Aspirin Lowers Blood Pressure in Patients With Renovascular Hypertension

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To clarify the role of renal prostanoid in hyperreninemia and high blood pressure in human renovascular hypertension, we measured prostaglandin E2 and renin activity in renal venous and abdominal aortic plasma before and after the intravenous administration of the cyclooxygenase inhibitor, aspirin dl-lysine. Subjects were six patients with unilateral renovascular hypertension and six with essential hypertension. In patients with renovascular hypertension, prostaglandin E2 concentration in renal venous plasma from the stenotic kidney was 9.25 ± 1.48 pg/ml, which was significantly higher ($p < 0.01$) than the concentration in the renal venous plasma from the normal kidney (4.97 ± 1.02 pg/ml) or in the aortic plasma (2.59 ± 0.15 pg/ml). Plasma renin activity was also higher in the renal vein of the stenotic kidney than in the other two sites. The stenotic side/normal side ratio of the renal venous prostaglandin E2 correlated significantly with a renin ratio greater than 1.5 ($r = 0.8211, p < 0.05$). Intravenous injection of aspirin dl-lysine (18 mg/kg) 30 minutes later markedly suppressed prostaglandin E2 and renin levels at all sites and clearly lowered arterial blood pressure (mean: from 120 ± 6 to 110 ± 5 mm Hg, $p < 0.01$). The reduction in blood pressure correlated significantly with the suppression of plasma renin activity in the aorta ($p < 0.05$) and in the renal vein of the stenotic kidney ($p < 0.01$). Conversely, in patients with essential hypertension, aspirin had little effect on renin levels and increased mean blood pressure. These data indicate that renal prostaglandin plays an important role in the augmented release of renal renin and the pathogenesis of hypertension in human renovascular hypertension. (Hypertension 1989;14:461–468)

Whether the renal synthesis of prostanoids is increased or decreased by ischemia due to renal arterial stenosis is still controversial. However, in human renovascular hypertension (RVH) associated with unilateral renal arterial stenosis, it has been shown that renal venous concentration of prostaglandin E2 (PGE2) is higher on the ischemic than on the normal side and that the stenotic side/normal side ratio of renal venous PGE2 correlates with the renal venous renin activity ratio.1–3 The increase of PGE2 concentration has been considered to be secondary to stimulation of the renin-angiotensin system.4–5

However, PGs (PGE2, PGI2) are known to stimulate renal renin secretion directly or indirectly.6–8 In renin-dependent hypertension such as RVH, if renal PGs increase and participate in hyperreninemia, a PG synthesis inhibitor (cyclooxygenase inhibitor) ought to suppress plasma renin activity (PRA) and lower blood pressure (BP). But, surprisingly, it is difficult to find reports of such effects in human RVH, and there are many reports on animals with RVH showing that indomethacin increases BP.4,5 This may be because the outcome depends on 1) the kind of inhibitor used, 2) whether inhibition is acute or chronic, and 3) the balance between inhibition of systemic vascular PGs producing vasodilation and inhibition of renal PGs that stimulate renin release. Recently, intravenously injectable aspirin, aspirin dl-lysine (ASP),9 has been made available for clinical use. We used it to produce rapid inhibition of PG synthesis and attempted to clarify the role of renal PG in renin release and BP in human RVH.

Subjects and Methods

Patients

The subjects studied consisted of two groups with normal renal function: six patients with unilateral RVH and six with essential hypertension. The patient...
profiles are summarized in Table 1. Renal arterial stenosis was detected by digital subtraction angiography or selective renal arterial angiography. All six patients with RVH had a unilateral renal arterial stenosis of over 75% that was caused by fibromuscular dysplasia in three and arteriosclerosis in three. Six patients with essential hypertension were confirmed to have normal renal arteries by angiography. The BP of patient I (30-year-old man, Table 1) with essential hypertension was almost normal when hypertensive changes. All patients were fully confined to bed for 1 hour and then trans-ferred, still supine, to the laboratories for investigation. BP in the left upper arm was measured twice at 4-minute intervals with an automatic ultrasound sphygmomanometer (BP-103, Nippon Colin Co., Ltd., Komaki City, Aichi Prefecture, Japan). Heart rate (HR) and electrocardiogram were also monitored. Thirty minutes after catheterization of the right femoral artery and vein by Seldinger’s method, abdominal aortic and bilateral renal venous blood samples were drawn simultaneously for measurement of PRA and plasma PGE2 concentration. 

