A KINETIC STUDY ON CHLORPROMAZINE DISPOSITION AND HYPOTHERMIC RESPONSE IN RATS

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Pharmacokinetic relationships were developed to characterize a multi-exponential drug disposition and pharmacologic response time courses. The derived expressions were applied to serum and cerebral concentrations and the hypothermic response data, which were obtained after rapid intravenous administration of chlorpromazine hydrochloride to rats.

The results of this study indicate that the magnitude of the pharmacologic effects of chlorpromazine such as decrease in metabolic heat production and increase in tail blood flow, at a given time, are logarithmic logistic functions of the cerebral chlorpromazine concentration at that time.

Keywords — chlorpromazine; hypothermia; pharmacokinetics; pharmacologic response; cerebral concentration; serum concentration; perfusion rate limited model; body temperature regulation

Chlorpromazine (CPZ), which has a wide range of activity arising from its depressant actions on the central nervous system (CNS) and its α -adrenergic blocking and weaker anticholinergic activities, inhibits the heat regulating center so that the subject tends to acquire the temperature of its surroundings.¹⁾

On the basis of experiments in the conscious monkey, Chai *et al.*²⁾ suggested that CPZ works principally through the CNS, *i.e.* the preoptic anterior hypothalamus and medulla oblongata, to mediate its hypothermic effect. Kirkpatrick *et al.*³⁾ reported, however, that CPZ caused a fall in body temperature when administered systemically to rats and that injection of CPZ directly into the rostral hypothalamic thermoregulatory centers led to a rise in temperature. In addition, reported responses of mammals treated with CPZ include a decrease in oxygen consumption,^{1a,b)} an increase in tail blood flow,^{1a)} and an inhibition in shivering.⁴⁾

Taking these results into consideration and applying a compartment model concept used in the previous studies on antipyretics,⁵⁾ pharmacokinetic analysis of hypothermic response of rats to CPZ was attempted. The aim of the present report is to describe a mathematical model and the results of simulation using the model.

THEORY

General Description of the Model

A schematic diagram of the model is shown in Fig. 1, which is essentially the same as the one proposed in the previous report.⁵⁾ The rat body is divided primarily into two compartments, core and skin. In accordance with a specific hyperthermic response of rat tail to CPZ, skin compartment is subdivided into two parts, pelt and tail, which are different from each other in thermal characteristics. Each compartment is considered to have uniform thermal properties and a single value of temperature. Each compartment gains or loses heat from adjacent compartments in proportion to the temperature difference between the two. In Fig. 1, the thick and thin lines represent heat flows and biological controls, respectively.

Metabolic heat (M) is generated in the core compartment. Heat loss by vaporization (V) is mainly respiratory effect and, therefore, occurs in the core compartment. In the pelt compartment, heat is gained from the core compartment by conduction (K) and is transferred to the ambient air by radiation and convection (L_2). In the tail compartment, however, heat is gained from core compartment mainly *via* tail blood flow (F) and is transferred to the ambient air by

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FIG. 1. *Diagrammatic Representation of Heat Flow, Thermoregulatory System and Drug Action*
Thick arrow: heat flow, thin arrow: path of control.

radiation and convection ($L1$). No thermal interactions between pelt and tail compartment are assumed.

The central nervous system commands, as a controller, the efferent signals for M , K , V and F to change their values according to the change in afferent signals from core, pelt and tail temperature. The effects of CPZ are assumed to act as afferent signals to the controller.

Mathematical interpretations of the model shown in Fig. 1 are as follow. Eqs 1, 2 and 3 give change in heat store in the respective compartment.

$$W_C C \frac{dT_C}{dt} = M - V - K(T_C - T_{S2}) - SF(T_C - T_{S1}) \quad (1)$$

$$W_{S2} C \frac{dT_{S2}}{dt} = K(T_C - T_{S2}) - L2(T_{S2} - T_A) \quad (2)$$

$$W_{S1} C \frac{dT_{S1}}{dt} = SF(T_C - T_{S1}) - L1(T_{S1} - T_A) \quad (3)$$

Definitions of the symbols used in all the equations are listed in Table I.

