Indomethacin Decreases Arterial Blood Pressure and Plasma Renin Activity in Rats with Aortic Ligation

EDWIN K. JACKSON, JOHN A. OATES, AND ROBERT A. BRANCH

SUMMARY Severe renovascular hypertension was produced in rats by complete aortic ligation between the origin of the renal arteries. Six days after coarctation, a carotid cannula was implanted and mean arterial blood pressure (MABP) and plasma renin activity (PRA) were determined. Subsequently, indomethacin (5 mg/kg in oil) or vehicle was administered subcutaneously three times in the following 24-hour period. On day 7, MABP and PRA were again determined. Indomethacin reduced MABP from 179.0 ± 6.7 to 158.4 ± 8.8 mm Hg (P < 0.002, n = 11) and PRA from 21.2 ± 7.3 to 9.3 ± 2.9 ng Al/ml per hr (P < 0.045, n = 10), whereas vehicle treatment did not alter either MABP or PRA (n = 6). There was a significant association between the decrease in MABP and the percentage decrease in PRA following indomethacin treatment (r = 0.786, P < 0.018). A similar study was performed in aortic ligated rats in which the left kidney was removed at the time of ligation. In these animals, 6 days after surgery, MABP and PRA were 126.0 ± 6.9 mm Hg and 0.11 ± 0.06 ng Al/ml per hr (n = 6), respectively, and indomethacin had no effect on either MABP or PRA. These data provide evidence that the prostaglandin system is involved in the release of renin and in the pathogenesis of elevated blood pressure in this model of renin-dependent hypertension. Circ Res 49: 180-186, 1981

CONSIDERABLE evidence exists which implicates prostaglandins as important mediators of renin secretion. Central to this hypothesis is the observation that prostaglandin cyclooxygenase inhibitors prevent the renin secretion induced by several stimuli, including intrarenal baroreceptor activation (Data et al., 1978; Berl et al., 1979; Henrich et al., 1979), macula densa activation (Henrich et al., 1979; Olson et al., 1980), blockade of the angiotensin II short-loop negative feedback mechanism (Campbell et al., 1979a, Abe et al., 1980), and, in some species, β-adrenoreceptor stimulation (Campbell et al., 1979b; Feuerstein and Feuerstein, 1980). Since the renin-angiotensin system may be responsible for the elevated arterial blood pressure in certain types of experimental and clinical hypertension, inhibition of renin release by cyclooxygenase inhibitors represents a potential antihypertensive action of this class of drugs. Hypothetically then, in renin-dependent hypertension in which the hyperreninemia is prostaglandin mediated, cyclooxygenase inhibitors should alleviate both the hyperreninemia and hypertension.

Total ligation of the aorta between the origin of the renal arteries in rats produces severe renovascular hypertension which is renin dependent (Carretero et al., 1971; Sweet et al., 1976; Fernandes et al., 1977; Nishikawa et al., 1978; Wolpert et al., 1979; Ogawa et al., 1980; Jackson et al., 1981). The purpose of this study was to determine whether indomethacin can decrease arterial blood pressure and plasma renin activity in rats with severe renovascular hypertension.
INDOMETHACIN DECREASES MABP AND PRA/Jackson et al. 181

al., 1978; Sweet and Columbo, 1979). Further, since most forms of renin release in the rat examined thus far are prostaglandin mediated (Leyssac et al., 1975; Campbell et al., 1978a, 1978b), it seemed likely that the hyperreninemia resulting from aortic ligation is also dependent upon renal prostaglandin synthesis. Therefore, the current study was designed to (1) determine if the excessive renin secretion in aortic ligated rats is prostaglandin mediated, and (2) observe the effects of cyclooxygenase inhibition on arterial blood pressure in a model of hypertension which is secondary to severe hyperreninemia.

Methods

Male Sprague-Dawley rats (250-300 g) obtained from Harlan Labs were used in all experiments. Rats were maintained on a diet of Wayne Lab-Blox (Allied Mills, Inc.) containing 170 mEq Na+/kg and 246 mEq K+/kg and tap water ad libitum.