Study Protocol

Subjects were placed on a constant dietary sodium intake of about 120 meq/day 1 week before and for the duration of the study. All medication was stopped for at least 2 weeks before the study, except in two patients with RVH with severe coronary arterial disease who continued to receive small doses of \( \beta \)-blockers and isosorbide dinitrate (Table 1). The study was performed in the cardiovascular laboratories of the Division of Radiology. All the patients were confined to bed for 1 hour and then transferred, still supine, to the laboratories for investigation. BP in the left upper arm was measured twice at 4-minute intervals with an automatic ultrasound sphygmomanometer (BP-103, Nippon Colin Co., Ltd., Komaki City, Aichi Prefecture, Japan). Heart rate (HR) and electrocardiogram were also monitored. Thirty minutes after catheterization of the right femoral artery and vein by Seldinger's method, abdominal aortic and bilateral renal venous blood samples were drawn simultaneously for measurement of PRA and plasma PGE2 concentration.

Measurement of Prostaglandin E2 in Plasma

The amount of PGE2 in the plasma was determined by using a \( [^{125}\text{I}] \)PGE2 radioimmunoassay (RIA) kit (New England Nuclear Research Products, Boston, Massachusetts). We used the modified assay procedure given in the kit manual, as reported. In brief, for extraction, 2 ml plasma at 4°C were equilibrated with 5,000 dpm \( [^{3}H] \)PGE2 (sp. act. 100 Ci/mmol, New England Nuclear Research Products) to monitor recovery and acidified with 0.05 M citrate at pH 3.5. Bond-Elut C-18 extraction cartridge columns (200 mg, Analytichem Intl., Inc., Harbor City, California) were pretreated with 2 ml methanol and 4 ml 0.05 M citrate. The acidified plasma was passed through the cartridge and eluted serially with 2 ml distilled water, 2 ml 10% metha-
nol, 2 ml cyclohexane, and 2 ml ethyl acetate. The last solvent was evaporated at 37°C under a stream of nitrogen. Additionally, Bond-Elut silica columns (500 mg, Analytichem Intl., Inc.) were prepared for further purification of PGE$_2$ using solvent mixtures of increasing polarity: benzene:ethyl acetate: methanol, 60:40:0 (solvent I), 60:40:15 (solvent II), 60:40:20 (solvent III). Extracted and dried residue samples were reconstituted with 1 ml solvent I and applied onto the silica columns washed in advance with solvent III and I. After washing the column with 6 ml solvent I, PGE$_2$ was eluted off with 6 ml solvent II into a siliconized glass vial. The eluted solvent was dried again under nitrogen gas and used in the RIA procedure.

All PGE$_2$ concentrations were determined with corrections made for each loss in extraction and purification. Percentage recovery of the added [3H]PGE$_2$ was 86.6±0.5% (mean±SEM, n=90) throughout the extraction and purification. We also examined the recovery of authentic PGE$_2$ (10 pg/ml) added to PG-free plasma (supplied by New England Nuclear Research Products) using the whole assay procedure described above, and 76.5±1.7% (n=20) was recovered.

**Plasma Renin Activity**

Plasma renin activity was determined by a RIA method reported elsewhere.\textsuperscript{12,13}

**Cyclooxygenase Inhibitor: Aspirin dl-Lysine**

ASP (Venopirin, The Green Cross Corporation) was used to achieve cyclooxygenase inhibition. Each vial contained 900 mg ASP, which is the salt of 497 mg aspirin and 403 mg DL-lysine, as the active ingredient. We used ASP (Venopirin) because 1) it is intravenously injectable, 2) indomethacin, a representative PG synthesis inhibitor, is not injectable for clinical use and has many other effects apart from its cyclooxygenase inhibitory action,\textsuperscript{14,15} and 3) acute inhibition of PG synthesis is necessary to investigate the change of PRA and BP without modification by other factors. After intravenous administration of ASP, the onset of the inhibitory action on cyclooxygenase activity of microsome fractions from renal medulla is rapid.\textsuperscript{9} Inhibition is approximately 60% after 5 minutes, reaches a peak at 1 hour, and slowly reduces thereafter (83% inhibition after 2 hours), when given in a dose of 10 mg/kg as aspirin.\textsuperscript{9}

