Kinetic Studies of the Pharmacologic Response to Captopril in Rats. I. Role of the Renin–Angiotensin System

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Pressor response to exogenous angiotensins was investigated in rats. Two-kidney Goldblatt hypertensive rats (GHR) and sodium-deficient normotensive rats (SDR), as well as normal rats, (NR) were used. Various amounts of angiotensin I (Ang I) or angiotensin (Ang II) were administered intravenously by constant infusion, with or without pretreatment with angiotensin converting enzyme (ACE) inhibitor, and the pressor response was determined. Captopril was used as the ACE inhibitor. From the data obtained, a simple kinetic model for the renin-angiotensin system was constructed. The model was based on a linear compartment model with the following assumptions; (a) there are compartments in respect to Ang I and II in the body; (b) in the steady-state condition, Ang I is produced at a constant rate; (c) a part of Ang I is converted to Ang II by a first-order rate process; (d) Ang I and II are eliminated from the respective compartments by first-order rate processes and (e) the relationship between mean arterial blood pressure and the amount of Ang II in the body can be described by Hill’s equation with a baseline effect. Then the pressor response to angiotensins in GHR, SDR or NR was fitted to the model. The result indicated that the pressor response to Ang I or Ang II can be described by the present model. The model parameters obtained were consistent with the actual physiological parameters of rats.

Keywords — captoril; angiotensin I; angiotensin II; renin-angiotensin system; angiotensin converting enzyme; hypertensive rat; kinetics

Introduction

Captopril, the first orally active angiotensin converting enzyme (ACE) inhibitor, is used widely in the treatment of hypertension, congestive heart failure and so on.1 Although there have been numerous reports on the effect of captopril in several animal species including humans,2 there is no established theory for the mechanism of the hypotensive effect.

The renin–angiotensin system plays an important role in the control of short-term arterial pressure.3 In high-renin essential hypertension, captopril certainly exerts its antihypertensive effect by inhibiting the (ACE) activity to lower the angiotensin II level in the body; however, the relationship between angiotensin II level and the hypotensive effect of captopril is still unclear, in the quantitative sense.

The purposes of this investigation were to clarify the operation of the renin–angiotensin system, and to construct a kinetic model which could describe the pressor response to exogenous angiotensin II in rats. Two kinds of disease-state rats, namely two-kidney Goldblatt hypertensive rats and sodium-deficient hypertensive rats, and also normotensive rats were used.

Materials and Method

Chemicals — Captopril was kindly supplied by Sankyo Co., Tokyo, Japan. Angiotensin I (Ang I, human), angiotensin II (Ang II, human) and benzoyl-glycyl-L-histidyl-L-leucine (HHL) were obtained commercially from the Peptide Institute, Inc. (Minoh, Japan). All other chemicals were of analytical grade and were used without further purification.

Animals — Male Wistar rats (5-week-old) were supplied by Shizuoka Laboratory Animal Center (Hamamatsu, Japan). Three types of rats, namely, sodium-deficient normotensive...
rats (SDR), 2-kidney-one-clip Goldblatt-type renal hypertensive rats (GHR) and normoten-
sive rats (NR), were used. These rats were prepared by the following procedures. (a) SDR: SDR was prepared by the method of Bengis et al. with a minor modification as follows. Five-week-old Wistar rats weighing 120 to 130 g were maintained on a sodium-deficient diet (sodium content was less than 0.01% by weight, Funabashi Farm Co., Funabashi, Japan) and deionized water ad libitum, for more than 3 weeks. The rats with indirect systolic blood pressure (ISP) of around 100 mmHg were employed in the experiment as SDR. (b) GHR: Goldblatt-type 2-kidney-one-clip renal hypertensive rats were prepared by the method of Bengis et al. Six-week-old rats weighing 130 to 150 g were subjected to surgery. Each rat was anesthetized with ether, the left renal artery was isolated by a flank incision, and a rectangular silver clip with a 0.20 mm gap was placed on that artery. The rectangular silver clips were prepared by the method of Brooks et al. The contralateral kidney and renal artery were untouched. After the surgery, rats were bred on a normal rat diet (CE-2, Nippon Clea Co., Tokyo, Japan) and tap water ad libitum, for at least 4 weeks. The rats with ISP of more than 180 mmHg were used as GHR. (c) NR: Five-week-old rats were bred on a normal rat diet and tap water ad libitum, for at least 4 weeks. The rats with ISP of around 120 mmHg were used as NR. All animals were housed in constant-temperature facilities under a 12:12 h light-dark cycle. In order to minimize the diurnal variation of animals, all of the experiments presented here were started at about 11 a.m.