Under ether anesthesia, complete ligation of the aorta between the origin of the renal arteries was done (No. 0000 silk thread), taking meticulous care to avoid occlusion of the left renal artery and mesenteric artery (Rojo-Ortega and Genest, 1968). In some rats, a left nephrectomy was performed at the time of aortic ligation. Six days after aortic ligation, the animals were lightly anesthetized with ether and a chronic carotid cannula (Silastic, 0.02" i.d. X 0.037" o.d.) was implanted and exteriorized to the dorsal neck region. The study was begun on day 6 because arterial blood pressure rises rapidly after aortic ligation and does not plateau until that time (Sweet et al., 1976).

Four to 6 hours after the second surgical manipulation, the carotid cannula was connected to a Statham pressure transducer (Statham Instruments) and blood pressure was recorded on a Hewlett Packard physiograph (model 7758A). All measurements were obtained in the conscious unrestrained rat. Each rat was allowed an interval of 30 minutes to acclimatize to its surroundings before the animals were lightly anesthetized with ether and a chronic carotid cannula (Silastic, 0.02" i.d. X 0.037" o.d.) was implanted and exteriorized to the dorsal neck region. The study was begun on day 6 because arterial blood pressure rises rapidly after aortic ligation and does not plateau until that time (Sweet et al., 1976).

Plasma renin activity was determined by an angiotensin I radioimmunoassay kit (Squibb) and the results were expressed as nanograms of angiotensin I generated at 37°C per milliliter of plasma per hour (ng AI/ml per hr). Statistical analyses were performed with either a two-tailed paired or unpaired Student's t-test. All values are expressed as mean ± SEM.

Results

Preliminary studies were conducted to determine the reproducibility of aortic ligation-induced hyperreninemic hypertension. In 16 aortic ligated rats in which the left ischemic kidney had been removed at the time of coarctation, MABP and PRA were 130.1 ± 3.4 mm Hg and 0.28 ± 0.09 ng AI/ml per hr, respectively, 6 days after aortic ligation (Fig. 1). In 26 other rats, in which the ischemic kidney was left intact, aortic ligation was associated with a significantly higher MABP of 180.7 ± 4.0 mm Hg (P < 0.001) (Fig. 1). PRA was determined in 24 of these animals (blood samples unobtainable in two) and was significantly elevated (14.9 ± 3.4 ng AI/ml per hr) when compared to aortic ligated plus left nephrectomized animals (P < 0.001). These values for MABP and PRA 6 days after aortic ligation are in close agreement with previously reported values (Sweet et al., 1976).

Figure 2 illustrates the effects of indomethacin treatment on PRA and MABP in another group of aortic ligated rats. After indomethacin treatment, PRA decreased by 56% from 21.2 ± 7.3 ng AI/ml per hr to 9.3 ± 2.9 ng AI/ml per hr (P < 0.045, n...
The effects of indomethacin treatment (5 mg/kg, sc, 3 × in 24 hours) on plasma renin activity (PRA) and mean arterial blood pressure (MABP) in aortic ligated rats. n = number of observations. Values are expressed as mean ± SEM.

Concomitant with this decrease in PRA there was a 13% reduction in MABP from 179.0 ± 6.7 to 156.4 ± 8.8 mm Hg (P < 0.002, n = 11). The percentage decrease in PRA and decrease in MABP following indomethacin treatment were significantly correlated (r = 0.766, P < 0.016) (Fig. 3). Unlike PRA and MABP, HR was not affected by indomethacin treatment (431 ± 18 beats/min vs. 410 ± 15 beats/min before and after indomethacin, respectively).

A control group of aortic ligated rats was treated with vehicle without indomethacin (olive oil, 1 ml/kg, sc) in a fashion similar to the group of rats that received indomethacin. In these rats, PRA and MABP were not significantly affected, although PRA did tend to increase somewhat during the vehicle treatment (Fig. 4).

