Indomethacin Does Not Attenuate the Hypotensive Effect of Captopril, a Converting Enzyme Inhibitor in Goldblatt Hypertensive Rats

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Omata, K., Otsuka, Y., Chiba, S., Itoh, T., Gotoh, T., Imai, Y., Sakurai, Y., Satoh, M., Haruyama, T., Hiwatari, M., Satoh, K., Kaitoh, A., Abe, K. and Yoshinaga, K. *Indomethacin Does Not Attenuate the Hypotensive Effect of Captopril, a Converting Enzyme Inhibitor in Goldblatt Hypertensive Rats.* Tohoku J. exp. Med., 1981, **134** (1), 9–19 —— Whether or not prostaglandins (PGs) have anything to do with the hypotensive effect of a converting enzyme inhibitor, captopril (SQ 14,225), was studied in two kidney one clip Goldblatt hypertensive rats. Four to 10 weeks after clipping the left renal artery of male Splague-Dawley rats, 50 mg/kg of captopril (Group 1, $n=7$) or 12.5 mg/kg of indomethacin (Group 2, $n=7$) were infused for 4 hr under the conscious state. For the subsequent 4 hr, both 50 mg/kg of captopril and 12.5 mg/kg of indomethacin were infused in both groups of rats. Mean blood pressure (MBP) was recorded continuously. Plasma renin activity (PRA) and urinary excretion rate of PGE (UPGE) were measured by radioimmunoassay. Urinary sodium (UNa) and potassium (UK) excretions were measured by a flame photometer. After captopril infusion the pressor response to the injection of 100 ng of angiotensin I decreased from 29.1 ± 4.2 to 4.8 ± 1.6 mmHg, and that of angiotensin II increased from 35.9 ± 3.6 to 75.0 ± 5.1 mmHg ($p<0.01$), while the response to norepinephrine did not change. Indomethacin did not affect these pressor responses. In the preinfusion period MBP, PRA or UPGE was not different significantly in the two groups of rats. The infusion of captopril decreased MBP from 202 ± 11 to 119 ± 7.5 mmHg ($p<0.01$) in the first group of rats. After the additional infusion of indomethacin MBP further decreased to 100 ± 12 mmHg, depsite the significant decrease of UPGE from 915 ± 34 to 109 ± 28 pg/hr ($p<0.01$), and PRA increased from 22.1 ± 4.2 to 34.1 ± 7.1 ng/ml/hr. UNa did not change after captopril infusion but decreased significantly after indomethacin infusion from 49.0 ± 5.0 to 22.8 ± 3.5 μEq/hr. In the second group captopril also decreased MBP from 187 ± 7 to 119 ± 15 mmHg ($p<0.01$), and increased PRA from 24.1 ± 6.1 to 43.3 ± 6.9 ng/ml/hr ($p<0.01$) despite the significant decrease of UPGE from 1219 ± 294 to 413 ± 101 pg/hr by the pretreatment with indomethacin. UNa did not change in any period. The decrease of MBP was significantly correlated with the level of PRA prior to the infusion of captopril in both groups ($r=-0.69$, $p<0.01$). UK did not change significantly in any period in the two groups of rats. Our data that indomethacin did not attenuate the hypotensive effect of captopril indicate that PGs do not

participate in the hypotensive effect of captopril and that the hypotensive effect
of captopril is mainly due to the inhibition of renin-angiotensin system in two
kidney one clip Goldblatt hypertensive rats. ——————— urinary prostaglandin E;
plasma renin activity; captopril; indomethacin; Goldblatt hypertensive rat