Because ASP contains DL-lysine and we could find no information about its nonspecific action on BP or PRA in human subjects, the subjects with essential hypertension were used as a control group for the subjects with RVH.

**Statistical Analysis**

Statistical assessment of the data was done by analysis of variance and Scheffe’s method for simultaneous multiple comparison.\textsuperscript{16} Student’s paired $t$ test was also used to compare control and treatment values of BP, HR, PRA, and PGE$_2$. In addition, the relation between renal vein PGE$_2$ ratio and PRA ratio, and between PRA and mean BP were subjected to linear regression analysis. Data are expressed as mean±SEM.

**Results**

**Prostaglandin E$_2$ Concentration in Plasma**

The data for plasma PGE$_2$ concentration in patients with RVH are presented in Figure 1 (I). Pretreatment PGE$_2$ concentrations in aortic plasma (A) and in renal venous plasma from the stenotic (S) and normal (N) side were 2.59±0.15, 9.25±1.48 (p<0.01 compared with values in A and N), and 4.97±1.02 pg/ml, respectively. Thirty minutes after the intravenous administration of ASP, the PGE$_2$ concentration in A, S, and N decreased to 1.95±0.25 (p<0.05 compared with control), 1.39±0.15 (p<0.01 compared with control), and 1.36±0.14 (p<0.05 compared with control) pg/ml, respectively. These results indicate the almost complete inhibition of renal PGE$_2$ synthesis by ASP. In patients with RVH, the pretreatment and posttreatment renal vein PGE$_2$ ratios (stenotic side/normal side) were 1.96±0.20 and 1.02±0.04 (p<0.01 compared with pretreatment values), respectively (Figure 2).

In patients with intact renal arteries, the renal venous PGE$_2$ concentration was significantly higher than the aortic PGE$_2$ concentration, and there was no difference in level between the right and the left side as shown in Figure 1 (II) (aortic PGE$_2$ concentration, 1.50±0.31; right side, 3.36±0.63 [p<0.05]; left side, 3.73±0.49 [p<0.01] pg/ml). ASP clearly inhibited renal PGE$_2$ production, as shown in Figure 1 (II) (aortic PGE$_2$ concentration, 1.14±0.22 [p<0.05 compared with control]; right side, 0.87±0.13 [p<0.05 compared with control]; left side, 1.04±0.21 [p<0.01 compared with control] pg/ml).

When analyzed by Student’s $t$ test, pretreatment aortic PGE$_2$ levels in the renovascular hypertensive patients were significantly higher than those in the essential hypertensive patients (p<0.05).

**Plasma Renin Activity**

In patients with RVH the PRA in A, S, and N was 5.28±0.88, 9.51±1.63 (p<0.05, S compared with values in A and N), and 5.39±0.86 ng/ml/hr, respectively [Figure 3 (I)]. This enhanced renin release from the ischemic kidney was markedly suppressed by ASP; PRA in A, S, and N decreased to 3.32±0.71, 4.55±0.94, and 3.49±0.69 ng/ml/hr (p<0.01), respectively [Figure 3 (I)]. Renal vein PRA ratio (stenotic side/normal side) was reduced from 1.76±0.12 to 1.29±0.03 (p<0.05, Figure 2). In patients with essential hypertension, PRA in the aorta, the right and the left renal vein was 2.70±0.89, 3.80±1.22, and 3.98±1.45 ng/ml/hr, respectively. These values tended to be decreased by injection of ASP, but there was statistically no significant suppression except in aortic PRA (aorta, 2.21±0.82 (p<0.05);
right renal vein, 2.92±0.90; left renal vein, 3.16±1.09 ng/ml/hr) as shown in Figure 3 (II).