The toxic effects of indomethacin on the gastrointestinal tract of rats have been well documented (Fang et al., 1977; Soldato and Meli, 1978; Brown et al., 1978; Kauffman et al., 1979; Cioli et al., 1979). In our studies, autopsies of rats treated with indomethacin for 21-24 hours revealed some non-perforating gastric ulcerations, but not macroscopic intestinal lesions or peritonitis. Nevertheless, the possibility existed that the hypotensive re-
induced response on plasma renin activity was due to the possible relationship of this excessive renin secretion to the prostaglandin system has not previously been evaluated. Assuming that the indomethacin-induced response on plasma renin activity was due to inhibition of prostaglandin synthesis, the induction in hyperreninemia (Fig. 2) provides evidence that prostaglandins mediate the excessive renin secretion in this model. This would be consistent with the involvement of prostaglandins in mediating the blood pressure response to indomethacin in this model contrasts to reports of increases in pressure observed in alternative models of hypertension (Romero et al., 1975; Pugsley et al., 1975a, 1975b; Strong and Romero, 1976; Romero and Strong, 1977; Cangiano et al., 1978). However, a feature of these models is that the contribution of the renin-angiotensin system to the blood pressure elevation is equivocal. These latter studies have led to the suggestion that cyclooxygenase inhibitors reduce the production of vasodilatory and natriuretic prostaglandins, and therefore accentuate the hypertension. In other studies, indomethacin either has not influenced blood pressure (Zimmerman et al., 1978; Ylitalo et al., 1978; Yun et al., 1979) or, in situations of high plasma renin activity, has lowered blood pressure. In particular, indomethacin lowered the blood pressure in a patient with bilateral renal artery stenosis (Frohlich et al., 1979), in two siblings with renin-dependent hypertension, hyperaldosteronism and hypokalemia (DeJong et al., 1980), and in conscious sodium-depleted dogs (DeForrest et al., 1980). It is well recognized that the prostaglandin system has an integral role in the mechanisms of renin release (Oates et al., 1979); thus, it is possible that cyclooxygenase inhibition of prostaglandin production could result in decreases in blood pressure in renin-dependent hypertension, in which the hyperreninemia is prostaglandin mediated. Evaluation of this hypothesis would be contingent on acquiring a model of renin-dependent hypertension, in which the excessive renin secretion is prostaglandin mediated.

Ligation of the aorta between the renal arteries of rats results in an ischemic left kidney and induces a severe form of hypertension associated with high plasma renin activities (Fig. 1). The mechanism for the elevation of renin levels in this model and the possible relationship of this excessive renin secretion to the prostaglandin system has not previously been evaluated. Assuming that the indomethacin-induced response on plasma renin activity was due to inhibition of prostaglandin synthesis, the reduction in hyperreninemia (Fig. 2) provides evidence that prostaglandins mediate the excessive renin secretion in this model. This would be consistent with the involvement of prostaglandins in mediating the hypertension. In this renin-dependent model of hypertension, indomethacin treatment lowered mean arterial blood pressure (Fig. 2). This was unlikely to be a non-specific effect due to indomethacin toxicity, as similar indomethacin administration to aortic ligated plus left nephrectomized animals failed to reduce blood pressure (Fig. 5). Although this low renin control group was not as hypertensive as the aortic ligated rats with an intact left ischemic kidney, these experiments indicate that the hypotensive action of indomethacin was not due to gastrointestinal toxicity, peritonitis, and shock. Along these lines, it is relevant to mention that we have examined the effects of indomethacin on the mean arterial blood pressure of aortic ligated plus left nephrectomized spontaneously hypertensive rats. These animals were hypertensive due to a genetic mechanism, had low plasma renin activities due to removal of the left ischemic kidney, and had been subjected to the surgical stress of aortic ligation. In these low renin, hypertensive, aortic ligated animals, 24-hour indomethacin treatment increased, rather than decreased, mean arterial blood pressure in each of the three rats investigated (173 ± 12 mm Hg vs. 198 ± 12 mm Hg). Since plasma renin activity was high in the aortic ligated rats and low in the aortic ligated plus left nephrectomized spontaneously hypertensive rats, it appears that the hypotensive action of indomethacin was dependent upon the presence of excessive renin secretion prior to treatment. Further support for a cause and effect relationship was a significant correlation between the decrease in mean arterial blood pressure and the percentage decrease in plasma renin activity following indomethacin treatment in aortic ligated rats (Fig. 3). This correlation indicated that at least 59% of the variability in mean arterial blood pressure following indomethacin administration was explainable on the basis of changes in plasma renin activity. Since the correlation coefficient for this association was only 0.766, physiological changes besides alterations in plasma renin activity may have contributed to the hypotensive action of indomethacin. However,
pertension is true, then chronic infusions of renin-din production can result in renin-dependent hypertension. Similarly, Colina-Chouria and those two-kidney Goldblatt rabbits in which renal blood flow. Similarly, Colina-Chouria and reported recently by Hockel and Cowley (1979) who demonstrated that chronic intrarenal prostaglandin E2 infusions produced both elevated plasma renin activity and hypertension in dogs. Further, the rise in blood pressure during intrarenal prostaglandin E2 infusions had an almost perfect linear relationship with the rise in plasma renin activity.