An orally active angiotensin converting enzyme inhibitor, captopril (SQ14,
225), has been shown to lower the blood pressure of high renin type of hypertension
by inhibiting the renin-angiotensin system in both animal models of hypertension
and hypertensive human subjects. Since many investigators have demonstrated
that captopril lowered also the blood pressure of low renin type of hypertension,
the mechanism of blood pressure lowering effect of captopril may not be explained
by the inhibition of the renin-angiotensin system alone. As Erdös and Yong
(1970) have demonstrated that angiotensin converting enzyme and kininase II are
the same protein, peptidyl dipeptide hydrolase, it is conceivable that the
angiotensin converting enzyme inhibitor not only reduces the pressor activity of
angiotensin I but also augments the vasodepressor activity of kinins. Recent
studies have demonstrated that bradykinin releases prostaglandins from the kidney
and blood vessels (McGiff et al. 1972) and prostaglandins potentiate the vasodilator
effect of bradykinin (McGiff et al. 1972). Moreover, renal prostaglandins modulate
the renal action of angiotensin (Aiken and Vane 1973), and mediate the renin
release (Yun et al. 1976). Thus, it is postulated that prostaglandins may be
involved in the mechanism of hypotensive effect of captopril.

To test this hypothesis, the hypotensive effect of captopril was compared in the
presence and absence of prostaglandin synthesis inhibitor, indomethacin in two
kidney one clip Goldblatt hypertensive rats.

METHODS

Male Splague-Dawley rats weighing 120–140 g were fed a standard rat chow (Oriental
Yeast Co., Tokyo), containing 0.44% sodium chloride, and tap water ad libitum. All
surgical procedures were done under ether anesthesia. Hypertension was induced by
placing a U-shaped silver clip with an internal gap of 0.22 mm around the left renal artery.
The contralateral kidney was left untouched. Systolic blood pressure was measured by a
tail cuff method. Four to 10 weeks after the clipping, those rats having a systolic blood
pressure of 160 mmHg or higher at two consecutive measurements were placed in metabolic
cages. Three days later, catheters were chronically implanted into the abdominal aorta
and into the inferior vena cava through the femoral artery and vein. The catheters were
threaded subcutaneously to the scapular region of rats. Two or three days after the vessel
catheterization direct mean blood pressure (MBP) was measured by a pressure transducer
(Narco, RP 1500) connected to the arterial catheter and recorded on a two channel recorder
(SAN-EI, Type 1236). Only those rats having MBP of 140 mmHg or above were used.
During the experiment, the rats were not anesthetized and were free to move about in their
metabolic cages, only partially restrained by a harness attached to springs on their backs.
After the blood pressure was stabilized, the effects of angiotensin converting enzyme inhibitor,
captopril (SQ 14,225), and indomethacin were studied in two groups of rats (7 rats in each
group). In the first group, isotonic phosphate buffer (0.01 M, pH 7.4) was infused through
the venous catheter at 17.2 μl/min using a Harvard pump for 4 hr, then 50 mg/kg of
captopril dissolved in the phosphate buffer were infused at 0.21 mg/kg/min for 4 hr. For
the subsequent 4 hr, both 50 mg/kg of captopril and 12.5 mg/kg of indomethacin dissolved

in the phosphate buffer were infused at 0.21 mg/kg/min and 0.05 mg/kg/min, respectively. In the second group, the same dose of indomethacin was infused after 4 hr of control period, then both captopril and indomethacin were infused for 4 hr. MBP was recorded continuously and urine was collected in each period. Food was withheld during the experiment. Water was available ad libitum. At the end of each period, blood (0.6 ml) was drawn from each rat for plasma renin activity (PRA) and hematocrit determinations. All blood samples were replaced immediately by injecting the same amount of blood obtained from donor rats which had been nephrectomized at least 2 hr earlier. Rats with hematocrit of 40% or less at any time during the study were eliminated. After the blood sampling at the end of each period, 100 ng/rat of angiotensin I (1-Asp-5-Ile-Ang I, Protein Research Foundation, Osaka) and angiotensin II (Hypertensin, CIBA) and DL-norepinephrine (Sankyo, Tokyo) were administered separately as bolus injections through the venous catheter as previously described (Otsuka et al. 1979). Urinary sodium (UNa) and potassium (UK) were measured using a flame photometer. The hematocrit was determined by centrifuging the blood samples at 3,000 rpm for 15 min.

