significant decrease in peripheral plasma renin activity (1).

The present study was designed to examine if smaller doses of indomethacin also exert this effect; to determine if this lowering effect on plasma renin activity is due to the interference with the release of renin; and to learn if this effect is also exerted by other anti-inflammatory drugs such as meclofenamate and aspirin.

The effects of three different doses of indomethacin (2, 9, and 18 mg/kg) on the basal values of peripheral plasma renin activity and on the release of renin elicited by hemorrhage (2, 3) were studied in three different groups of normal conscious rabbits. These results were compared with results obtained in a control group that was not treated with indomethacin. The effect of the highest dose of indomethacin (18 mg/kg) on the basal values of plasma renin activity and on the release of renin elicited by furosemide (4) was also studied in an additional group of rabbits to define whether the interference of indomethacin on the release of renin is specifically exerted against hemorrhage.

Direct recordings of blood pressure and measurements of renal blood flow, glomerular filtration rate, and urinary sodium and potassium levels were obtained in the group of rabbits that received 18 mg of indomethacin to determine if the interference of indomethacin on the release of renin was indirectly mediated by systemic or intrarenal (or both) hemodynamic changes.

Finally, special laboratory tests also were performed to ensure that the observed effect was not due to the interference of indomethacin with the formation of angiotensin in vivo or in vitro or with the radioimmunoassay reaction.

METHODS

Animal protocol. The effects of three different doses of indomethacin (2, 9, and 18 mg/kg) on peripheral plasma

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renin activity during basal conditions and during the rapid withdrawal of 24 ml of blood were studied in three groups (six rabbits each) of unanesthetized New Zealand rabbits weighing between 2.5 and 3 kg. The rabbits were placed in comfortable restrainers at room temperature, and a 21-gauge butterfly needle was inserted into the central artery of the right ear to collect blood samples for measurement of plasma renin activity. After 15 min, each group was given 2, 9, and 18 mg/kg of indomethacin, respectively. These doses were given 2 h apart in two intravenous injections diluted in 1 ml of phosphate buffer. A fourth group of six rabbits given two intravenous injections of an identical amount of phosphate buffer without indomethacin was used as a control. 6 h after the first injection, each rabbit of each group underwent a 24-ml bleeding.

Plasma renin activity was determined by radioimmunoassay (5) of blood samples collected before and at 2, 4, and 6 h after the administration of indomethacin or phosphate buffer and in five samples, each of 2 ml of blood, withdrawn from the central artery of the ear during the 24-ml bleeding.

The effect of the highest dose of indomethacin (18 mg/kg) on the release of renin elicited by furosemide was studied in an additional group of five rabbits submitted to a protocol similar to that previously described, with the exception that 6 h after the initiating of treatment with indomethacin, each rabbit was given an intravenous bolus injection of 5 mg/kg of furosemide instead of undergoing bleeding. In these rabbits, plasma renin activity values were measured in blood samples removed before and at 3 and 6 h after the intravenous administration of indomethacin and at 2.5, 5, 10, 20, and 40 min after the intravenous administration of furosemide. These results were compared with those obtained in a control group of five rabbits submitted to the same protocol in which furosemide was given 6 h after the administration of phosphate buffer without indomethacin.

In the group of rabbits that were given 18 mg of indomethacin and underwent bleeding and in the respective control group, determinations of renal blood flow, glomerular filtration rate, and urinary sodium and the constant recording of blood pressure also were performed for the purpose of determining whether the changes in the release of renin induced by indomethacin could be explained on the basis of systemic or intrarenal hemodynamic changes that are known to suppress the release of this hormone. In these rabbits, a priming injection of inulin and paraaminohippurate was given in 1 ml of physiologic solution through the marginal vein of the left ear, followed by a constant sustaining infusion of 0.05 ml/min. This infusion was started 1 h before treatment with indomethacin was begun and was continued during the whole experiment. Plasma concentrations of inulin and para-aminohippurate were determined in blood samples withdrawn from the central artery of the right ear. The concentrations of these substances in urine and of urinary sodium were determined in samples collected from a 7-F Foley cannula inserted into the bladder through the urethra. Blood pressure was recorded constantly on a polygraph (Grass Instrument Co., Quincy, Mass.) from a 21-gauge butterfly needle placed in the central artery of the left ear and connected to a transducer (Statham 23 Db). (Statham Instruments, Oxnard, Calif.)