As mentioned previously, with other experimental models, prostaglandin synthesis inhibition may exacerbate hypertension. Romero and Strong (1977) have clearly demonstrated that chronic indomethacin treatment increases the blood pressure of one-kidney Goldblatt rabbits. Furthermore, indomethacin induced malignant hypertension in those two-kidney Goldblatt rabbits in which renal artery constriction was associated with a decrease in renal blood flow. Similarly, Colina-Chouria and co-workers (1979) reported that chronic indomethacin administration to normotensive rabbits also increased arterial blood pressure. Several explanations are possible for these apparent discrepancies. First, species differences must be taken into account. In the rat kidney, prostaglandin E2 is considered to be a vasoconstrictor whereas, in the rabbit kidney, prostaglandin E2 is a vasodilator (Malik and McGiff, 1975). Second, the time frame of indomethacin administration must be considered. The effects of indomethacin on blood pressure in rabbits were assessed over several days, whereas the present study was necessarily limited to 24 hours because of the gastrointestinal toxicity of chronic indomethacin treatment in rats. Third, the qualitative different response to indomethacin observed in aortic ligated rats may relate to the high degree of renin-dependency of this hypertensive model. Prostaglandin synthesis inhibitors prevent the synthesis of vasodilatory and natriuretic prostaglandins and inhibit the release of renin. The former effect is potentially hypertensive, whereas the latter effect is potentially antihypertensive. The net effect, then, of prostaglandin synthesis inhibition on blood pressure would depend upon which is more prominent, prostaglandin-mediated vasodilation or prostaglandin-mediated renin release. This, of course, would depend upon the experimental model under investigation. Since the blood pressure elevation in aortic ligated rats is unequivocally renin dependent, it is not surprising that indomethacin lowers blood pressure in this hypertensive model.

In summary, aortic ligation in rats produces severe renovascular hypertension which is, in part, secondary to prostaglandin-mediated renin release. In addition, these studies demonstrate that, in this model of renin-dependent hypertension, inhibition of prostaglandin synthesis with indomethacin can alleviate, rather than exacerbate, the hypertension.

Acknowledgments

We wish to express our appreciation to James A. Porter for his excellent technical assistance with the renal assay.

References


Feuerstein G, Feuerstein N (1980) The effect of indomethacin...
INDOMETHACIN DECREASES MABP AND PRA

Jackson et al.

185

on isoprenaline-induced renin secretion in the cat. Eur J Pharmacol 61: 85-88
Indomethacin decreases arterial blood pressure and plasma renin activity in rats with aortic ligation.

E K Jackson, J A Oates and R A Branch

doi: 10.1161/01.RES.49.1.180

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/49/1/180