PRA was determined by a radioimmunoassay of modified Abe's method (Abe et al. 1972). Plasma, 0.25 ml, was incubated with sodium ethylendiamine tetraacetic acid (EDTA) and diisopropyl fluorophosphate (DFP) at 37°C, pH 5.5 for 6 hr. After 2.25 ml of saline were added, the samples were boiled for 15 min. Then $10 \mu l$ of samples were mixed with 6,000 cpm of angiotensin I and $100 \mu l$ of dilute antiserum. One ml of Tris acetate buffer 0.2 M, pH 7.4 containing lysozyme 0.1% and EDTA 0.05% was added to the samples and the mixture was incubated at 4°C for 24 hr. The seperation of bound and free angiotensin I was done using dextran coated charcoal. PRA was expressed as ng of generated angiotensin I/ml plasma/hr incubation.

Urinary excretion rate of prostaglandin E (UPGE) was measured radioimmunologically. One ml of urine sample was used for PGE determination. For the chemical conversion of PGE to PGB, 2 ml of 1 N KOH were added to each sample with shaking for 1 hr. Then the mixture was acidified with 1 N HCl and extracted with 15 ml of ethyl acetate. After the organic solution was dried, the residue was applied to a silicic acid column, and the PGB fraction was eluted with 4 ml of a solvent (Abe et al. 1977). The separated PGB was radioimmunologically assayed using PGB antiserum. The PGB antisera were produced in our Laboratory according to Jaffe's method (Jaffe and Behrman 1974).

When comparing groups, statistical analysis was performed by Student's t test, and all results were expressed as mean±S.E.M. The difference between mean values was considered to be significant when p values were less than 0.05.

RESULTS

PGB radioimmunoassay

Validation of RIA. The mean recovery of added tracer through the entire procedure was 65.6±0.5% (Chiba et al. in press).

Sensitivity. A 50% change in binding occurred at 48 pg of PGB_2. The binding in the presence of 6 pg of PGB_2 was always different from that in the absence of PGB_2, and this was used as the lowest dose for the standard curve. An RIA standard curve for PGB_2 is shown in Fig. 1. The titer of antiserum used was ×1600.

Specificity. The antiserum showed a 4.3% affinity to $PGA_2(A_2)$, and 0.3% affinity to $PGE_2(E_2)$, 0.03% to $PGF_{2\alpha}(F_{2\alpha})$ and 0.01% to 15 keto PGE_2. 13-14 dihydro 15 keto PGE_2, $PGF_{2\alpha}$ MUM, or 6 keto $PGF_{1\alpha}$ was not cross reacted. But PGB_1 cross reacted 100% (Fig. 1).
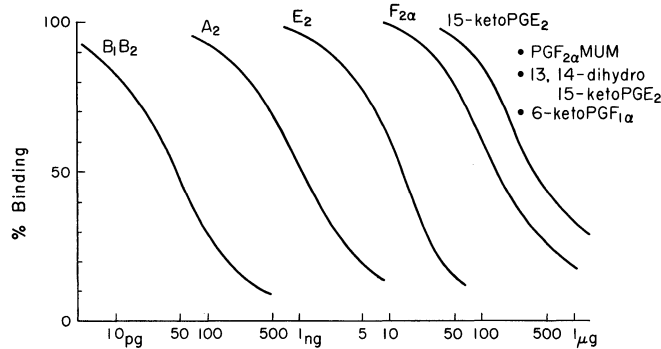
Fig. 1. A radioimmunoassay standard curve for PGB_2 and cross reactions of various prosta-
glandins with an antiserum to PGB_2.   Abbreviations; A_2, PGA_2; B_1, PGB_1; B_2, PGB_2;
E_2, PGE_2; $F_{2\alpha}$, $PGF_{2\alpha}$.

