A Kinetic Study of Chlorpromazine on the Hyperglycemic Response in Rats. II. Effect of Chlorpromazine on Plasma Glucose

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Kinetics of the pharmacologic effect of chlorpromazine was investigated in intact fed rats. After i.v. bolus administration of chlorpromazine (0.5, 2, 4 mg/kg), the time courses of plasma glucose, insulin, adrenaline and noradrenaline levels as well as serum and brain concentrations of the drug were determined. Since the hyperglycemic effect of chlorpromazine is known to be attributable to the endogenously released catecholamines, the effects of adrenaline and noradrenaline on the plasma glucose and insulin regulation system were also determined. The plasma glucose regulation system in rats was investigated by an i.v. glucose tolerance test. From the data obtained, a pharmacokinetic (PK)-pharmacodynamic (PD) model as well as the plasma glucose regulation model was constructed. The hyperglycemic effects of catecholamines during and after i.v. infusion were reasonably well correlated with the plasma concentrations of catecholamines using the PK-PD model. Since a quantitative relationship between plasma concentrations of catecholamines and the brain concentration of chlorpromazine was established in the previous report, the time course of hyperglycemic effect of chlorpromazine was analyzed. The result indicated that the hyperglycemic effect can be described quantitatively by a simple PK-PD model with plasma glucose regulation system, using brain concentrations of chlorpromazine in rats.

Keywords — chlorpromazine; hyperglycemia; adrenaline; noradrenaline; catecholamine; pharmacokinetics; pharmacodynamics; plasma glucose regulation; plasma insulin

Introduction

Since Courvoisier et al. 1a) first reported the hyperglycemic effect of chlorpromazine (CPZ), many investigations have been made to elucidate the mechanism of the hyperglycemic effect of CPZ. 1) It has been generally agreed that the hyperglycemic effect of CPZ was closely related to the sympathetic nerve stimulation and adrenaline release from the adrenal medulla. 13) It has been reported that the hyperglycemic response of catecholamines may be mediated through the following three mechanisms, a) stimulation of hepatic glycogenolysis, 2) b) inhibition of pancreatic insulin release 3) and c) decrease of peripheral glucose uptake. 4) It was evident from these results that the role of catecholamines appears important for the elevation of plasma glucose induced by CPZ. Thus, in order to clarify the relationship between the hyperglycemic effect of CPZ and its disposition, it was necessary initially to elucidate the catecholamine-induced hyperglycemia and the CPZ-induced catecholamines release. In the previous study, 5) we clarified that CPZ-induced elevation of plasma catecholamines was correlated reasonably well with the disposition of CPZ using a pharmacokinetic (PK) and pharmacodynamic (PD) model. The purposes of this investigation were 1) to clarify the relationship between the hyperglycemic effect of catecholamine and its plasma disposition after i.v. infusion of exogenous catecholamines in rats, and 2) to correlate the hyperglycemic effect of CPZ with its disposition, using a PK, PD and plasma glucose regulation model.

Materials and Methods

Chemicals — Chlorpromazine hydrochloride (CPZ, JP grade, Nakarai Chemical Co., Kyoto, Japan), l-adrenaline (ADR, Bosmin® Injection, JP grade, Daiichi Seiyaku Co., Tokyo, Japan), l-noradrenaline (NOR, reagent grade,
Nakarai Chemical Co.) were purchased commercially and were used without further purification. Unless otherwise stated, these reagents were dissolved in normal saline solution (JP grade, Otsuka Pharmaceutical Co., Tokyo, Japan) and were administered intravenously. All other chemicals including glucose (d-(-)-glucose) were of reagent grade and were also obtained commercially.

Animal Experiments — Male albino rats (Wistar strain) weighing 250 to 350 g were used. Under light ether anesthesia, the rats were cannulated into the left femoral vein (for ADR and NOR infusion) and into the right jugular vein (for drug administration and for blood sampling) with a PE50/Silastic tubing in the same manner as described previously. After surgery, the animals were kept in individual metabolic cages (Toyo Riko, Tokyo, Japan) and were allowed to recover overnight with water and food ad libitum.