Hemodynamics

Figure 4 gives the data for BP and HR before and after the inhibition of PG synthesis. Intravenous administration of ASP significantly lowered BP in patients with RVH (systolic, \( p<0.05 \); diastolic, \( p<0.01 \); mean, \( p<0.01 \)). In patients with essential hypertension, there was a small but significant increase in mean BP (\( p<0.05 \)). HR was not changed by ASP in either group.

Correlation Between Prostaglandin E\(_2\) and Plasma Renin Activity in Patients With Renovascular Hypertension

The renal venous stenotic side/normal side ratio of PGE\(_2\) significantly correlated with the ratio of PRA under basal conditions (\( r=0.8211, p<0.05 \)) (Figure 5). ASP inhibited renal PGE\(_2\) synthesis and eliminated the stenotic side–normal side difference of PGE\(_2\) (Figures 1 and 2). The difference in PRA between S and N was diminished, but still remained (Figure 2). The correlation of stenotic side/normal side ratio between PGE\(_2\) and PRA disappeared after PG synthesis inhibition.

Relation Between Blood Pressure and Plasma Renin Activity in Patients With Renovascular Hypertension

The correlation between mean BP and aortic PRA of each patient with RVH was not significant. So, as ASP suppressed PRA and lowered mean BP, we assessed the relation between the reduction of mean BP (\( \Delta \) mean BP) and the suppression of PRA (\( \Delta \) PRA) in A or S (Figure 6). The \( \Delta \) mean BP was significantly correlated with the \( \Delta \) PRA in A (\( r=0.8205, p<0.05 \)), and more closely correlated with the \( \Delta \) PRA in S (\( r=0.9224, p<0.01 \)).

Discussion

It remains uncertain whether the production of prostanoids is increased or decreased in kidneys.
RVH: renovascular hypertension; EHT: essential hypertension.

§p<0.05, simultaneous multiple comparisons using Scheffe's method. *p<0.05; **p<0.01; comparing treatment values with controls by paired t test.

with significant renal arterial stenosis. There are few reports in human RVH and there is no unanimity of opinion about the change of renal prostanoids in experimental animals with RVH.4,17-19 Recently, however, in two-kidney, one clip (2K1C) hypertensive rats, only PGE2 formation was found to be significantly increased in the glomeruli of the clipped kidney.20 Anderson et al21 reported that the production of PGs and thromboxane was increased in ischemic renal cortical slices from humans with RVH, though it was decreased in the ischemic medulla. Although we did not measure renal blood flow and, therefore, could not assess the secretion rate of PGE2, the present data suggest that PGE2 synthesis is increased in the stenosed kidney of

FIGURE 3. Panel (I): Renovascular hypertensive patients' plasma renin activity in aorta (A) and renal vein of stenotic (S) and normal (N) side before and 30 minutes after the intravenous (iv) injection of aspirin DL-lysine (ASP) (18 mg/kg) (n=6). Panel (II): Essential hypertensive patients' plasma renin activity in aorta (A) and renal vein of right (R) and left (L) side before and 30 minutes after the intravenous injection of ASP (18 mg/kg) (n=6).

FIGURE 4. Blood pressure (BP) and heart rate of the subjects with renovascular hypertension (RVH) and with essential hypertension (EHT) before and 30 minutes after the injection of aspirin DL-lysine.

FIGURE 5. Correlation between renal venous stenotic side/normal side (S/N) ratio of prostaglandin E2 (PGE2) and the S/N ratio of plasma renin activity (PRA) in each patient with renovascular hypertension.
RVH. We base this suggestion on 1) the renal 
veno-arterial difference in PGE2 concentration (about 
three times higher in S-A than in N-A), 2) the higher 
aortic levels of PGE2 in RVH compared with essential 
hypertension (despite the effects of avid pulmonary 
extraction), and 3) the significant correlation 
with renal venous stenotic side/normal side ratios 
between PGE2 and PRA and the suppression of 
excessive renin release by ASP.

