EFFECT OF ENVIRONMENTAL TEMPERATURE ON THERMAL RESPONSE TO CHLORPROMAZINE. I. SIMULATION OF TEMPERATURE REGULATION IN RATS

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Using the basic equations for heat balance, a compartment model was constructed to simulate the physiological responses to heat and cold in rats. The model predicted steady-state situations of rectal temperature, skin temperature (pelt and tail), metabolic rate and evaporative heat loss.

Keywords — temperature regulation; rat; rectal temperature; skin temperature; metabolic rate; environmental temperature

In the previous report, a quantitative correlation between chlorpromazine disposition and hypothermic response at an environmental temperature of 23 °C was successfully described using the compartment model concept.¹⁾ In order to investigate thermal responses to the drug at various ambient temperatures, effects of change in ambient temperature on body temperatures of rats must first be clarified. A simulation of temperature regulation in rats was attempted for this purpose.

The dynamics of the temperature regulation mechanism in man have been of interest to physiologists for years.²⁾ Murgatroyd *et al.*³⁾ carried out a study designed to extend data on behavioral thermoregulation of rats to hot environments and to examine the relative role of peripheral and preoptic-anterior hypothalamic temperature in shaping such activity. Hainsworth *et al.*⁴⁾ examined some of the central and peripheral factors involved in regulating water loss through the salivary glands during heat stress.

This report describes details of analyses carried out to clarify dynamic responses of rats to hot and cold environmental temperature using the compartment model adopted in the previous report.¹⁾

THEORY

General Description of the Model

A schematic diagram of the model is shown in Fig. 1. As in the previous report,¹⁾ rat body is

divided primarily into two compartments, core and skin. 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. Thick and thin lines in Fig. 1 represent heat flows and biological controls, respectively.

Expressing temperatures and coefficients as variations from the reference steady-state values obtained at 23 °C (T_{A0}), mathematical interpretations of the model are as follow.

$$W_C C \frac{dT_C}{dt} = \Delta M - \Delta V - K(\Delta T_C - \Delta T_{S2}) - \Delta K(T_{C0} - T_{S20}) - SF(\Delta T_C - \Delta T_{S1}) - S\Delta F(T_{C0} - T_{S10}) \quad (1)$$

$$W_{S2} C \frac{dT_{S2}}{dt} = K(\Delta T_C - \Delta T_{S2}) + \Delta K(T_{C0} - T_{S20}) - L2(\Delta T_{S2} - \Delta T_A) \quad (2)$$

$$W_{S1} C \frac{dT_{S1}}{dt} = SF(\Delta T_C - \Delta T_{S1}) + S\Delta F(T_{C0} - T_{S1}) - L1(\Delta T_{S1} - \Delta T_A) \quad (3)$$

Where $\Delta X = X - X_0$ ($X = M, V, K, T_C, T_{S1}, T_{S2}, T_A$ and F). Definitions of symbols used in all equations are listed in Table I.

Assuming that the reference steady-state

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average body temperature (T_{B0}) is the "set point" temperature, the values of M , V , K and F are modified in a negative feed back manner depending on the change in average body temperature (ΔT_B). Physiological responses are expressed mathematically as follow.

$$\begin{aligned} M &= M_0 & (\Delta T_B > 0) \\ M &= M_0 - \alpha_M \Delta T_B & (\Delta T_B \leq 0) \end{aligned} \quad (4)$$

$$\begin{aligned} V &= V_0 + \alpha_{V1} \Delta T_B + \alpha_{V2} \Delta T_B^4 & (\Delta T_B > 0) \\ V &= V_0 & (\Delta T_B \leq 0) \end{aligned} \quad (5)$$

$$K = K_0 + \alpha_K \Delta T_B + \gamma_K \frac{dT_B}{dt} \quad (K \geq 0.946 K_0) \quad (6)$$

$$\begin{aligned} F &= F_0 + \alpha_F \Delta T_B & (\Delta T_B > 0) \\ F &= F_0 & (\Delta T_B \leq 0) \end{aligned} \quad (7)$$

In Eq. 5, ΔT_B^4 term originates from Stefan-Boltzmann's law of radiation and has been adopted in theoretical studies.²⁾ In addition to the proportional control ($\alpha \Delta T_B$), a term indicative of rate control ($\gamma dT_B/dt$) is included in Eq. 6. This requirement was necessitated by the tran-

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

sient physiological data observed when man is moved quickly from one thermal environment to another, and was adopted by Crosbie *et al.*⁵⁾