Adrenalectomized rats were prepared by the method of Ingle et al. under light ether anesthesia. After surgery, prednisolone succinate (JP grade, 5 mg/kg) was administered subcutaneously to prevent acute corticosterone deficiency. Two days after adrenalectomy, the rats were also cannulated into the right jugular vein as described above.

CPZ Administration and Blood Sampling — After i.v. administration of CPZ (0.5, 2 and 4 mg/kg), blood samples (0.45 ml) were withdrawn from the jugular vein at 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 min and were centrifuged at 10000 rpm for 2 min to obtain 0.2 ml of plasma samples. The plasma samples were stored at −20 °C until analysis.

Glucose Tolerance Test — Glucose was dissolved in distilled water and was injected into the jugular vein in the dose level of 1 g/kg. Blood samples (0.45 ml each) were withdrawn and the plasma samples were obtained in the same manner as described above.

Infusion of ADR and NOR — ADR (4, 10, 20, 40 μg/kg/h) or NOR (4, 20, 40, 80 μg/kg/h) was infused into the femoral vein at the rate of 0.032 ml/min for 30 min, using an infusion pump (KN type, Natsume Seisakusho Co., Tokyo, Japan) and blood samples were obtained from the jugular vein. The blood samples were treated in the same manner as described above.

Analytical Methods of Plasma Glucose and Insulin — Plasma glucose concentrations were determined by the method of Sasaki. Plasma insulin concentrations were measured by radioimmunoassay (Insulin-Radioimmunoassay Kit PR method, CEA-IRE-SORIN, Commissariat a L’Energie Atomique, Gif-sur-Yvette, France).

Estimation of model parameters was carried out as described previously.

Results

Effect of CPZ on Plasma Glucose Levels
The time courses of plasma glucose levels after i.v. administration of CPZ (0.5, 2, 4 mg/kg) are shown in Fig. 1. At each dose, plasma glucose concentrations showed a prominent increase just after CPZ administration and gradually returned to the pre-medication level thereafter. The maximum plasma glucose level was observed at 1 h after 4 mg/kg dose of CPZ and was about 160 mg/dl. In the adrenalectomized rats, plasma glucose level showed only a marginal increase even after 4 mg/kg dose of CPZ. This fact indicated that the hyperglycemic effect of CPZ is closely related to the adrenal hormones, namely ADR and NOR. It is reasonable to consider that the plasma glucose level after CPZ administration might correlate with plasma concentrations of catecholamines rather than with plasma CPZ concentration.

In the previous paper, we elucidated that the plasma ADR and NOR concentrations after CPZ i.v. administration in normal rats was reasonably correlated with the brain concentrations of CPZ using a simple PK, PD and link model. Since a plasma glucose regulation system, including a catecholamine regulation system might play an important role in the hyperglycemic effect of CPZ, we investigated the changes of plasma glucose and insulin concentrations before and after administration of glucose, ADR, NOR or a combination of ADR and NOR.
Fig. 1. Plasma Glucose Concentrations after i.v. Administrations of CPZ in Normal and Adrenalectomized Rats

Each value of the data is shown as the mean ± S.E. (a) CPZ 0.5 mg/kg \((n = 3)\), (b) CPZ 2 mg/kg \((n = 3)\), (c) CPZ 4 mg/kg \((n = 3)\), (d) CPZ 4 mg/kg \((n = 5)\). Open symbols represent normal rats and closed symbols represent adrenalectomized rats.

Fig. 2. Plasma Glucose Concentration after an i.v. Administration of Glucose

Each value of the data is shown as the mean ± S.E. \((n = 4)\). The solid line represents the calculated values according to the Eqs. 1 and 2 in the text.

Fig. 3. Plasma Immuno-Reactive Insulin Levels after an i.v. Administration of Glucose

Each value of the data is shown as the mean ± S.E. \((n = 3)\). The solid line represents the calculated values according to the Eqs. 1 and 2 in the text.
Time courses of plasma glucose and insulin levels after i.v. administration of glucose are shown in Figs. 2 and 3, respectively. The plasma glucose level showed a rapid increase just after injection, and it returned to the basal level within 30 min. Plasma insulin level was also increased and reached a maximum level of 200 μU/ml at about 5 min after glucose injection and then returned to the basal level within 30 min.