At steady state, Eqs. 1, 2 and 3 are reduced to Eqs. 4, 5 and 6.

$$0 = M_0 - V_0 - K_0(T_{C0} - T_{S20}) - SF_0(T_{C0} - T_{S10}) \quad (4)$$

$$0 = K_0(T_{C0} - T_{S20}) - L2(T_{S20} - T_A) \quad (5)$$

$$0 = SF_0(T_{C0} - T_{S10}) - L1(T_{S10} - T_A) \quad (6)$$

Expressing temperatures and coefficients as variations from the steady state values, Eqs. 7, 8 and 9 are obtained.

$$W_C C \frac{dT_C}{dt} = \Delta M - \Delta V - K(\Delta T_C - \Delta T_{S2}) - \Delta K(T_{C0} - T_{S20}) - SF(\Delta T_C - \Delta T_{S1}) - S\Delta F(T_{C0} - T_{S10}) \quad (7)$$

$$W_{S2} C \frac{dT_{S2}}{dt} = K(\Delta T_C - \Delta T_{S2}) + \Delta K(T_{C0} - T_{S20}) - L2 \Delta T_{S2} \quad (8)$$

$$W_{S1} C \frac{dT_{S1}}{dt} = SF(\Delta T_C - \Delta T_{S1}) + S\Delta F(T_{C0} - T_{S10}) - L1 \Delta T_{S1} \quad (9)$$

where $\Delta T_C = T_C - T_{C0}$, $\Delta T_{S1} = T_{S1} - T_{S10}$, $\Delta T_{S2} = T_{S2} - T_{S20}$, $\Delta M = M - M_0$, $\Delta K = K - K_0$ and $\Delta F = F - F_0$. $L1$, $L2$ and T_A are assumed constant.

Assumptions on Physiological Response

The average body temperature (T_B) is defined as Eq. 10.

$$T_B = \frac{W_C T_C + W_{S2} T_{S2} + W_{S1} T_{S1}}{W_C + W_{S2} + W_{S1}} \quad (10)$$

Assuming that $W_C : W_{S2} : W_{S1} = 6 : 2 : 1$, Eq. 10 is reduced to Eq. 11, and Eq. 12 is obtained at steady state.

$$T_B = 0.67 T_C + 0.22 T_{S2} + 0.11 T_{S1} \quad (11)$$

$$T_{B0} = 0.67 T_{C0} + 0.22 T_{S20} + 0.11 T_{S10} \quad (12)$$

Steady state average body temperature (T_{B0}) is considered as the set point temperature in the present model. According to the change in T_B , values of M , V , K and F are modified by means of proportional control ($\alpha \Delta T_B$) and/or rate control ($\gamma dT_B/dt$). Conceptions of proportional