The effect of the different doses of indomethacin on the renal synthesis of prostaglandin was measured in kidneys removed from the three groups of rabbits treated with different doses of indomethacin and removed from the non-treated control group after hemorrhage. The effect of the administration of indomethacin on prostaglandin synthesis was studied in two additional groups of normal rabbits that did not undergo hemorrhage. The procedures used to accomplish this measurement are outlined in detail below.

In addition, attempts were made to determine if other inhibitors of prostaglandin synthesis with a molecular configuration different from that of indomethacin, such as meclofenamate and aspirin, also exhibit similar effects on the release of renin. This was accomplished by treating two different groups of six rabbits each with 9 mg/kg of meclofenamate or aspirin. Because of the poor effects obtained with 9 mg in inhibiting prostaglandin synthesis, a third group of six rabbits was treated with 18 mg of aspirin and was studied. The protocol used to test the effects of these drugs on resting and posthemorrhagic levels of plasma renin activity was identical to that outlined above for indomethacin.

Chemical methods. Preparation of renal tissue for determination of prostaglandin concentration. The prostaglandin concentration in excised tissue that is allowed to remain at room temperature is much higher than the concentration in the same tissue aliquot that is frozen immediately on removal (6). This phenomenon has been confirmed in our laboratories, although increases after incubation have never exceeded fivefold to sixfold (7). Because the measurements of prostaglandin concentration in renal tissue proposed in this study were used to evaluate the inhibition produced by indomethacin rather than to estimate the true changes in tissue concentration, the lack of postremoval enhancement of prostaglandin synthesis could be used to assess the effect that the three selected doses of indomethacin have in blocking prostaglandin synthesis (7). Thus, the kidney from each of the rabbits was rapidly removed and cut into equal halves (transverse section through the hilus). One half was immediately immersed in liquid nitrogen, whereas the second half was kept at room temperature for 10 min before being frozen in the same manner.

After the completion of the experiment, the frozen kidneys were thawed at 3°C (cold room) and the prostaglandins were extracted and measured by radioimmunoassay, according to the procedures reported previously (8). This approach of evaluating the inhibition of prostaglandin synthesis has been used in previous studies (7).

Chemical test to determine the validity of measurements of plasma renal activity. Determinations of plasma renin activity do not measure the actual concentration of circulating renin in plasma but measure the capacity of plasma to release angiotensin in a given unit of time and under defined laboratory conditions. The amount of angiotensin I released from plasma is primarily dependent on the concentration of renin but is also influenced by the concentration of renin substrate (9). Thus, a change in plasma renin activity after indomethacin administration might be due to an in vivo change in the plasma level of renin or renin substrate (or both) or to a change in the velocity of the renin-angiotensinogen reaction. Additionally, when the amount of angiotensin I released from plasma is estimated by radioimmunoassay (5), a falsely low estimate would result if indomethacin interfered with the binding capacity of angiotensin I antiserum for angiotensin I.

The possibility that the values of plasma renin activity seen after the administration of indomethacin were due to a large change in plasma renin substrate or to an in vivo production of a metabolite that could interfere with the formation of circulating angiotensin was examined in an

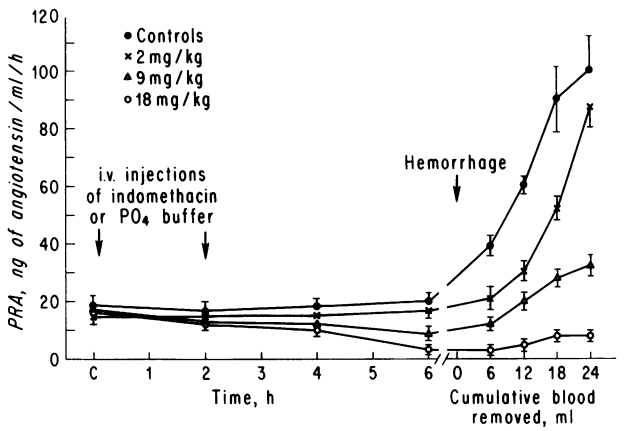

FIGURE 1 Effect of three different doses of indomethacin on resting values of plasma renin activity (PRA) and on its peripheral increase elicited by withdrawal of 24 ml of blood.