Pressor response to angiotensin I, II and norepinephrine

Fig. 2 shows the pressor response to 100 ng of angiotensin I (AI), angiotensin II
(AII) and norepinephrine (NE) at the end of control period and the period in
which both captopril and indomethacin were infused in 11 renal hypertensive rats.
Since no difference in the pressor response to the pressor substances between the
first group and the second was found, the results of these two groups were pooled.
Since no difference was found between control period and indomethacin period in
the second group, and between captopril period and captopril plus indomethacin
period in the first group, the results were compared between control period and
captopril plus indomethacin period.   Captopril in a dose used in this study almost
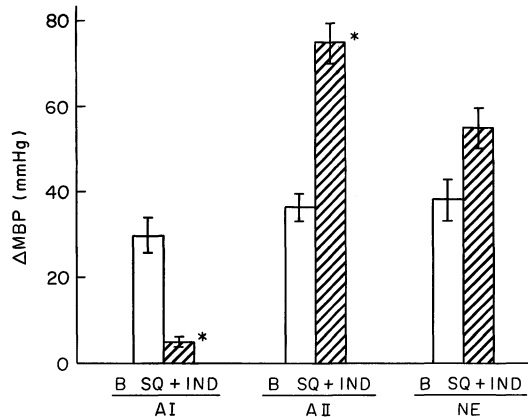completely blocked the pressor response to AI from 29.1 ± 4.2 to 4.8 ± 1.6 mmHg

Fig. 2. The blood pressure response (MBP) to 100 ng of angiotensin I (AI), angiotensin II
(AII) and norepinephrine (NE) at the end of the control period (B, open bars) and the
period in which both captopril and indomethacin (SQ+IND, hatched bars) were infused.
Each value is the mean±s.e. for 11 renal hypertensive rats. *Significantly different
($p<0.01$, $n=11$) from the response in the control period.

and augmented the pressor response to AII from 35.9±3.6 to 75.0±5.1 mmHg. The pressor response to NE increased from 39.3±4.7 to 54.4±9.7 mmHg, but the difference was not statistically significant.

Changes in MBP, PRA and UPGE

MBP, PRA and UPGE in the control period in each group are shown in Fig. 3. In the first group of renal hypertensive rats, MBP was 202±11 mmHg, PRA was 22.1±4.1 ng/ml/hr and UPGE was 915±234 pg/hr. In the second group of rats MBP was 206±8 mmHg, PRA was 24.1±6.1 ng/ml/hr and UPGE was 1219±294 pg/hr. Thus PRA was grossly elevated and MBP was extremely high in both groups. There were no significant differences between two groups in each parameter.

As shown in Fig. 4, the level of PRA ranged from 5 to 62 ng/ml/hr and the value of UPGE varied widely between 169 and 2171 pg/hr. There was no significant correlation between them.

Fig. 5 shows the changes in MBP, PRA and UPGE in the first group of rats. After the captopril infusion, MBP markedly decreased from 206±8 to 119±7.5 mmHg, but PRA or UPGE did not change significantly. Subsequent addition of indomethacin resulted in marked decrease in UPGE from 915±234 to 109±28 pg/hr. PRA increased from 22.1±4.2 to 34.1±7.1 ng/ml/hr, while MBP decreased further to 100±12 mmHg.

Fig. 6 shows the changes in MBP, PRA and UPGE in the second group of rats. The first infusion of indomethacin resulted in a marked decrease in UPGE
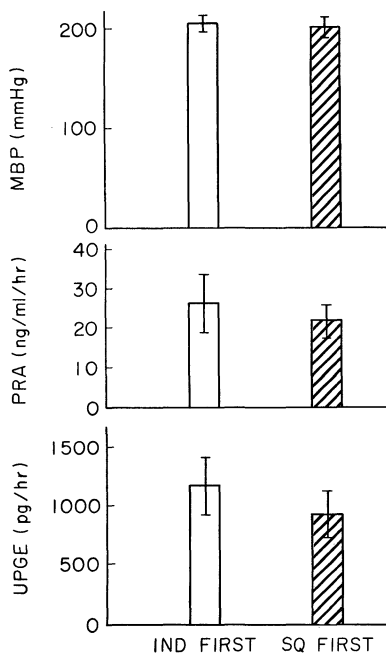