TABLE I. *List of Symbols and Definitions*

A_i ($i = 1, 2, \dots$)	$\mu\text{g/ml}$	Coefficient of CPZ serum concentration
A_{BF}	cm^2	Cross sectional area of tail blood flow
α_K	$\text{kcal/h/}^\circ\text{C}^2$	Proportional control coefficient of heat transfer
α_M	$\text{kcal/h/}^\circ\text{C}$	Proportional control coefficient of metabolic rate
α_V	$\text{kcal/h/}^\circ\text{C}$	Proportional control coefficient of vaporization
B_S	cm/s	Linear velocity of tail blood flow
C	$\text{kcal/kg/}^\circ\text{C}$	Specific heat of tissue
C_{BR}	$\mu\text{g/ml}$	Cerebral concentration of CPZ
C_{SR}	$\mu\text{g/ml}$	Serum concentration of CPZ
$C_{\text{F}}(50)$	$\mu\text{g/ml}$	Cerebral concentration of CPZ which causes 50% of maximum effect on tail blood flow
$C_{\text{K}}(50)$	$\mu\text{g/ml}$	Cerebral concentration of CPZ which causes 50% of maximum effect on heat transfer
$C_{\text{M}}(50)$	$\mu\text{g/ml}$	Cerebral concentration of CPZ which causes 50% of maximum effect on metabolic heat production rate
F	kg/h	Volumetric tail blood flow rate
γ_K	$\text{kcal/}^\circ\text{C}^2$	Rate control coefficient of heat transfer
K	$\text{kcal/}^\circ\text{C}$	Coefficient of heat transfer (core to pelt)
K_{P}		Brain to serum equilibrium distribution ratio
L_1	$\text{kcal/h/}^\circ\text{C}$	Coefficient of heat transfer (tail surface to air)
L_2	$\text{kcal/h/}^\circ\text{C}$	Coefficient of heat transfer (pelt to air)
λ_i ($i = 1, 2, \dots$)	h^{-1}	Rate constant of CPZ serum concentration
M	kcal/h	Metabolic heat production rate
Q_{BR}	ml/h	Brain blood flow rate
R	—	Pharmacologic response
R_{max}	—	Maximum pharmacologic response
R_{Fmax}	kg/h	Maximum effect of CPZ on tail blood flow
R_{Kmax}	$\text{kcal/h/}^\circ\text{C}$	Maximum effect of CPZ on heat transfer
R_{Mmax}	kcal/h	Maximum effect of CPZ on metabolic heat production rate
S	$\text{kcal/kg/}^\circ\text{C}$	Specific heat of blood
s		Hill constant
s_{F}		Hill constant of CPZ effect on tail blood flow
s_{K}		Hill constant of CPZ effect on heat transfer
s_{M}		Hill constant of CPZ effect on metabolic rate
t	h	Time after CPZ administration
T_{A}	$^\circ\text{C}$	Ambient temperature
T_{B}	$^\circ\text{C}$	Average body temperature
T_{C}	$^\circ\text{C}$	Temperature of core compartment
T_{S1}	$^\circ\text{C}$	Temperature of tail compartment
T_{S2}	$^\circ\text{C}$	Temperature of pelt compartment
V	kcal/h	Rate of heat loss by vaporization
W_{BR}	g	Weight of brain tissue
W_{C}	kg	Mass weight of core compartment
W_{S1}	kg	Mass weight of tail compartment
W_{S2}	kg	Mass weight of pelt compartment

control and rate control have been reviewed by Hardy⁶⁾ in detail.

Assumptions on Pharmacologic Response

The magnitude of many types of pharmacologic response is related to the logarithmic logistic function of the dose or concentration of the

drug in the biophase.⁷⁾ Therefore, the pharmacologic response intensity (R) is defined as a logarithmic logistic function (Hill equation) of cerebral concentration of CPZ.

$$R = \frac{C_{\text{max}} C_{\text{BR}}^s}{C_{\text{BR}}(50)^s + C_{\text{BR}}^s} \quad (13)$$

Hypothermic effect of CPZ is incorporated into the model as an element that modifies metabolic heat production (M), heat conduction (K) between core and pelt compartment and tail blood flow (F). Physiological and pharmacological responses are expressed mathematically as follow.

$$M = M_0 - \alpha_M \Delta T_B - \frac{R_{M\max} C_{BR}^{sM}}{C_M(50)^{sM} + C_{BR}^{sM}} \quad (14)$$

$$V = V_0 + \alpha_V \Delta T_B \quad (15)$$

$$K = K_0 + \alpha_K \Delta T_B + \gamma_K \frac{dT_B}{dt} + \frac{R_{K\max} C_{BR}^{sK}}{C_K(50)^{sK} + C_{BR}^{sK}} \quad (16)$$

$$F = F_0 + \frac{R_{F\max} C_{BR}^{sF}}{C_F(50)^{sF} + C_{BR}^{sF}} \quad (17)$$

The reason for the omission of the pharmacological response term in Eq. 15 is that no appreciable effects were observed on V .