additional group of five rabbits treated with the highest dose of indomethacin (18 mg/kg). Blood samples for the determination of plasma renin activity, renin initial velocity, and renin substrate were collected before and at 2, 4, and 6 h after indomethacin administration. Blood samples were collected in precooled tubes containing ethylene glycol bis-(β-aminoethyl ether)N,N,N',N'-tetraacetic acid. Renin substrate concentration and angiotensin generation were measured by techniques published in previous studies (9, 10).

To determine whether indomethacin interfered with the renin angiotensinogen reaction in vitro, the rates of angiotensin formation at 4 and 8 min were measured in a reaction mixture containing a 1-ml aliquot of plasma pooled from three rabbits that were nephrectomized 24 h previously, 0.1 ml of renin solution containing 0.2 dog U/ml of hog renin (Nutritional Biochemicals Co., Cleveland, Ohio) and 0.075 ml of phosphate buffer containing sufficient indomethacin to obtain a final concentration of 60 μg/ml in the mixture. Tubes treated in an identical manner but incubated with 0.075 ml of phosphate buffer without indomethacin were used as controls.

The incubations were performed at 37°C, pH 7.4, and in the presence of 1.5 mg/ml of EGTA and 1.0 mg/ml of diisopropylfluorophosphate. The reaction was stopped by the adding of 0.1 ml of 5 N HCl solution, and the tubes were immediately transferred to a water bath at 85°C for 3 min (9). To ensure that indomethacin was not precipitated during the incubation, its concentration was measured by a fluorometric procedure (11) in duplicate tubes submitted to the same procedure, with the exception that the reaction was stopped by placing the tubes in ice. The rationale underlying the validity of the methods of estimating the initial velocity of the hog renin-rabbit angiotensinogen reaction has been extensively discussed in previous studies (9, 10).

The measurement of plasma renin activity by radioimmunoassay (5) assumes that the concentration of angiotensin I released in plasma after incubation can be calculated by comparing the displacement of ^{125}I-angiotensin I from angiotensin I antiserum with the displacement produced by known amounts of nonlabeled angiotensin I. Under our experimental conditions, the highest concentration of indomethacin in plasma which was detected by fluorometric techniques (11) 4–10 min after the intravenous injection of 9 mg/kg of indomethacin never exceeded 50 μg/ml. Thus, the possible interference of indomethacin with the radioimmunoassay reaction was studied by performing the standard radioimmunoassay curve using plasma from nephrectomized rabbits that contained either 60 μg/ml of indomethacin or Tris buffer in which indomethacin was dissolved to obtain a final concentration of 60 μg/ml.

Statistical analysis. The significance of the differences in basal levels of plasma renin activity and in the increments of plasma renin activity elicited by either hemorrhage or furosemide seen in the treated groups with respect to the control group was tested using analysis of variance (nonpaired t test). The same test was applied to determine the significance of the changes induced by indomethacin on renin substrate and on angiotensin generation.

RESULTS

The effects of three different doses of indomethacin on the basal values and on the elevation of peripheral plasma renin activity elicited by hemorrhage are presented in Fig. 1. The administration of 9 or 18 mg/kg of this drug resulted in a significant ($P < 0.01$) decrease in the values of peripheral plasma renin activity.

The average (Mean±SE) plasma renin activity of the group of rabbits treated with 2 mg/kg was 14.5±1.5 ng/ml per h before the treatment and 17.3±1.9 6 h after the treatment. This change is not significantly different when compared with the change obtained in the untreated controls.

Fig. 1 also shows that the rapid removal of 24 ml of blood resulted in a fivefold elevation of plasma renin activity in the untreated control group, whereas there was no hemorrhage effect in the group treated with 18 mg/kg of indomethacin. The administration of 9 mg/kg of indomethacin did not completely prevent the elevation of plasma renin activity elicited by hemorrhage, but the observed increase was significantly less ($P < 0.01$) than that for the control group.