Fig. 3. Comparison of mean blood pressure (MBP), plasma renin activity (PRA) and urinary excretion of PGE (UPGE) in the control period between the first group (SQ FIRST, hatched bars, n=7) and the second group (IND FIRST, open bars, n=7) of renal hypertensive rats. Values are means ±S.E.
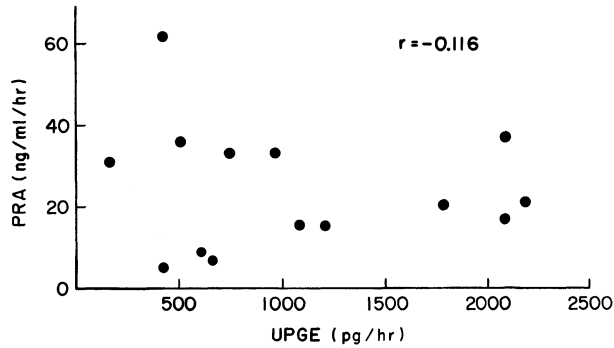
Fig. 4. Relationship between the level of plasma renin activity (PRA) and urinary excretion of PGR (UPGE) in the control period in two kidney one clip Goldblatt hypertensive rats.

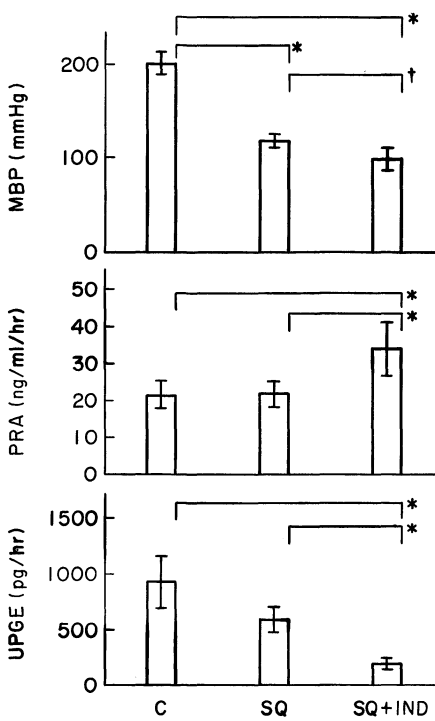Fig. 5.   Fig. 6.

Fig. 5. Changes of mean blood pressure (MBP, top), plasma renin activity (PRA, middle) and urinary excretion of PGE (UPGE, bottom) in the control period (C), after captopril infusion (SQ) and after the addition of indomethacin (SQ+IND) in the first group of renal hypertensive rats. Values are means±s.e. In this figure and in Fig. 6, significant difference is given by *$p<0.01$ and †$p<0.05$.
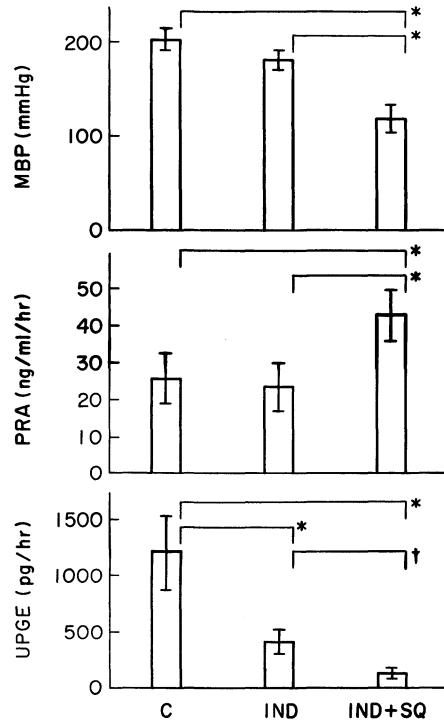
Fig. 6. Changes of mean blood pressure (MBP, top), plasma renin activity (PRA, middle) and urinary excretion of PGE (UPGE, bottom) in the control period (C), after indomethacin infusion (IND) and after the addition of captopril (IND+SQ) in the second group of renal hypertensive rats. Values are means±s.e.
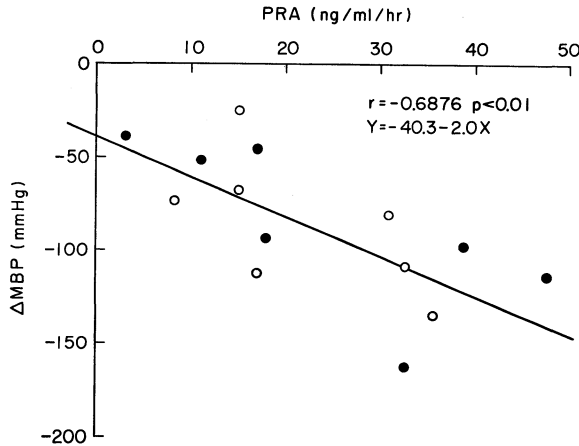
PRA (ng/ml/hr)