**Effect of ADR on Plasma Glucose and Insulin Levels**

The time courses of plasma glucose and insulin levels after constant rate intravenous infusion of ADR (4, 10, 20, 40 μg/kg/h for 30 min) are shown in Fig. 4. A dose dependent increase in plasma glucose was observed during the infusion of ADR. It returned gradually to the basal level after cessation of the infusion, whereas the plasma insulin level was decreased during the infusion. After cessation of the infusion, the insulin level showed a significant increase, followed by a gradual decrease to the basal level.

**Effect of NOR on the Plasma Glucose and Insulin Levels**

The time courses of plasma glucose and insulin levels during and after constant intravenous infusion of NOR (4, 20, 40, 80 μg/kg/h for 30 min) are shown in Fig. 5. NOR showed a dose dependent increase in plasma glucose level. At 80 μg/kg/h dose study, the maximum plasma glucose level of 150 mg/dl was observed at 30 min after the start of infusion, and it recovered gradually to the normal level thereafter. The hyperglycemic effect of NOR was smaller than that of ADR. On the other hand, the plasma insulin level was slightly increased during NOR infusion, and it returned to the control level after cessation of the infusion.

**Effect of Concomitant Administration of ADR and NOR on the Plasma Glucose and Insulin Levels**

![Graphs showing plasma glucose and insulin levels](image)

**Fig. 4. Plasma Glucose and Insulin Concentrations during and after ADR Infusion**

Each value of the data is shown as the mean ± S.E. The solid lines represent the calculated values according to the Eqs. 5 through 8 in the text. The plasma concentration of ADR was calculated as shown in the previous report. (a) ADR 4 μg/kg/h for 30 min (n = 3), (b) ADR 10 μg/kg/h for 30 min (n = 4), (c) ADR 20 μg/kg/h for 30 min (n = 3), (d) ADR 40 μg/kg/h for 30 min (n = 3).
Time courses of plasma glucose level during and after constant infusion of the combinations of ADR and NOR (4 and 20, 10 and 40, 20 and 80 µg/kg/h) are shown in Fig. 6. Plasma glucose levels were increased in accordance with the dose of ADR or NOR; however the increase of plasma glucose levels was smaller than was expected from the individual effect of the catecholamines. This fact indicates that there might be a drug-drug interaction between ADR and NOR in respect to the hyperglycemic effect, and that this interaction might not be attributable to the simple additive interaction.

**Construction of the Model**

From the observed data described above, we attempted to construct a PK-PD model which describes the time course of the hyperglycemic effect of CPZ in relation to its disposition in rats. The description of the model was in terms of differential equations and it was based on several hypotheses, assumptions or established facts.

(1) **Plasma Glucose Regulation Model**

The mathematical model for the plasma glucose regulation system used in this study was based on the following assumptions; (a) plasma glucose is produced by zero order rate and eliminated by a first order rate process, (b) when the plasma glucose level is above the normal level, glycogenesis is stimulated by insulin to maintain the plasma glucose level at the normal level and (c) plasma insulin is eliminated by a first order process. These relationships are described mathematically by Eqs. 1 and 2.

\[
\frac{d\text{Glu}}{dt} = k_{g0} - \beta_{ig}\text{Ins} - k_{ge}\text{Glu} \tag{1}
\]

\[
\frac{d\text{Ins}}{dt} = \alpha_{gi}\text{Glu} - k_{ie}\text{Ins} \tag{2}
\]

where Glu is the plasma concentration of glucose, Ins is the plasma concentration of insulin.
and $k_{g0}$ is the intrinsic glucose production rate. The constants, $k_{ge}$ and $k_{ig}$ are the first order elimination rate constants of glucose and insulin, respectively. $\beta_{ig}$ is a proportional coefficient in respect to the insulin-mediated plasma glucose consumption and $\alpha_{gi}$ is a proportional coefficient in respect to the glucose-induced insulin production. At steady state, the left sides of Eqs. 1 and 2 equal to zero. Then, rearrangement of Eqs. 1 and 2 yield Eqs. 3 and 4 respectively.