The administration of 2 mg/kg of indomethacin reduced the enhancement of plasma renin activity in the early stages of hemorrhage (Fig. 1). The averaged (Mean±SE) values of plasma renin activity measured in this group at the end of the removal of 6 and 12 ml of blood were, respectively, 20.5±2.5 and 30.7±3.0 ng/ml per h. These values are significantly lower ($P < 0.01$) as compared with the respective values obtained in the nontreated controls, which were 38.5±2.2 and 60.2±2.2 ng/ml per h. However, the elevation of plasma renin activity after the removal of 18 ml of blood (56.2±3.7 ng/ml per h) from the rabbits treated with 2 mg/kg of indomethacin was slightly lower ($P < 0.05$) than the value for the nontreated controls (90.2±9.2 ng/ml per h). The average after the withdrawal of 24 ml of blood (87.5±6.0 ng/ml per h) was not statistically different from the respective value after similar withdrawal in the nontreated control (100.3±9.5 ng/ml per h).

The cited changes in the basal values of plasma renin

activity in the rabbits treated with 18 mg/kg of indomethacin occurred in the absence of significant changes in the renal clearances of para-aminohippurate or inulin or in systemic blood pressure. Before treatment began, the calculated values of renal blood flow and glomerular filtration rate were 45.3±4.3 and 9.7±1.06 ml/min, respectively, whereas 6 h after the first injection of indomethacin, they were 39.9±1.46 and 8.2±0.5 ml/min. In these rabbits, the excretion of urinary sodium before and 6 h after treatment was 6.8±0.5 and 6.1±0.9 μeq/min, respectively.

In addition, the administration of 18 mg/kg of indomethacin did not affect significantly the basal values of blood pressure. The systolic and diastolic average blood pressures before treatment were 94±3.0 and 65±3.6 mm Hg, whereas 6 h after, they were 92±3.4 and 63±3.7 mm Hg.

The effects of 18 mg/kg of indomethacin on the basal levels and on the enhancement of peripheral plasma renin activity induced by the intravenous administration of 5 mg/kg of furosemide are presented in Fig. 2. The results are comparable to those obtained in the group treated with 18 mg/kg indomethacin after hemorrhage—that is, the basal values of plasma renin activity were significantly decreased ($P < 0.01$) and indomethacin completely prevented the 2.7-fold increase induced by furosemide in the untreated controls ($P < 0.01$).

The concentrations of prostaglandin E in the kidney halves frozen 6 s after removal from the untreated controls that did not undergo hemorrhage were significantly lower than the concentrations in their respective halves allowed to stand at room temperature for 10 min (Fig. 3 left panel). The postremoval enhancement of prostaglandin concentration was effectively abolished 6 h after the administration of 18 mg/kg of indomethacin (Fig. 3 left panel). These results contrast with results obtained from kidneys of control animals after hemorrhage (Fig. 3 right panel), in which renal ischemia due to decreased perfusion pressure increased the basal rate of prostaglandin synthesis so that the concentration of prostaglandin measured in the halves frozen 6 s after removal

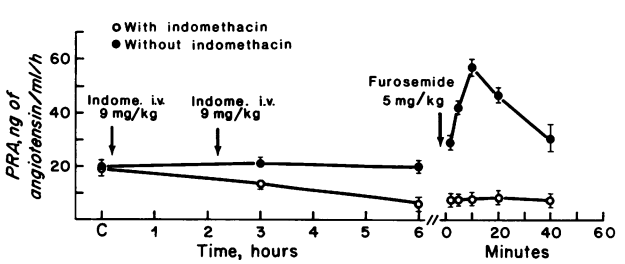

FIGURE 2 Effect of indomethacin on resting values of plasma renin activity (PRA) and on its peripheral increase elicited by intravenous injection of 5 mg/kg of furosemide. Mean±SE is indicated.