MATERIALS AND METHODS

Measurements of Body Temperature — Male albino rats (Wistar strain) bred at an environmental temperature of 23 °C and weighing 200

TABLE I. List of Symbols and Definitions

α_F	kg/h/°C	Proportional control coefficient of tail blood flow rate
α_K	kcal/h/°C ²	Proportional control coefficient of heat transfer
α_M	kcal/h/°C	Proportional control coefficient of metabolic rate
α_{V1}	kcal/h/°C	Proportional control coefficient of vaporization
α_{V2}	kcal/h/°C ⁴	Proportional control coefficient of vaporization
C	kcal/kg/°C	Specific heat of tissue
F	kg/h	Volumetric tail blood flow rate
γ_K	kcal/°C ²	Rate control coefficient of heat transfer
K	kcal/h/°C	Coefficient of heat transfer (core to pelt)
$L1$	kcal/h/°C	Coefficient of heat transfer (tail surface to air)
$L2$	kcal/h/°C	Coefficient of heat transfer (pelt to air)
M	kcal/h	Metabolic heat production rate
S	kcal/kg/°C	Specific heat of blood
t	h	Time
T_A	°C	Ambient temperature
T_B	°C	Average body temperature, $T_B = 0.67 T_C + 0.22 T_{S2} + 0.11 T_{S1}$ ^{a)}
T_C	°C	Temperature of core compartment (determined at the rectum)
T_{S1}	°C	Temperature of tail compartment
T_{S2}	°C	Temperature of pelt compartment (determined at the thigh)
V	kcal/h	Rate of heat loss by vaporization
W_C	kg	Mass weight of core compartment
W_{S1}	kg	Mass weight of tail compartment
W_{S2}	kg	Mass weight of pelt compartment

a) See reference 1.

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 the thigh skin and on the tail surface, respectively. Ambient temperature was controlled in a prefabricated air-conditioned chamber (Yamatake-Honeywell AC-13). Assuming that Steady-state is attained in 2 h, measurements were continued for 2 h at each of the following ambient temperatures, 11, 15, 18, 20, 23, 25, 28 and 32 °C.

Measurement of Heat Production and Heat Loss — Rates of heat production and heat loss were determined by indirect calorimetry as in the previous report.¹⁾ Assuming that one liter of CO₂ is equivalent to 5 kcal of heat production, the concentration of CO₂ in the expired air was determined using a breath analyzer (Fukuda R-1000S). The latent heat of water vaporization being 0.6 kcal/g of water, the rate of heat loss was calculated from the amount of water in the expired air. The rat was caged in a box ventilated (120 ml/min) by a suction pump built into the breath analyzer. The air from the box was led to the analyzer *via* moisture traps (CaCl₂) and CO₂ concentration was continuously recorded (Riken SP-G-7P).

FIG. 2. *Effect of Environmental Temperatures on Metabolic Rate*

Breath analyzer observations are shown as closed circles; solid line shows computer solution for steady-state.

—, with limits on ΔK ; ----, without limits on ΔK .

Estimation of Model Parameters — A nonlinear least squares regression program, FKDM, which is based on the algorithm of Berman *et al.*,⁶⁾ was used to fit a model to observed data to estimate model parameters on a digital computer (Digital Equipment Corp., PDP-11/34).

RESULTS AND DISCUSSION

Effect of Environmental Temperature on Body Temperatures

Effects of ambient temperature on the rat's physiological data are shown in Figs. 2 to 4. Although the metabolic heat production rate was constant around 1.4 kcal/h at a higher temperature environment (23–32 °C), it increased as the ambient temperature decreased below 23 °C, and at 11 °C, it was twice as much the rate at the higher ambient temperature (Fig. 2). The vaporization loss was constant around 0.2 kcal/h at a lower temperature environment (11–20 °C). It increased as the ambient temperature increased and it was 1.5 times greater at 32 °C than at 11–20 °C (Fig. 3).

Rectal temperature was constant around 37 °C at a lower ambient temperature (11–25 °C). It increased slightly as the environment temperature increased. At 32 °C, the increase in rectal temperature was about 3 °C (Fig. 4a). It was observed that, according to the change in an environmental temperature from 11 to 32 °C, the tail temperature changed from 12 to 33 °C

FIG. 3. *Effect of Environmental Temperature on Vaporization Loss*

Moisture-trap observations are shown as closed circles; solid line shows computer solution for steady-state.

—, with limits on ΔK ; ----, without limits on ΔK .