Monitoring of Indirect Systolic Blood Pressure — ISP was measured with an inflatable cuff and piezoelectric crystal transducer (Narco Bio Systems, Inc., Houston, TX) after warming the rats with an electric lamp at about 39.0 °C for 5 min. ISP values were averaged for three consecutive recordings for each animal. ISP monitoring was carried out at least once a week.

Measurement of Blood Pressure — Each rat was cannulated in the right femoral artery and in the left jugular vein, under light ether anesthesia. Restrained on the supine position, the animals were allowed to awaken on a surgical board for at least 1 h. All studies were then carried out in the conscious animals, with topical infiltration anesthesia of lidocaine jelly, Fujisawa pharmaceutical Co., Osaka, Japan). Mean arterial blood pressure (MAP) was measured continuously via a strain gauge transducer (MPU-0.5, Toyo Baldwin Co., Tokyo, Japan) and a San-ei Polygraph (System, 360, NEC San-ei Co., Tokyo, Japan). The blood pressure data were transferred simultaneously to an HP-85 microcomputer (Hewlett-Packard, Corvallis, OR) via an A/D converter (AD 412T, Sho-ei Denshi Co., Nagoya, Japan) and also stored on a magnetic tape. Catheters were periodically flushed with heparinized saline.

Measurement of the Pressor Response to Angiotensins — Ang I or II was dissolved in 5% dextrose solution (Otsuka Pharmaceuticals, Tokyo, Japan) and administered via the left jugular vein by constant infusion for 4 min, at dose levels of 0.006 to 45.14 nmol/kg/min. Captopril was also dissolved in 5% dextrose solution and administered via the jugular vein as a single bolus injection. The dose levels of captopril were 100 mg/kg for NR, 10 mg/kg for SDR and 50 mg/kg for GHR. The values of mean arterial blood pressure (MAP) before and during infusion of angiotensins were measured as described above. The difference between the plateau value of MAP during infusion, and the preinfusion value of MAP, was calculated as the pressor response to angiotensins. The pressor response was determined consecutively for 5 to 6 dose levels of angiotensins in increasing order, using the same rat at intervals of 30 min. Angiotensins were administered to NR, SDR or GHR, under the following 3 different conditions. (a) Treatment I: Thirty minutes before Ang II infusion, captopril was administered. In the preliminary experiment, administration of captopril at the dose level employed showed a complete suppression of ACE activity in each type of rat within the experimental period. (b) Treatment II: Only Ang II was infused into each rat, without captopril administration. (c) Treatment III: Ang I was infused into each rat without administration of captopril.

Analytical Methods — Blood samples were
collected from the jugular vein and plasma samples were obtained by centrifugation at 3000 rpm for 10 min at 4°C. Plasma ACE activity was determined by the method of Cushman and Cheung with a minor, modification as described in the previous paper. Plasma renin activity (PRA) and plasma Ang I concentration were determined by using the CEA-IRE-SORIN Renin Angiotensin Radioimmunoassay Kit (Commissariat à L’Energie Atomique, Gif-sur-Yvette, France).

Statistics — The differences among various experimental conditions were compared by using ANOVA and Tukey’s HSD (honesty significant difference) test. The 0.01 level of probability was used as the level of significance.

Data Analysis — The pharmacologic effect-time or amount-time data were analyzed by using a nonlinear regression program FKDM based on the algorithm of Gauss-Newton and Berman using a PDP11/34 minicomputer (Digital Equipment Corp., Maynard, MS). The weighting and the condition of convergency were described elsewhere.

Theoretical

In order to clarify the role of the renin-angiotensin system in the three types of rats mathematically, a simple kinetic model was constructed. The description of the model was in terms of differential equations and it was based on the compartment model analysis with several assumptions; (a) there are compartments in respect to Ang I and II in the body; (b) in the steady-state condition, Ang I is produced at a constant rate; (c) a part of Ang I is converted to Ang II by a first-order rate process; (d) Ang I and II are eliminated from the respective compartments by first-order rate processes and (e) the relationship between mean arterial blood pressure and the amount of Ang II in the body can be described by Hill’s equation with a baseline effect. A schematic representation of the model is shown in the Fig. 1.