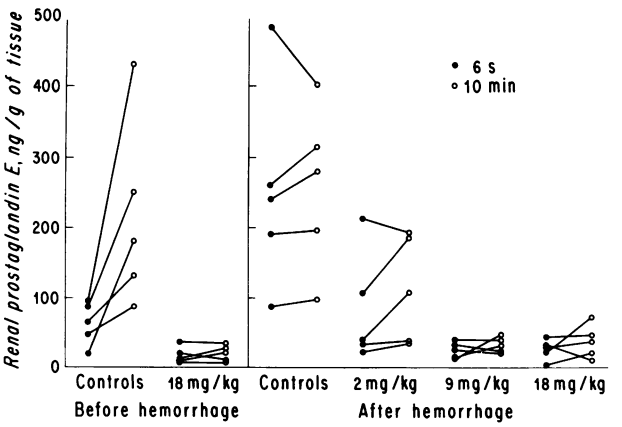

FIGURE 3 Effect of three different doses of indomethacin on concentration of renal prostaglandins measured at 6 s (solid circle) and at 10 min (open circle) after removal of kidney.

was as high as those estimated in the respective aliquots that were allowed to remain 10 min at room temperature (Fig. 3 right panel). Therefore, the incubation of the kidney at 24°C did not increase the synthesis rate of prostaglandin higher than that already induced by hemorrhage. Comparison of the concentration of renal prostaglandin found at 6 s and at 10 min in kidneys removed from the group of rabbits that underwent hemorrhage after being treated with 9 and 18 mg of indomethacin showed that these doses prevented the enhancements elicited either by hemorrhage or by postremoval incubation at 24°C.

The administration of 2 mg/kg of indomethacin probably was not so effective in blocking the synthesis of prostaglandin because its concentration measured at 6 s and 10 min in kidneys from three rabbits of this group was twofold to fourfold higher than that found in the group treated with 9 or 18 mg/kg, that is, within the range of the nontreated controls (Fig. 3 right panel).

The effects of indomethacin on plasma renin activity, plasma substrate concentration, and angiotensin generation in five normal rabbits are shown in Table I. In

TABLE I

Effect (Mean±SE) of Indomethacin on Plasma Levels of Renin Substrate and on Angiotensin Generation

	Renin substrate (n = 5)	Angiotensin generation (n = 5)	Plasma renin activity (n = 5)
	ng/ml per min	*ng/ml per min*	*ng/ml per h*
Control	230.4±15.7	5.12±0.29	18.4±2.1
After 1st injection, *h*			
2	222.2±24.7	5.28±0.13	15.6±0.68
4	214.0±8.0	4.86±0.20	8.3±1.7
6	239.0±10.3	5.40±0.36	6.1±1.1

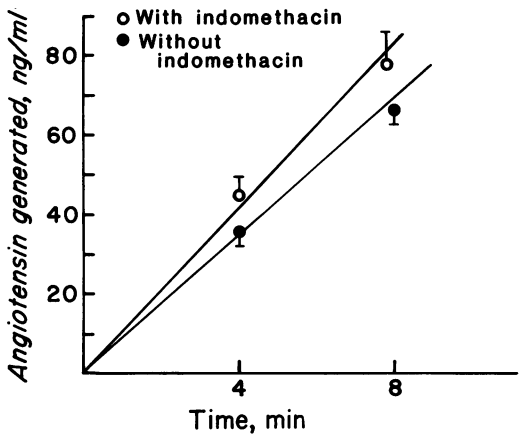

FIGURE 4 Rate of angiotensin I formation from nephrectomized rabbit plasma incubated with (solid circle) and without (open circle) 60 μg/ml of indomethacin.

spite of the progressive decrease in plasma renin activity, the values for renin substrate and angiotensin generation recorded at 2, 4, and 6 h after the administration of indomethacin were within the range recorded during the period before the injection of indomethacin.

The angiotensin that was generated at 4 and 8 min from 1 ml of plasma pooled from nephrectomized rabbits was 8.1±0.6 ng/ml per min, and this rate was not altered by indomethacin (Fig. 4). The yield of angiotensin in the presence of 60 μg/ml of indomethacin was 9.9±0.8 ng/ml per min.