Angiotensin II is known to stimulate the produc-
tion of PGs, but PGE2 and PGI2 are also 
known to accelerate renin secretion. Both sys-
tems must be able to act on each other in RVH, 
but our data indicate that renal PGE2 acts as one 
mediator in stimulation of renin release from the 
ischemic kidney.

PGI2 is also active in release of renin and is 
abundantly produced by the vascular endo-
thelium. Unfortunately, plasma 6-keto-PGF1alpha, a 
stable metabolite of PGI2, was not measured in the 
present study; thus, we cannot comment on the part 
played by PGI2 in the observed results. It is likely 
that the changes of PGE2 are paralleled by changes 
of PGI2 synthesis in the ischemic kidney.

It is possible that ASP further decreased renal 
blood flow to the stenotic kidney. However, the 
reduction in aortic PRA was not simply caused by 
the decrease of renal blood flow to the stenotic 
kidney because renal venous PRA on that side was 
markedly suppressed. If blood flow to the ischemic 
kidney had decreased drastically, PRA in the renal 
vein should have increased because of secretion of 
renin into a much reduced volume of blood. We 
believe it is reasonable to conclude that the suppres-
sion of PRA level resulted from the inhibition of 
renal PG synthesis by ASP.

The effect of PG synthesis inhibitors on BP in 
patients with RVH has not been confirmed. In 
2K1C hypertensive animals, both indomethacin and 
and aspirin accelerate hypertension after long-
term oral administration. This acceleration in hyper-
tension is considered to be attributable to a reduc-
tion of vascular PG (PGI2) biosynthesis and to be 
unrelated to renal PG production. In contrast, 
when indomethacin was acutely and intravenously 
jectected, the inhibitor showed a vasodilator action 
in 2K1C rats. Jackson et al reported that, in rats 
under the severe hyperreninemic condition caused 
by complete aortic ligation between the origin of the 
renal arteries, hypertension was reduced by indo-
methacin. In human unilateral RVH, our current 
study showed that intravenously injected ASP 
reduced hypertension, and the reduction appeared 
highly correlated with a substantial decrement in 
PRA. The discrepancy of the inhibitors’ action on 
BP may be because of the difference in administra-
tion route (orally or intravenously), that is, the 
effect of indomethacin or aspirin on BP depends on 
whether the suppressive effect on renin release or 
the attenuation of systemic vasodilatory PGs is 
dominant. Several years ago, a PG synthesis inhib-
itor could not be intravenously administered to 
human subjects with safety. Now it is possible to 
use injectable ASP, and by this means we have 
demonstrated the vasodepressor effect of a PG 
synthesis inhibitor as a result of PRA suppression in 
unilateral RVH.

In patients with essential hypertension, ASP pro-
duced a small increment in mean BP as was also 
noted with indomethacin. Acute administra-
tion of ASP appears to cause an acute reduction in 
vascular PG synthesis, thus leading to a pressor 
response in essential hypertension. In contrast, the 
dominant effect appears to be suppression of exces-
sive renin release and a depressor response in 
RVH. These different responses of BP to ASP may 
be useful for differential diagnosis of unilateral 
RVH from essential hypertension.

Two of the six patients with RVH could not 
discontinue /3-blocker or isosorbide dinitrate ther-
py because of ischemic heart disease (Table 1). 
However, the dosage used was small, and several 
investigators have already confirmed that the 
/3-adrenergic mechanism of renin release is indepen-
dent of the PG system. In fact, /3-blocker and
dinitrate slightly lowered the basal PRA and BP in these two patients compared with the other four patients (Table 1, Figure 4), but ASP obviously and independently suppressed their PRA and showed a depressor action. These results imply that the action of the cyclooxygenase inhibitor was independent of the medication.

In conclusion, the present data provide evidence that renal PG (PGE₂) plays an important role in acceleration of renal renin secretion and in the pathogenesis of BP elevation in RVH. The vasodepressor action of ASP in unilateral RVH may be helpful for differential diagnosis of RVH from other types of hypertension.

References


KEY WORDS • renin • renovascular hypertension • aspirin • prostaglandins
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