MATERIALS AND METHODS

Materials — Chlorpromazine hydrochloride of J.P. grade was dissolved in a physiological saline solution in a concentration giving an injection volume of 1 ml. All other chemicals used were of reagent grade.

Measurement of Body Temperature — Male albino rats (Wistar strain) weighing 200 to 250 g were restrained in a supine position. Food was withheld overnight prior to experiments. Rectal temperature was measured with a thermister type self-resistering thermometer (Takara K-923), by inserting the probe into the rectum of the rat as far as 3 cm. For pelt and tail temperature measurements, sensors were fastened on thigh skin and on tail surface, respectively. Environmental temperature was controlled at $23 \pm 1^\circ\text{C}$. Measurements of rectal, thigh and tail temperature were continued for 10 h after drug administration. Chlorpromazine hydrochloride (0.5, 2, 4 mg/kg) was injected *via* the jugular vein.

Measurement of Heat Production and Heat Loss — Rates of heat production and heat loss were determined by indirect calorimetry as de-

scribed in the previous report⁵⁾ with minor modification.

The energy released within the body was estimated from the release rate of carbon dioxide, the oxidative end-product. Concentration of CO_2 in the expired air was determined using a breath analyzer (Fukuda R-1000S). It was assumed that one liter of CO_2 expired is equivalent to 5 kcal of heat production. Since the latent heat of water vaporization is 0.6 kcal per g of water, the rate of heat loss was calculated from the amount of water in the expired air, which was absorbed on calcium chloride.

The rat was caged in a box made of acrylic acid resine, which was ventilated (120 ml/min) by a suction pump built in the breath analyzer. The air from the box was led to the analyzer *via* moisture traps (CaCl_2) and CO_2 concentration was recorded continuously on a recorder (Riken SP-G-7P).

Measurement of Tail Blood Flow Rate — The probe of an ultrasonic blood flow meter (Sanei Nippon Denki 1935) was fitted to the tail artery. Blood flow rate (average during 5 s) was automatically recorded.

Determination of CPZ Concentration in Serum and Brain — Decapitation was followed by exsanguination and decerebration at 5, 10, 20, 30, 45, 60, 120, 180, 240, 300 and 360 min after intravenous administration of the drug. Samples were stored in congelation until they were used for the assay.

Assay of Chlorpromazine — CPZ in serum and brain tissue was assayed with high performance liquid chromatography (HPLC).

Serum: To a test tube containing trifluoperazine (internal standard), 0.5 ml of serum sample and 0.1 ml of 1 N NaOH and 5 ml of hexane-isomyl alcohol (98:2) were added and mixed well. Four ml of organic solvent layer were transferred to another test tube. After the solvent was evaporated to dryness, the residue was dissolved in 50 μl of methanol. Ten μl of the methanol solution were injected to HPLC (Shimadzu LC-3A).

Brain: To one gram portion of excised brain tissue, 2 ml of 1 N NaOH and the internal standard were added and homogenized. Chlorpromazine in the homogenate was assayed as in the serum.

Measurement Conditions: Column: 4 mm $\times$ 150 mm stainless steel column packed with Merck Lichrosorb® RP-18; detector: shimadzu

SPD-2A (254 nm); mobile phase: acetonitril/methanol/0.1 M acetate buffer (pH 4.2) = 820/80/100 + 1-heptanesulfonate (0.02 M); flow rate: 1.3 ml/min.

Estimation of Model Parameters — A nonlinear least squares regression program FKDM which is based on the algorithm of Berman *et al.*⁸⁾ was used to fit a model to observed data and to estimate model parameters on a digital computer (Digital Equipment Corp., PDP-11/34).

Since concentration data, temperature data and blood flow data were obtained with different rat groups, averages of observed values were used for model adaptation.