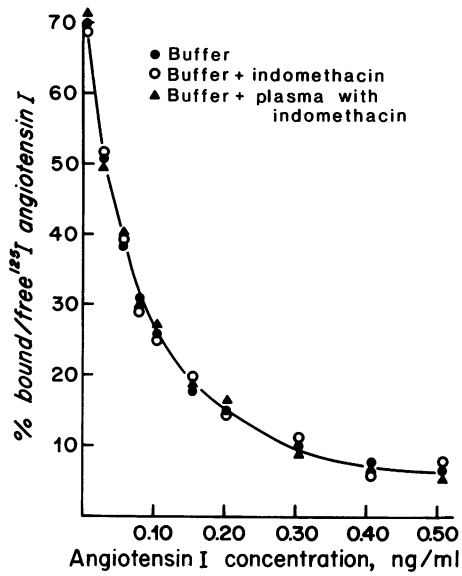

FIGURE 5 Standard curves for radioimmunoassay of angiotensin I performed (1) in presence of 60 μg/ml of indomethacin added to reaction mixture (open circle) or transferred with assayed plasma (triangle) or (2) in absence of indomethacin (solid circle).

A typical radioimmunoassay equilibrium curve shows that the percentage of bound to free labeled angiotensin to angiotensin I antiserum decreased asymptotically as the concentration of synthetic angiotensin I increased (Fig. 5). The characteristics of the equilibrium curve

TABLE II

Effects (Mean±SE) of Aspirin and Meclofenamate on Plasma Renin Activity and on Renal Synthesis of Prostaglandin E

	Untreated (n = 6)	ASA, *9 mg/kg* (n = 6)	ASA, *18 mg/kg* (n = 5)	Meclofenamate *9 mg/kg* (n = 6)
PRA, *ng/ml per h*				
Control	18.8±2.1	17.5±2.0	15.4±1.6	17.8±1.1
After onset of treatment, *h*				
2	16.8±2.2	17.4±1.2	15.6±1.4	19.2±1.6
4	18.2±2.0	17.8±1.9	16.6±3.0	18.0±1.6
6	20.0±2.0	17.5±1.3	16.8±1.9	18.6±1.6
During hemorrhage, *ml*				
6	38.5±2.2	37.5±2.0	21.0±4.1*	18.6±2.2*
12	60.2±2.2	60.6±3.3	25.6±5.0*	28.5±3.6*
18	90.2±9.2	91.8±4.3	35.2±2.7*	52.1±6.4*
24	100.3±9.5	96.5±4.3	44.2±4.4*	74.6±5.2†
PGE, *ng/g of tissue*				
After kidney removal				
6 s	252.0±64.0	213.0±42.0	18.8±6.3	22.6±3.2
10 min	258.9±52.0	253.0±51.6	20.2±6.7	31.0±5.3

Significantly different from control: * $P < 0.01$; † $P < 0.05$.
ASA, acetylsalicyclic acid; PGE, prostaglandin E; PRA, plasma renin activity.

did not change when the radioimmunoassay reaction was performed in the presence of 60 μg of indomethacin in Tris buffer or plasma containing 60 μg of indomethacin.

Finally, Table II shows the effects of 9 mg/kg of meclofenamate and 9 and 18 mg/kg of aspirin on basal levels of plasma renin activity and on its peripheral enhancement produced by hemorrhage. The effects of 9 mg/kg of meclofenamate on plasma renin activity were similar to those obtained by 18 mg of aspirin in that these doses resulted in an effective blockade of prostaglandin synthesis in the kidney and they exerted an interference of a similar magnitude on the increase of peripheral renin produced by hemorrhage.

On the contrary, 9 mg/kg of aspirin were insufficient to diminish renal synthesis of prostaglandins and did not alter the increase in renin during hemorrhage.

DISCUSSION

This study shows that the ability of indomethacin to decrease the basal values of plasma renin activity and to prevent its peripheral elevation elicited by hemorrhage depends largely on the administered dose.