$$\text{Glu}_0 = \frac{k_{ie} k_{g0}}{\beta_{ig} \alpha_{gi} - k_{ie} k_{ge}} \quad (3)$$

$$\text{Ins}_0 = \frac{\alpha_{gi} k_{g0}}{\beta_{ig} \alpha_{gi} - k_{ie} k_{ge}} \quad (4)$$

where $\text{Glu}_0$ is the plasma glucose level at steady state and $\text{Ins}_0$ is the plasma insulin level at steady state.

(2) Effect of ADR or NOR on the Plasma Glucose — The effect of ADR or NOR on the plasma glucose regulation was described using the following assumptions; (a) ADR or NOR increases the glucose production rate, (b) ADR or NOR also decreases the intrinsic production rate of plasma insulin and (c) the relationship between plasma ADR or NOR level and the pharmacologic effect of ADR or NOR at active site is described by Hill’s equation. These relationships were expressed by Eqs. 5 through 8 (ADR administration) or Eqs. 9 through 12 (NOR administration).

$$\frac{d\text{Glu}}{dt} = k_{g0} + R_{a,\text{glu}} - \beta_{ig} \text{Ins} - k_{ge} \text{Glu} \quad (5)$$

$$\frac{d\text{Ins}}{dt} = (\alpha_{gi} - R_{a,\text{ins}}) \text{Glu} - k_{ie} \text{Ins} \quad (6)$$
where \( R_{a,\text{glu}} \) and \( R_{a,\text{ins}} \) are the pharmacologic effects of ADR on the plasma glucose regulation and the plasma insulin regulation, respectively, and where \( R_{n,\text{glu}} \) and \( R_{n,\text{ins}} \) are the pharmacologic effects of NOR on the plasma glucose regulation and the plasma insulin regulation, respectively. \( C_{\text{ADR}} \) and \( C_{\text{NOR}} \) are the plasma concentrations of ADR and NOR, and the subscripts \( a \) and \( n \) represent the administration of ADR and NOR, respectively. \( E_{\text{glu}} \) and \( E_{\text{ins}} \) are the maximum effects of the catecholamine on the plasma glucose and the plasma insulin, respectively. \( K_{a,\text{glu}} \), \( K_{a,\text{ins}} \), \( K_{n,\text{glu}} \), and \( K_{n,\text{ins}} \) are the catecholamine concentrations at the half of the maximum effect and \( rag \), \( rai \), \( rng \) and \( rni \) are the Hill’s constants.

(3) Hyperglycemia after i.v. Administration of the Combination of ADR and NOR — The hyperglycemic effect after i.v. administration of the combination of ADR and NOR was expressed by the following assumptions; (a) ADR and NOR bind the common receptor, (b) ADR and NOR antagonize each other in a competitive manner and (c) there is no PK interaction between ADR and NOR.

\[
\frac{d\text{Glu}}{dt} = k_{g0} + R_{n,\text{glu}} - \beta_{ig} \text{Ins} - k_{ge} \text{Glu}
\]

\[
\frac{d\text{Ins}}{dt} = (\alpha_{gi} + R_{n,\text{ins}}) \text{Glu} - k_{ic} \text{Ins}
\]

\[
R_{n,\text{glu}} = \frac{E_{n,\text{glu}} C_{\text{NOR}}}{C_{\text{NOR}} + K_{n,\text{glu}}}
\]

\[
R_{n,\text{ins}} = \frac{E_{n,\text{ins}} C_{\text{NOR}}}{C_{\text{NOR}} + K_{n,\text{ins}}}
\]