RESULTS AND DISCUSSION

Disposition of Chlorpromazine

The declines in serum and cerebral concentrations of CPZ after rapid intravenous injection of chlorpromazine hydrochloride (CPZ-HCl, 0.5 and 4 mg/kg) to rats are shown in Fig. 2. The data are plotted semilogarithmically as a function of time. Graphical analysis of serum concentrations by the method of residuals^{9a)} indicated that the decline of the data was multi-exponential. Assuming perfusion rate limited distribution^{9b)} to brain, Eqs. 18 and 19 were obtained for time courses of serum and cerebral CPZ concentrations.

$$C_{SR} = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t} \quad (18)$$

$$\frac{dC_{BR}}{dt} = \frac{Q_{BR}}{W_{BR}} (C_{SR} - \frac{C_{BR}}{K_P}) \quad (19)$$

By a nonlinear least squares computer fit of the data shown in Fig. 2 to Eqs. 18 and 19, pharmacokinetic parameters of Table II were ob-

tained. When performing the computer fit, brain plasma flow rate ($Q_{BR} = 24.3$ ml/h/200 g) and brain tissue weight ($W_{BR} = 1.69$ g/200 g) were fixed to the literature values.^{10,11)} The solid lines in Fig. 2 represent the computer fit to the respective data. Although observed serum data

FIG. 2. Time Course of Serum and Cerebral Concentration of Chlorpromazine after Intravenous Administration of Chlorpromazine Hydrochloride in Rats

●, cerebral concentration (4 mg/kg); ■, cerebral concentration (0.5 mg/kg); ○, serum concentration (4 mg/kg). Lines: calculated concentration. Each point represents mean $\pm$ S.E. of 3 experiments.

TABLE II. Pharmacokinetic Parameters on Chlorpromazine Disposition

A_1	($\mu\text{g/ml}$)/(dose mg/kg)	20.0
A_2	($\mu\text{g/ml}$)/(dose mg/kg)	0.166
A_3	($\mu\text{g/ml}$)/(dose mg/kg)	0.038
λ_1	(h^{-1})	97.0
λ_2	(h^{-1})	1.50
λ_3	(h^{-1})	0.078
K_P		17.2
Q_{BR}	(ml/h)/0.2 kg	24.3
W_{BR}	(g)/0.2 kg	1.69

FIG. 3. Time Course of Metabolic Heat Production Rate after Intravenous Administration of Chlorpromazine Hydrochloride in Rats
(a) 2 mg/kg, (b) 4 mg/kg. Each point represents mean $\pm$ S.E. of 3–4 experiments.

FIG. 4. Time Course of Rectal Temperature after Intravenous Administration of Chlorpromazine Hydrochloride in Rats
(a) 0 mg/kg, (b) 0.5 mg/kg, (c) 2 mg/kg, (d) 4 mg/kg. Each point represents mean $\pm$ S.E. of 3–6 experiments.

during the distribution phase are deficient, agreement between the observed data and calculated values is satisfactory.

Serum volume calculated from the parameter values of Table II is 49.49 ml/kg or 9.90 ml/200 g, which agrees with the value adopted by Bischoff *et al.* (9.0 ml/200 g).¹¹⁾ That the time course of cerebral CPZ concentrations after 0.5 and 4 mg/kg intravenous dosing were fit successfully with the same parameter values suggests the disposition of CPZ is linear among these dose levels.

In accordance with reports by a few investigators,^{1b,c,12)} CPZ concentrations in the brain exceeded greatly those in serum, with the brain/serum concentration ratio greater than 10 ($K_p = 17.2$). Any preferential uptake of CPZ into the hypothalamus, the proposed site at which CPZ acts to cause hypothermia, however, has not been demonstrated.^{1b,c)}

Effect of CPZ on Body Temperatures

FIG. 5. Time Course of Thigh Skin Temperature after Intravenous Administration of Chlorpromazine Hydrochloride in Rats
(a) 0 mg/kg, (b) 0.5 mg/kg, (c) 2 mg/kg, (d) 4 mg/kg. Each point represents mean $\pm$ S.E. of 3–6 experiments.