From the above assumptions, the following equations can be derived.

\[
\frac{dA_1}{dt} = R - (k_{a1} + k_{12}) A_1
\]

\[
\frac{dA_2}{dt} = k_{12}A_1 - k_{a2}A_2
\]

where \( A_1 \) and \( A_2 \) are the amounts of Ang I and II in the body, respectively. \( R \) is the zero-order production rate of Ang I. \( k_{a1}, k_{12} \) and \( k_{a2} \) are first-order rate constants of elimination of Ang I, conversion of Ang I to Ang II and elimination of Ang II, respectively. Under a steady-state condition, the left sides of Eq. 1 and Eq. 2 equal zero, and then the following equation is obtained.

\[
A_2 = \frac{Rk_{12}}{(k_{12} + k_{a1}) k_{a2}}
\]

The relationship between mean arterial blood pressure (MAP) and \( A_2 \) is described by Eq. 4.

\[
\text{MAP} = \text{MAP}_0 + \frac{V_{\text{max}} A_2 r}{k_m r + A_2 r}
\]

![Fig. 1. A Shematic Representation of the Model for the Renin-Angiotensin System](image-url)
where $MAP_0$ is the baseline value of mean arterial blood pressure, $V_{\text{max}}$ is the maximum response to Ang II, $K_m$ is the amount of Ang II at half the maximum pressor response and $r$ is the Hill's constant. By substituting $A_2$, according to Eq. 3, into Eq. 4, the following equation is obtained.

$$MAP = MAP_0 + \frac{V_{\text{max}} \left\{ \frac{Rk_{12}}{(k_{12} + k_{a1})k_{a2}} \right\}^r}{K_m^r + \left\{ \frac{Rk_{12}}{(k_{12} + k_{a1})k_{a2}} \right\}^r}$$  

(5)

If all of the parameters in Eq. 5 were obtained in each type of rats used, the pressor response to Ang II in the steady state could be calculated.

As described in the experimental section, angiotensin infusion was carried out under 3 different conditions, namely treatments I, II and III. Since $k_{12}$ might be negligible in the case of pretreatment with captopril, the amount of Ang II in the body during Ang II infusion (treatment I) at the steady state can be described by Eq. 6.

$$A_2 = \frac{K_2}{k_{a2}}$$  

(6)

where $K_2$ is the infusion rate of Ang II. Similarly, substituting for $A_2$, according to Eq. 6, in Eq. 4, and simplifying yields Eq. 7.

$$MAP = MAP_0 + \frac{V_{\text{max}} K_2^r}{(K_m \cdot k_{a2})^r + K_2^r}$$  

(7)

In treatment II, the amount of Ang II at the steady state is described by Eq. 8.

$$A_2 = \frac{Rk_{12}}{k_{a2}(k_{12} + k_{a1})} + \frac{K_2}{k_{a2}}$$  

(8)

Then, MAP during treatment II at the steady state is given by Eq. 9.

$$MAP = MAP_0 + \frac{V_{\text{max}} \left\{ \frac{R}{(k_{a1}/k_{12})+1} + K_2 \right\}^r}{(K_m \cdot k_{a2})^r + \left\{ \frac{R}{(k_{a1}/k_{12})+1} + K_2 \right\}^r}$$  

(9)

In treatment III, the amounts of Ang II and MAP at the steady state are described by Eqs. 10 and 11, respectively.

$$A_2 = \frac{1}{\left( \frac{R + K_1}{k_{a1}/k_{12}} + 1 \right) k_{a2}}$$  

(10)

$$MAP = MAP_0 + \frac{V_{\text{max}} \left\{ \frac{R + K_1}{(k_{a1}/k_{12})+1} \right\}^r}{(K_m \cdot k_{a2})^r + \left\{ \frac{R + K_1}{(k_{a1}/k_{12})+1} \right\}^r}$$  

(11)

where $K_1$ is the infusion rate of Ang I.

The parameter values for $V_{\text{max}}$, $r$, $K_m$, $k_{a2}$, $k_{a1}/k_{12}$ and $R$ can be estimated by fitting the experimental MAP data obtained by treatments I, II and III to Eqs. 7, 9 and 11, simultaneously.