![Fig. 7. Diagrammatic Representation of the PD Model for the Hyperglycemic Effect of CPZ in Rats](image-url)
\[ \frac{d\text{Ins}}{dt} = (\alpha_{g1} - R_{a+n,\text{glu}}) \text{Glu} - k_{ie} \text{Ins} \] (14)

\[ R_{a+n,\text{glu}} = \frac{E_{a,\text{glu}} C_{\text{ADR}}^{rag}}{C_{\text{ADR}}^{rag} + (K_{a,\text{glu}}(1 + \frac{C_{\text{NOR}}}{K_{a,\text{glu}}}))^{rag} + \frac{E_{n,\text{glu}} C_{\text{NOR}}^{rng}}{C_{\text{NOR}}^{rng} + (K_{n,\text{glu}}(1 + \frac{C_{\text{ADR}}}{K_{a,\text{glu}}}))^{rng}} \] (15)

\[ R_{a+n,\text{ins}} = \frac{E_{a,\text{ins}} C_{\text{ADR}}^{rai}}{C_{\text{ADR}}^{rai} + (K_{a,\text{ins}}(1 + \frac{C_{\text{NOR}}}{K_{n,\text{ins}}}))^{rai} + \frac{E_{n,\text{ins}} C_{\text{NOR}}^{rni}}{C_{\text{NOR}}^{rni} + (K_{n,\text{ins}}(1 + \frac{C_{\text{ADR}}}{K_{a,\text{ins}}}))^{rni}} \] (16)

where \( R_{a+n,\text{glu}} \) and \( R_{a+n,\text{ins}} \) are the effects of concomitant administration of ADR and NOR on plasma glucose and insulin, respectively.

(4) The Hyperglycemic Effect of CPZ — It was evident from the experimental results that the hyperglycemic effect of CPZ was caused by ADR and NOR, which were released from the adrenal medulla. Since the relationship between brain CPZ concentration and plasma catecholamine concentrations was shown to be correlated reasonably well in the previous study, the pharmacokinetic and pharmacologic models for CPZ disposition and plasma catecholamine secretion in the previous report were also used in the present study, without any additional assumptions. The schematic diagram of the whole model is summarized in Fig. 7.

**Computer Fitting and Simulation**

The solid lines in Figs. 2 and 3 represent the calculated values of plasma glucose and insulin concentrations after i.v. administration of glucose, respectively. The physiological parameters used in the calculation are listed in Table I. Although the plasma glucose regulation model used in this study was simple, the calculated values for plasma glucose and insulin levels were described reasonably well.

The solid lines in Fig. 4 are the calculated values for plasma glucose and insulin levels during and after i.v. infusion of ADR, using Eqs. 5 through 8. Although the temporal increase of insulin concentration, which was observed just after the cessation of ADR infusion, could not be described by the model, the dose dependent increase in plasma glucose levels as well as their time courses during and after ADR infusion were adequately described by the model. All of the PK parameters in respect to ADR disposition were taken from the previous paper, assuming that the desposition of ADR is linear among these dose levels. The pharmacologic parameters used in the calculation are listed in Table II.

The solid lines in Fig. 5 show the calculated values for plasma glucose and insulin levels during and after infusion of NOR, according to Eqs. 9 through 12. All of the PK parameters in respect to NOR disposition were also taken from the previous paper, assuming that the disposition of NOR is linear among these dose levels. The time courses of plasma glucose as well as

**Table I. List of Physiological Parameters**

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<tr>
<th>Parameter</th>
<th>Dimension</th>
<th>Estimate</th>
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<td>( k_{g1} )</td>
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<td>( \beta_{g1} )</td>
<td>mg/dl/h/(\mu U/ml)</td>
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<tr>
<td>( k_{ge} )</td>
<td>h(^{-1})</td>
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<tr>
<td>( \alpha_{gi} )</td>
<td>\mu U/ml/(mg/ml)</td>
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<tr>
<td>( k_{ie} )</td>
<td>h(^{-1})</td>
<td>24.94</td>
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**Table II. List of Pharmacologic Parameters**