Time courses of metabolic heat production rate, rectal temperature, thigh skin temperature, tail temperature and tail blood flow rate after intravenous dosing of CPZ-HCl 0.5, 2 and 4 mg/kg are shown in Figs. 3–7, respectively.

Metabolic heat production rate, rectal temperature and thigh temperature decreased dependently on the amount of CPZ administered. At 4 mg/kg, maximum decrease in metabolic heat production rate was about 0.4 kcal/h at one hour after dosing and recovered gradually to the normal level thereafter. Maximum decrease in rectal temperature was about 4.5 °C at 1.5 h after CPZ injection and the rectal temperature recovered thereafter. Time courses of thigh temperature were similar to those of rectal temperature, except that the extent of decrease was much less. On the other hand, tail temperature increased about 5 °C in 0.5 h after CPZ intravenous injection and the temperature recovered to

the normal level in 4 h. At 4 mg/kg CPZ-HCl injection, maximum increase in blood flow rate was about 5 cm/s, which was observed at 1 h after CPZ dosing. Blood flow rate recovered thereafter and returned to the normal level in about 4 h. Responses of tail temperature and tail blood flow rate were abrupt and ephemeral. After administration of CPZ, no appreciable changes in vaporization rate were observed. Similar results on vaporization rate were reported with haloperidol¹³⁾ and with antipyretics.⁵⁾

Simulation of Thermal Response to Chlorpromazine

At an environmental temperature of T_A , without administration of CPZ, rectal temperature T_{C0} , tail temperature T_{S10} , thigh skin temperature T_{S20} , metabolic heat production rate M_0 and vaporization rate V_0 were determined and used to calculate K_0 , L_1 and L_2 from Eqs. 4, 5 and 6. F_0 was calculated from Eq. 20, where B_{S0}

FIG. 6. Time Course of Tail Temperature after Intravenous Administration of Chlorpromazine Hydrochloride in Rats

(a) 0 mg/kg, (b) 0.5 mg/kg, (c) 2 mg/kg, (d) 4 mg/kg. Each point represents mean $\pm$ S.E. of 3–6 experiments.

FIG. 7. Time Course of Linear Velocity of Tail Blood Flow after Intravenous Administration of Chlorpromazine Hydrochloride in Rats

(a) 0 mg/kg, (b) 0.5 mg/kg, (c) 2 mg/kg, (d) 4 mg/kg. Each point represents mean $\pm$ S.E. of 3–4 experiments.

TABLE III. *Physiological Parameters at Steady State*

		CPZ	Anipyretics
W_C	(kg)	0.133	0.133
W_{S1}	(kg)	0.022	—
W_{S2}	(kg)	0.045	0.067
T_{C0}	(°C)	37.28	38.2
T_{S10}	(°C)	24.03	22.0
T_{S20}	(°C)	33.13	—
T_{B0}	(°C)	34.96	32.8
T_A	(°C)	23.00	21.0
M_0	(kcal/h)	1.379	1.70
V_0	(kcal/h)	0.200	0.20
B_{S0}	(cm/s)	3.14	—
A_{BF0}	(cm ²)	0.00032	—
C	(kcal/kg/°C)	0.50	0.50
S	(kcal/kg/°C)	0.92	—
K_0	(kcal/h/°C)	0.274	0.092
F_0	(kg/h)	0.0036	—
L_1	(kcal/h/°C)	0.0426	1.50
L_2	(kcal/h/°C)	0.1123	—
α_M	(kcal/h/°C)	0.010	0.233
α_V	(kcal/h/°C)	0.000	0.000
α_K	(kcal/h/°C ²)	0.028	0.028
γ_K	(kcal/°C ²)	0.051	0.051