**Results**

Figure 2 shows the time courses of ISP after initiation of the treatments. In GHR, ISP was increased gradually and reached the plateau level of about 200 mmHg, within 4 weeks after the surgery. In SDR, ISP was slightly decreased from the control level and reached a constant level of around 110 mmHg within 4 weeks after initiation of the sodium-deficient breeding. The ISP value of NR was about 120 mmHg, and was constant over the experimental period.

PRA and plasma Ang I concentration before

![Fig. 2. Time Courses of Indirect Systolic Pressure after Initiation of the Treatments](image)

Each value is the mean ± S.E.

☐, GHR ($n = 5$); △, SDR ($n = 7$); ●, NR ($n = 20$).
medication were measured in the three different types of rats, and the results are listed in Table I. In GHR, PRA and plasma concentration of Ang I were 5 times and 4 times greater than those of NR, respectively. Similar results were also obtained in SDR. These results indicated that the renin-angiotensin system was significantly activated in SDR and GHR.

In order to compare the ACE activity in the 3 types of rats, plasma ACE activity was determined in vitro, over a wide concentration range of substrate. HHL was used as the substrate of ACE. The results are shown in Fig. 3 as a Lineweaver-Burk plot, and the maximum velocity ($V_{mc}$) and Michaelis constant ($K_{mc}$) are listed in Table II. As shown in Fig. 3, each value of $1/V$ of GHR was smaller than those of the other two types of rats, though the differences were not statistically significant. These facts indicated that the high PRA and plasma Ang I concentration in both GHR and SDR did not affect plasma ACE activity itself.

The baseline value of the mean arterial blood pressure, namely, MAP$_0$ in Eqs. 4, 5, 7, 9 and 11 was estimated by the following procedure. After i.v. administration of captopril, at dose levels of 1 to 100 mg/kg to each type of rat, MAP was continuously measured. By subtracting each MAP value from the corresponding pre-medication MAP value, the time courses of the hypotensive effect of captopril were determined. The maximum hypotensive effect

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### Table I. Plasma Renin Activity and Plasma Angiotensin I Concentration in NR, SDR and GHR

<table>
<thead>
<tr>
<th></th>
<th>Plasma renin activity (ng/ml/h)</th>
<th>Plasma angiotensin I concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR ($n = 14$)</td>
<td>4.97 ± 2.22</td>
<td>2.27 ± 0.85</td>
</tr>
<tr>
<td>SDR ($n = 9$)</td>
<td>13.6 ± 5.02</td>
<td>8.61 ± 1.35</td>
</tr>
<tr>
<td>GHR ($n = 22$)</td>
<td>22.8 ± 15.6</td>
<td>7.25 ± 3.28</td>
</tr>
</tbody>
</table>

![Fig. 3. Lineweaver-Burk Plot of Plasma ACE Activity in GHR, SDR and NR](image1)

<table>
<thead>
<tr>
<th></th>
<th>NR</th>
<th>SDR</th>
<th>GHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{mc}$ mm</td>
<td>1.59</td>
<td>1.28</td>
<td>2.02</td>
</tr>
<tr>
<td>$V_{mc}$ mmol/min</td>
<td>5.48</td>
<td>6.54</td>
<td>6.02</td>
</tr>
</tbody>
</table>

![Fig. 4. The Relationship between the Maximum Hypotensive Effect and Logarithm of Dose of Captopril in NR, SDR and GHR](image2)

Each value is the mean ± S.E. Upper, middle and lower plots are for in NR, SDR and GHR, respectively.
TABLE III. List of Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NR</th>
<th>SDR</th>
<th>GHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_H )</td>
<td>mmHg</td>
<td>25.0 ± 3.8</td>
<td>21.1 ± 2.1</td>
</tr>
<tr>
<td>( K_H )</td>
<td>mm/kg</td>
<td>0.978 ± 0.622</td>
<td>0.330 ± 0.085</td>
</tr>
<tr>
<td>rh</td>
<td></td>
<td>0.576 ± 0.195</td>
<td>1.24 ± 0.71</td>
</tr>
<tr>
<td>MAP_0</td>
<td>mmHg</td>
<td>92.0</td>
<td>74.9</td>
</tr>
<tr>
<td>MAP_00</td>
<td>mmHg</td>
<td>117.0</td>
<td>96.0</td>
</tr>
</tbody>
</table>

TABLE IV. Pharmacokinetic and Pharmacodynamic Parameters for the Renin–Angiotensin System in Rats