Several theoretic ways exist by which indomethacin or its degradation products could decrease the basal levels of plasma renin activity and slow the peripheral elevation produced by hemorrhage. One of these would be to decrease plasma substrate (9). This is a definite possibility if one considers that plasma renin activity is not a true estimate of the actual concentration of circulating renin but is a measurement of the rate of angiotensin formation that could be limited by the concentration of substrate in plasma. Thus, the increased dose of indomethacin given to different groups of rabbits might increase the impairments in the rate of synthesis of substrate by the liver. This would eventually account not only for the progressive decrements in the basal levels of plasma renin activity seen in the different groups but also for the progressive suppression of angiotensin formation after hemorrhage. Simultaneous determinations of plasma renin activity, renin substrate, and generation of angiotensin during the 6 h after the administration of indomethacin showed that the decrease in angiotensin formation produced by endogenous renin (plasma renin activity) occurred in the absence of any significant change in the concentration of plasma renin substrate. Furthermore, the unaltered rate of angiotensin formation elicited by minute amounts of exogenously added hog renin indicated that the available substrate is also reactive to minimal enzymatic stimulation. Thus, the decrease seen in plasma renin activity does not seem to be due to inhibition of the renin-angiotensinogen reaction by indomethacin or its metabolic derivatives.

The unaffected formation of angiotensin by hog renin in plasma from nephrectomized rabbits with and without added indomethacin indicates that the effect of indomethacin on plasma renin activity values is not due to in vitro interference with the renin-angiotensinogen reaction. It could be argued that indomethacin exerts an inhibitory effect on the endogenous rabbit renin-normal rabbit plasma reaction that is not seen in the hog renin-nephrectomized plasma reaction. However, data in the literature (12) show that differences in the renin angiotensinogen reaction between different species are quantitatively small. Hence, the rationale underlying this test was that any gross and nonspecific change produced in vitro by indomethacin on the molecular structure of renin or renin substrate should be detected by the use of any heterologous renin, which is reactive with rabbit plasma.

The results of this study also showed that the decreases in plasma renin activity produced by indomethacin were not due to artifactual interferences with radioimmunoassay determinations. This lack of interference was expected because the final concentration of indomethacin tested in the TRIS buffer mixture reaction was very low. However, this concentration corresponded to the highest concentration that has been attained in plasma under our experimental conditions.

These points of evidence give strong support to the hypothesis that indomethacin or its degradation product alters the ability of the kidney to release renin. Confirmatory evidence was provided by our finding that indomethacin not only interfered with the enhancement of peripheral plasma renin activity induced by hemorrhage but also blocked the increase that was elicited by furosemide. The increase in the release of renin produced by this diuretic has been attributed to a mechanism that operates primarily at the level of the macula densa (13) rather than at the level of the stretch receptors of the afferent arteriole (which are believed to be stimulated mainly by hemorrhage). These observations, therefore, indicate that the blockade of renin release produced by indomethacin is not specifically exerted on any particular receptor but is exerted at a more distal level involving a final common pathway for renin release.

The other important aspect related to this study concerns the question of whether or not the lowering effect of indomethacin on the release of renin is exerted indirectly through the blockade of prostaglandin synthesis. The finding that other blockers of prostaglandin synthesis—blockers with a molecular configuration different from the configuration of indomethacin—such as meclofenamate and aspirin, produced the same effect on the release of renin seems to offer indirect support to this concept (14). However, much caution should be exercised in interpreting these data because the possibility still remains that the lowering effect on the release

of renin is a phenomenon related to the benzoic rings contained in the molecular structure of these anti-inflammatory compounds and thereby is nonfunctionally related to the blockade of prostaglandin synthesis. At any rate, the notion that renal synthesis of prostaglandins could be acting as an important permissive factor in the release of renin is not so surprising considering that other investigators (15, 16) have described experimental circumstances in which changes in renin were accompanied by changes of similar direction in prostaglandins. Zusman et al. (15) found that plasma levels of prostaglandin A increased during a low salt diet and decreased during a high salt diet in parallel with changes in plasma renin activity, while Tobian et al. (16) reported that the renal levels of prostaglandin E were decreased in kidneys of rats exposed to a high salt diet.

In conclusion, all the evidence presented herein shows that indomethacin alters the ability of the kidneys to release renin and that this effect is also exhibited by other anti-inflammatory compounds, such as meclofenamate and aspirin. This observation enhances the interest in knowing the intimate mode of action of aspirin-like drugs on renin and prostaglandins. This subject has obvious important clinical and therapeutic implications.

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