TABLE IV. *Pharmacologic Parameters on Chlorpromazine Hypothermia*

$R_{K \max}$	(kcal/h/°C)	0.209
$C_K(50)$	(μg/ml)	2.22
S_K		0.600
$R_{F \max}$	(kg/h)	0.049
$C_F(50)$	(μg/ml)	6.12
S_F		1.71
$R_{M \max}$	(kcal/h)	0.256
$C_M(50)$	(μg/ml)	2.31
S_M		2.50

and A_{BF0} are normal values of linear rate and cross sectional area of the tail blood flow, respectively.

$$F_0 = B_{S0} A_{BF0} 3.6 \text{ (kg/h)} \quad (20)$$

Values obtained are shown in Table III. For the purpose of comparison, parameters of heat transfer obtained in the previous report⁵⁾ are also listed in Table III. Since skin compartment is divided into two parts, pelt and tail, $SF_0 + K_0$

and $L_1 + L_2$ in this study correspond to K_0 and L of the previous report,⁵⁾ respectively. An appreciable difference in magnitude is noted, however, between these values listed in Table III. These differences are results of different control temperatures caused by different sites of measurement. Assuming the surface area of a rat to be 0.03 m²/200 g, $L_1 + L_2$ becomes 5.16 kcal/h/°C/m² which agrees with 5.3 kcal/h/°C/m², the value reported by Crosbie *et al.* for man.¹⁴⁾

FIG. 8. Comparison of Simulated Values with Observed Data after Intravenous Administration of Chlorpromazine Hydrochloride in Rats

Points are observed data shown in Figs. 3–6 and lines are calculated values by a digital computer.

(a) 4 mg/kg, (b) 2 mg/kg, (c) 0.5 mg/kg.

On performing a digital computer simulation of thermal response according to the model described in the Theory section, physiological parameters such as α_K and γ_K were set to the values reported previously,⁵⁾ whereas α_M was set to 0.01 kcal/h/°C. With greater values for α_M , the least squares method failed to obtain proper fit of observed data and simulated temperatures. Pharmacokinetic parameters such as A_i , λ_i ($i = 1, 2, 3$), Q_{BR} , W_{BR} and K_P were set to the values shown in Table II. For the evaluation of the rest of the parameters, a nonlinear least squares fit of the temperature data was carried out. Observed and model simulated temperatures after intravenous administration of CPZ to rats are compared in Fig. 8. Except for the case of 0.5 mg/kg dose, simulated curves agree reasonably well with observed data. The analytical

procedures and the model adopted in the present study are almost validated. Pharmacological parameters obtained by simulation are listed in Table IV.

At maximum increase, simulated volumetric blood flow rate is ten times greater than the normal level (Fig. 8). According to Honda,¹⁵⁾ ten fold increase in cutaneous blood flow is physiologically acceptable. Corresponding maximum linear velocity of the tail blood flow measured with an ultrasonic flow meter was only two fold that of the control level, as shown in Fig. 7. A logical explanation of this discrepancy lies in the five fold expansion of the cross sectional area of blood flow, which is anatomically possible by cross sectional deformation of the blood vessel.

Pharmacokinetics of CPZ and effect of CPZ on physicochemical mechanisms of temperature

regulation in rats have been investigated. The analysis of the data was carried out using a physical model adaptation technique. The results of the study show that the magnitude of the pharmacologic effects of CPZ such as, decrease in metabolic heat production and increase in tail blood flow rate, at a given time are logarithmic logistic functions of the cerebral CPZ concentration at that time. Cerebral concentrations of CPZ after intravenous administration to rats were ten times higher than the corresponding serum concentrations. The time courses were simulated with a simple perfusion rate limited model concept as a function of serum levels. Time courses of rectal, thigh and tail temperatures were consistently simulated by the proposed thermoregulatory model which is a slight modification of a model presented in a previous report on antipyretics.⁵⁾

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