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NR</th>
<th>SDR</th>
<th>GHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{max} )</td>
<td>mmHg</td>
<td>93.4 ± 2.2</td>
<td>80.5 ± 1.5</td>
</tr>
<tr>
<td>( K_m/k_{al} )</td>
<td>nmol/kg/min</td>
<td>0.451 ± 0.046</td>
<td>0.670 ± 0.047</td>
</tr>
<tr>
<td>( R )</td>
<td>nmol/kg/min</td>
<td>0.292 ± 0.073</td>
<td>0.653 ± 0.140</td>
</tr>
<tr>
<td>( k_{al}/k_{12} )</td>
<td></td>
<td>0.521 ± 0.257</td>
<td>1.76 ± 0.36</td>
</tr>
<tr>
<td>r</td>
<td></td>
<td>1.21 ± 0.12</td>
<td>1.33 ± 0.10</td>
</tr>
</tbody>
</table>

(MAP_M in mmHg) after each dose was obtained graphically and these values were plotted against the logarithm of captopril dose. As shown in Fig. 4, each dose-response relationship showed a sigmoid curve and thus, it was fitted to the following Hill’s equation. The model parameters were estimated by the non-linear least-squares method.

\[
MAP_M = \frac{V_H D^{r_H}}{K_H E^{r_H} + D^{r_H}}
\]  
(12)

Where \( V_H \) is the maximum value of MAP_M, \( K_H \) is the dose of captopril at half of \( V_H \) and \( r_H \) is the Hill’s constant. The fitted values are shown in Fig. 4 as the solid lines, and the estimated parameters are listed in Table III. The \( V_H \) value is attributable to the pressor effect of endogenous Ang II in each type of rat. MAP_0 was estimated by means of the following equation.

\[
MAP_0 = MAP_{00} - V_H
\]

Where MAP_0 is the mean value of MAP before captopril administration of each type of rat. The values for MAP_0 and MAP_00 are also listed in Table III.

The relationship between infusion rate of angiotensins and the pressor response in the three different types of rats is summarized in Fig. 5.

Fig. 5. The Relationship between the Pressor Response to Angiotensins and Infusion Rate in Three Different Types of Rats
Each value is the mean ± S.E.; in some cases, the S.E. values were smaller than the size of the symbols. Upper, middle and lower plots are for NR, SDR, and GHR, respectively.

O, treatment I; ●, treatment II; △, treatment III.
Each pressor response to angiotensins showed a sigmoid curve and these results were fitted to the kinetic model described in the theoretical section. At first, the initial values for the model parameters, $V_{\text{max}}$, $K_m$, $k_{a2}$ and $r$, were obtained by fitting the dose–response curves of treatment I to Eq. 7. Then, all of the dose–response curves obtained by treatments I, II and III in each type of rat were fitted to Eqs. 7, 9, and 11, respectively, and all of the parameters were estimated simultaneously. The results are shown as the lines in Fig. 5 and the estimated parameters are listed in Table IV. The pressor response to Ang I or II was reasonably described by a linear pharmacokinetic model with Hill’s equation, as a function of Ang II level, regardless of the disease state of rats.

Discussion

In order to eliminate the pressor effect of endogenous Ang II, various doses of captopril were used in each type of rat in treatment I. Since each dosage of captopril was based on the actual ACE activity (data not shown), these differences in dosage might be attributable to the difference in pharmacokinetics and/or pharmacodynamics of captopril among the three types of rats.

In the determination of the pressor responses to angiotensins, doses were not randomized because of the tendency for tachyphylaxis development when high doses are administered before smaller dose of angiotensins. However, Gross et al. reported that 10 min was a sufficient time interval between injections of Ang I that would not produce tachyphylaxis in the pressor response, in the dosage range of 150 to 600 ng/kg i.v. in rats. Although the dosage levels in the present study were slightly higher than those in the report of Gross et al., a 30 min time interval might be sufficient time to avoid tachyphylaxis.

For the analysis of the renin–angiotensin system in rats, a simple linear model was used in this study. The transformation of Ang I to Ang II was described by a first-order rate process, though in vitro ACE activity was analyzed by using the Michaelis-Menten equation. Although ACE is known to exist in a variety of tissues and cells in the body, it has been generally agreed that the endothelial cells of the lung and of peripheral blood vessels, and the epithelial cells of the kidney tubules are major sources of the enzyme. These facts indicated that in vivo total ACE activity might be much greater than that predicted from the in vitro study. Since we did not determine the total ACE activity in the body directly, we assumed the transformation process to be first order. The results of curve fitting indicates that the assumption was appropriate.