Fig. 7. The relationship between the fall in mean blood pressure (ΔMBP) produced by captopril infusion and the level of plasma renin activity (PRA) prior to the infusion of captopril in renal hypertensive rats of the first (●) and the second (○) group ($r=-0.6876$, $p<0.01$).

from 1219 ± 294 to 413 ± 101 pg/hr, but did not produce any change in MBP or PRA. The additional infusion of captopril lowered the MBP from 187 ± 19 to 119 ± 15 mmHg and induced significant increase in PRA from 24.1 ± 6.1 to 43.3 ± 6.9 ng/ml/hr.   UPGE decreased further to 96 ± 42 pg/hr.

Fig. 7 shows the correlation between the level of PRA prior to the infusion of captopril and the decrease of MBP in the rats of either group.   Significant negative correlation was found between these two parameters ($r=-0.6876$, $p<0.01$).

Changes in UNa and UK excretion

Table 1 shows UNa and UK excretion in each period in the first group of rats.   UNa excretion was 95.6 ± 23.5, UK excretion was 63.2 ± 11.7 μEq/hr in the control period.   UNa excretion did not increase after captopril infusion, but decreased significantly by the additional infusion of indomethacin from 49.0 ± 5.4 to 22.8 ± 3.5 μEq/hr.   UK excretion did not change significantly in any period in the first group of rats.

Table 2 shows the data in the second group of rats.   There were no significant

Table 1.   *Urinary sodium excretion (UNa) and urinary potassium excretion (UK) in the control period, after captopril infusion (SQ) and after the addition of indomethacin (SQ+IND) in the first group of renal hypertensive rats*

	Control	SQ	SQ+IND
UNa (μEq/hr)	95.6 ± 23.5	49.0 ± 5.4	22.8 ± 3.5*
UK (μEq/hr)	63.2 ± 11.7	50.0 ± 10.8	54.9 ± 14.7

Values are mean$\pm$S.E.
* $p<0.01$ significantly different from control.

TABLE 2. *Urinary sodium excretion (UNa) and urinary potassium excretion (UK) in the control period (C), after indomethacin infusion (IND) and after the addition of captopril (IND+SQ) in the second group of renal hypertensive rats*

	Control	IND	IND+SQ
UNa (μEq/hr)	138.6±55.2	70.8±11.7	46.3± 8.3
UK (μEq/hr)	74.6±18.6	72.3±13.0	70.1±14.8

Values are means±s.e.

change in UNa or UK excretion in any period. In the control period UNa excretion was 138.6±55.2 μEq/hr, and UK excretion was 74.6±18.6 μEq/hr. There were no significant changes in UNa or UK excretion between the two groups of rats in the control period.