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<td>( r_{agi} )</td>
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<td>( r_{n} )</td>
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<td>( K_{a,\text{glu}} )</td>
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<td>( \gamma_{n} )</td>
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<tr>
<td>( E_{a,\text{glu}} )</td>
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<td></td>
<td>1.000</td>
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<tr>
<td>( K_{a,\text{ins}} )</td>
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<td>( K_{n,\text{ins}} )</td>
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<td>( E_{a,\text{ins}} )</td>
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<td>( E_{n,\text{ins}} )</td>
<td>h(^{-1})</td>
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plasma insulin were described by the model fairly well. On performing the model fitting, the pharmacologic parameters such as \( rni \) and \( K_{n,ins} \) were set to 1.0 and 0.00037, respectively. With smaller values for \( rni \) and \( K_{n,ins} \) the least squares method failed to obtain the proper fit to the observed data. All other pharmacologic parameters used in the calculation are also listed in Table II.

The solid lines shown in Fig. 6 represent the calculated values for plasma glucose and insulin levels during and after the concomitant infusion of ADR and NOR, according to Eqs. 13 through 16. Assuming that there was no PK interaction between ADR and NOR, all of the PK parameters in respect to ADR and NOR disposition were taken from the previous report. As shown in Fig. 6, the calculated values described the observed data reasonably well. As mentioned above, the calculated values were obtained under the assumption that ADR and NOR acted as competitive antagonists to each other. On the other hand, the dotted lines shown in Fig. 6 also represent the calculated values assuming that ADR and NOR showed a simple additive interaction. The simple additive interaction was calculated by the following Eqs. 17 and 18, and Eqs. 13 and 14.

\[
R_{a+n,glu} = \frac{E_{a,glu} C_{ADR}^{rag}}{C_{ADR}^{rag} + K_{a,glu}^{rag}} + \frac{E_{n,glu} C_{NOR}^{rng}}{C_{NOR}^{rng} + K_{n,glu}^{rng}} \quad (17)
\]

\[
R_{a+n,ins} = \frac{E_{a,ins} C_{ADR}^{rai}}{C_{ADR}^{rai} + K_{a,ins}^{rai}} + \frac{E_{n,ins} C_{NOR}^{rni}}{C_{NOR}^{rni} + K_{n,ins}^{rni}} \quad (18)
\]

The observed data for plasma glucose levels were much smaller than the prediction values and this result indicated that the PD interaction between ADR and NOR could be attributable to

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**Fig. 8. Comparison of Theoretical Values with Observed Data after i.v. Administration of CPZ in Rats**

Upper graph represents the plasma glucose concentration and the lower graph represents the plasma insulin concentration. Each value of the data is shown as the mean ± S.E. The solid lines represent the computer predicted values. (a) CPZ 0.5 mg/kg i.v. \((n = 3)\), (b) CPZ 2 mg/kg i.v. \((n = 3)\), (c) CPZ 4 mg/kg i.v. \((n = 3)\).
the competitive antagonism rather than simple additive interaction.

Figure 8 shows the comparison of theoretical values with observed data after i.v. bolus administration of CPZ in rats. The plotted symbols are the observed data and the solid lines are the computer simulated values. The PK parameters for CPZ disposition in rats were taken from the previous report.\textsuperscript{8a} The PK and PD parameters for describing the relationship between CPZ brain concentrations and plasma catecholamine concentrations were taken from the previous report.\textsuperscript{8} Other physiological and PD parameters for plasma glucose, insulin and catecholamines regulation system in rats were taken from Table II without any modification. The prediction values describe the observed data reasonably well and this fact indicates that the PK and PD model used in the study was appropriate.

**Discussion**

In the present study, a simple kinetic model for plasma glucose and insulin regulation was used. There have been numerous kinetic models used for the several species studied including human.\textsuperscript{10} As suggested in the report of Atkins,\textsuperscript{10a} the glucose–insulin regulation system was too complex to make a choice among several models, if data were obtained for only plasma glucose and insulin levels. Therefore, many models will fit the curves for plasma glucose and insulin levels after an i.v. glucose loading in rats. Since we chose the simplest model which could describe glucose–insulin regulation in rats, we do not claim that the model used in this study is unique.