In the present study, we excluded the influence of other hormones such as the aldosterone system, prostaglandins and the kallikrein–kinin systems from the model. McCaa et al. pointed out that the aldosterone system is important only for the long-term pressure control. Although many studies have shown that some of the prostaglandins decrease the arterial blood pressure, there has been no established theory for the role of the prostaglandins in blood pressure regulation. There are some reports that the anti-hypertensive effect of captopril is closely related to the activity of the kallikrein–kinin system, especially in low-renin hypertension. In the present work, we used two-kidney one-clip hypertensive rats and sodium-deficient rats. These rats are known to be high-renin models, and therefore, we considered that the contribution of kinin to the pressor response to angiotensins was negligible.

Among the parameters shown in Table III, MAP$_0$ represents the arterial pressure controlled by the regulation system other than the renin–angiotensin system. Since MAP$_{00}$ values in NR, SDR and in GHR were 117, 96 and 198 mmHg, respectively, about 21% (NR), 22% (SDR) and 41% (GHR) of the total MAP were dependent on the renin–angiotensin system.

The $R$ value in Table IV represents the intrinsic production rate of Ang I in each type of rat in the steady state of the body. Each $R$ value was consistent with the respective PRA and plasma concentration of Ang I.

The values of the parameters $V_{\text{max}}$, $K_m$, $k_{a2}$ and $r$ in Table IV indicate that the pressor response to Ang II in SDR was similar to that in

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NR. However, the \( k_{a1}/k_{a2} \) value in SDR was much greater than that of GHR or NR. These facts suggest that the amount of endogenous Ang II produced in the body might be much smaller than that expected from the high \( R \) value in SDR. This might be the reason for the absence of any hypertensive symptoms in SDR, in spite of the high PRA and Ang I concentrations. On the other hand, the high \( V_{\text{max}} \) and small \( K_m\cdot k_{a2} \) values in GHR indicate that the sensitivity to the pressor response to Ang II is much higher than that of NR. Since the \( k_{a1}/k_{a2} \) value of GHR was similar to that in NR, high PRA and Ang I concentrations might reflect high endogenous Ang II concentration in the body, and therefore high arterial blood pressure in GHR.

As shown in Table IV, the elimination rate constants \( k_{a1} \) and \( k_{a2} \), and the transformation rate constant \( k_{12} \) could not be estimated separately from other parameters, but were estimated as the hybrid constants, \( k_{a1}/k_{12} \) and \( K_m\cdot k_{a2} \).

After cessation of Ang II infusion in treatment II, the time course of Ang II level in the body can be described by Eq. 14.

\[
A_2 = \frac{k_{12}R}{(k_{a1} + k_{12}) k_{a2}} + \frac{k_2}{k_{a2}} e^{-k_{a2}t} \tag{14}
\]

where \( t \) represents time after cessation of infusion. The time course of MAP after cessation of Ang II infusion is also expressed by Eq. 15.

\[
V_{\text{max}} \left\{ \frac{k_{12}R}{(k_{a1} + k_{12}) k_{a2}} + \frac{k_2}{k_{a2}} e^{-k_{a2}t} \right\}'
= MAP_{0} + \frac{k_{12}R}{(k_{a1} + k_{12}) k_{a2}} e^{-k_{a2}t} \tag{15}
\]

In order to obtain the \( k_{a2} \) value separately, the time course of MAP after cessation of Ang II infusion in treatment II was also fitted to Eq. 15, but a satisfactory result was not obtained. The reason for the lack of convergence is that the decline of MAP after cessation of infusion was too rapid to obtain a sufficient number of data with high accuracy. Further investigation is necessary in this respect.

In conclusion, ACE activity was not influenced by the disease state of rats (GHR or SDR). However, the renin-angiotensin system was significantly activated by the disease state. The pressor response to angiotensins in rats was reasonably described by a simple pharmacokinetic model with Hill’s equation. The fraction of MAP dependent on the renin-angiotensin system in rats can be calculated as a function of Ang II level.

Since captopril is known to inhibit the ACE activity, the anti-hypertensive or hypotensive effect might be closely related to the Ang II level in the body. The relationship between captopril disposition and the hypotensive effect in different disease states of rats will be elucidated in the subsequent paper.

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References

5) B. Brooks, G. B. Brown and E. E. Muirhead: Rectangu-