DISCUSSION

Recently, many attempts have been made to clarify the mechanism of hypotensive action of captopril, a newly developed angiotensin converting enzyme inhibitor. The kinin accumulation as well as the inhibition of angiotensin converting enzyme by captopril is assumed to be related to the hypotensive action of this drug, but the detailed mechanism of the hypotensive action remains still to be elucidated. Indomethacin, an inhibitor of prostaglandin synthesis (Vane 1971) has been widely used as a tool to assess the physiological role of PGs. Rubin et al. (1978) have shown that indomethacin attenuates the response to bradykinin in normal rabbits, thus postulating that renal PGs may play a major role in the bradykinin induced hypotension. McGiff et al. (1970, 1972) have reported that PGs antagonize the vasoconstrictor effect of pressor substances and potentitate the vasodilator effect of bradykinin. These studies may lend support to the hypothesis that PGs mediated by the kinin accumulation induced by captopril may participate in the hypotensive effect of captopril. In this hypothesis, indomethacin could attenuate the hypotensive effect of captopril. In our experiments, however, indomethacin did not attenuate the hypotensive effect of captopril depsite a marked decrease in urinary excretion of PGE in two kidney one clip Goldblatt hypertensive rats. These data indicate that this hypothesis is unlikely. Our data were in accordance with the study of Murthy et al. (1978) in which indomethacin did not attenuate the hypotensive effect of captopril in normal rabbits. Antonaccio et al. (1979) also reported that indomethacin did not alter the hypotensive effect of captopril in spontaneously hypertensive rats. Our data, however, do not eliminate the possibility that the captopril-induced kinin accumulation could participate in the hypotensive effect of captopril through its direct vasodilator action, since antibody against kinin attenuates the hypotensive effect of captopril in renovascular hypertension in rats (Carretero et al. 1981).

In our experiments, captopril completely blocked the pressor response to angiotensin I, and the magnitude of the reduction of MBP was related to the PRA

level prior to the administration of captopril. These data indicate that the hypotensive effect of captopril is mainly due to the inhibition of the conversion of angiotensin I to angiotensin II in renovascular hypertension in rats.

In the first group, MBP decreased significantly after the subsequent dose of indomethacin. It seems that this reduction of MBP was not the effect of indomethacin since administration of indomethacin alone did not decrease the MBP in the second group of rats.

Renal PGs have been shown to play an important role in renin release under basal as well as stimulated conditions (Larsson et al. 1974; Patak et al. 1975; Bailie et al. 1976). In our experiments, however, indomethacin did not decrease the basal level of PRA nor did inhibit the enhanced renin secretion by captopril despite a decrease in UPGE excretion. There are several possible reasons for the difference between our study and previous reports. First, it may come from the species difference. Secondly, since Romero et al. (1976) reported that the ability of indomethacin to decrease the basal value of PRA and to prevent its elevation by hemorrhage depends largely on the administered dose, the dose of indomethacin we used may be too small to decrease the PRA. In other words, the effective dose of indomethacin to inhibit renal PGE synthesis may differ from that of indomethacin to inhibit another PGs which participate in the renin secretion. Our data are in accordance with the study of Antonaccio at al. (1979) in which indomethacin did not inhibit the renin increase induced by captopril in spontaneously hypertensive rats. Therefore, it is unlikely that renal PGs may participate in the renin secretion after captopril administration in rats.

McCaa et al. (1978) reported that the administration of captopril resulted in natriuresis and diuresis in sodium depleted dogs. In our study, however, UNa excretion did not increase after the administration of captopril. It may be possible that this discrepancy comes from the changes of blood pressure. When the blood pressure does not decrease, blockade of the renin-angiotensin system results in natriuresis due to the reduced aldosterone secretion and renal vasodilatation. When the blood pressure falls, UNa excretion does not increase because of the increase in the proximal sodium reabsorption and the decrease in the glomerular filtration. Indeed, Miurhead et al. (1978) also reported that captopril decreased MBP but did not change UNa excretion in spontaneously hypertensive rats. In the first group of rats, UNa excretion decreased significantly after the subsequent treatment with indomethacin. It could be that this decrease in sodium excretion results from the decrease in renal PGs which have been shown to participate in the renal sodium handling.

In conclusion, our data that indomethacin did not attenuate the hypotensive effect of captopril indicate that PGs do not participate in the hypotensive action of captopril and that the hypotensive action of captopril is mainly due to the inhibition of renin-angiotensin system in two kidney one clip Goldblatt hypertensive rats.

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