Among the physiological parameters shown in Table I, the value for $k_{g0}$ can be regarded as the liver glucose production rate in rats. Assuming that the distribution volume of glucose is 2.9 d/kg in rats, the glucose production rate was estimated to be 1417 mg/h/kg. This value is much higher than that used for of human study, and this discrepancy may be attributable to the high glucose turnover rate in rats. The values for $\alpha_{gi}$ and $\beta_{ig}$ are the coupling coefficient between glucose and insulin, and *vice versa*, respectively. Segre *et al.*\textsuperscript{10b} also determined these parameters in their human study using the same model. They reported that the mean values for $\alpha_{gi}$ and $\beta_{ig}$ were 1.08 and 1.25, respectively. The present result indicates that sensitivity for the effect of insulin on the plasma glucose balance and for the effect of glucose concentration on insulin secretion is much greater in rats than that in humans.

In the PD model description, we assumed that the hyperglycemic effect of CPZ was caused only by endogenously released catecholamines. Therefore, all of the pharmacologic parameters shown in Table II are only referred to as the dose response relationship between catecholamine levels and plasma glucose, or between catecholamine levels and plasma insulin. Although these parameters were estimated independently by the respective catecholamine administration study (Figs. 4 and 5), the hyperglycemic effect of CPZ (Fig. 8) could be described using these parameters without any modification. This fact indicates that, to a large extent, the hyperglycemic effect of CPZ is attributable to the endogenous catecholamines. It has been found that various adrenergic blocking drugs can inhibit both hyperglycemic effect of CPZ in rodents,\textsuperscript{1d,11} and that the $\alpha$-blocker, phentolamine, and $\beta$-blocker, propranolol, can inhibit the hyperglycemic and hyperlipoproteinemic effect.\textsuperscript{12} Thus, the predominant theory concerning the effect of CPZ on glucose concentration in the literature is that there is a CPZ-mediated release of catecholamines which, in turn, causes an increased plasma influx of glucose from hepatic glycogen or gluconeogenesis. Therefore the assumptions made in the present study are appropriate.

Besides the activation of adrenergic mechanisms, Jori *et al.*\textsuperscript{13} suggested that CPZ also inhibited the peripheral utilization of glucose directly. This possibility was further investigated by Rafaelsen *et al.*\textsuperscript{14} in rats; however, they showed that the inhibition of glucose uptake occurred only at relatively high CPZ concentration. On the other hand, Ammon *et al.*\textsuperscript{15} also showed that CPZ directly inhibited the glucose-loading-induced increase in plasma insulin level in rats. Erle *et al.*\textsuperscript{16} suggested that higher acute dose of CPZ could inhibit insulin secretion both
in normal men and in patients with latent diabetes mellitus. Nakadate et al. 17 have shown that CPZ (10 mg/kg, i.p.) did not inhibit the glucose-loading-induced increase in plasma insulin level in mice. These facts suggested that only a high dosage of CPZ could inhibit the utilization of plasma glucose or the secretions of insulin. This was the reason why we excluded the direct effect of CPZ from the PD model.

As shown in Eqs. 5 and 6 (and also shown in Eqs. 9, 10, 13 and 14), we assumed that the catecholamines increased plasma glucose production rate and inhibited the secretion of insulin. Nakaki et al. 3c showed in their in vitro study that NOR also had an inhibitory effect on insulin secretion. Although, NOR showed only a marginal decrease of plasma insulin level in the present results, the assumptions in respect to the effect of catecholamines on the glucose regulation system were appropriate.

In Eqs. 15 and 16, we assumed that ADR and NOR antagonized each other in a competitive manner. The experimental result of plasma glucose levels under concomitant administration of ADR and NOR was reasonably well described by this model; however, there is no direct evidence for the antagonism. Further investigation is required in this respect.

In conclusion, the hyperglycemic effect of CPZ in rats was attributable to the effect of the catecholamines which were secreted in the body. The time course of the effect was well described by a simple PK-PD model with the plasma glucose regulation system.

References


9. R. J. Tallarida, A. Cowan and M. W. Adler: pA2 and
Hypercglycemic Effect of Chlorpromazine