FIG. 4. *Effect of Environmental Temperature on Rectal, Thigh and Tail Temperatures*
Thermometer observations are shown as closed circles; solid line shows computer solution for steady-state.
a) rectal, b) thigh and c) tail temperature.
—, with limits on ΔK ; ----, without limits on ΔK .

TABLE II. *Physiological Parameters at Reference Temperature (23 °C)*

W_C	(kg)	0.133
W_{S1}	(kg)	0.022
W_{S2}	(kg)	0.045
T_{C0}	(°C)	37.46
T_{S10}	(°C)	23.52
T_{S20}	(°C)	31.31
T_{B0}	(°C)	34.58
T_{A0}	(°C)	23.00
M_0	(kcal/h)	1.379
V_0	(kcal/h)	0.200
C	(kcal/kg/°C)	0.500
S	(kcal/kg/°C)	0.920
K_0	(kcal/h/°C)	0.184
F_0	(kg/h)	0.0036
L_1	(kcal/h/°C)	0.089
L_2	(kcal/h/°C)	0.136

and the thigh temperature from 27 to 37 °C (Fig. 4b, c).

Simulation of the Effect of Environmental Temperature

Since the vaporization loss (V) increased as the ambient temperature increased above 23 °C and the metabolic rate (M) increased as the environmental temperature decreased below 23 °C, this temperature was conveniently chosen as the initial condition for the analysis or as the reference temperature. This selection also fixed the initial conditions for other temperatures and parameters, which are shown in Table II. Actually, the rats used in this study had been bred at the environmental temperature of 23 °C. The effects of the ambient temperature were analyzed below and above this temperature, separately.

At a lower temperature environment, the average body temperature was lower than the reference average body temperature of “set point” temperature ($\Delta T_B < 0$), and the temperature regulatory units that accelerate cooling, such as vaporization (V) and tail blood flow (F), were likely at the lowest level. Consequently, under this condition, values of V and F were fixed constants without control (Eqs. 5 and 7) whereas the values of M and K were assigned to be regulated in a negative feed back manner (Eqs. 4 and 6). Contrary to this, at a higher temperature environment, the average body temperature was higher than “set point” temperature ($\Delta T_B > 0$), and, the heat producing unit (M) was likely at the lowest level (Eq. 4). The values of V , K and F were assumed to be controlled (Eqs. 5, 6 and 7). Vaporization loss increased rapidly as the body temperature rose above its neutral value but is maintained a rather constant value as the body was cooled below the neutral temperature as shown in Fig. 3. According to Crosbie *et al.*,⁵⁾ Eq. 5 was assumed for V with two coefficients, α_{V1} and α_{V2} . Assuming that physiological responses changed depending on the environmental temperature, the values of the coefficients, α_M , α_F , α_{V1} and α_{V2} were evaluated by means of a model adaptation technique using a nonlinear least squares program with a digital computer. For physiological parameters of heat transfer, α_K and γ_K , however, values of the previous report¹⁾ were used throughout the environmental temperature, from 11 to 32 °C.

The computed steady-state data are shown in Figs. 2 to 4, superimposed on the physiological

TABLE III. *Physiological Parameters Obtained by Model Adaptation*

		Cold environment ($11 \leq T_A < 23$ °C)	Neutral environment ^{a)} ($T_A = 23$ °C)	Warm environment ($23 < T_A \leq 32$ °C)
α_M	(kcal/h/°C)	0.4998	0.010	—
α_{V1}	(kcal/h/°C)	—	—	0.04032
α_{V2}	(kcal/h/°C ⁴)	—	—	0.00045
α_F	(kg/h/°C)	—	—	0.00486
α_K ^{a)}	(kcal/h/°C ²)	0.028	0.028	0.028
γ_K ^{a)}	(kcal/°C ²)	0.051	0.051	0.051

a) Values reported previously in reference 1.

steady-state data designated by closed circles. Dotted lines at a low temperature region show the values computed with unlimited ΔK . Without limits on ΔK , decrease in the heat transfer rate from core compartment to pelt compartment caused an increase in rectal temperature, which did not agree with the observed results. Heat transfer from core to pelt compartment (K) was operated by conduction of heat and skin blood flow and was not free from temperature regulation due to vasoconstriction or vasodilation. Expression for K of the present model (Eq. 6) contains a limiting term. Crosbie *et al.*⁵⁾ adopted similar assumptions. The physiological parameters obtained from model adaptation are shown in Table III.

Changes in rectal, thigh skin and tail surface temperature depending on change in environmental temperature, are shown in Fig. 4. The calculated pelt and tail temperatures exceeded calculated rectal temperature at an environment of 41 °C and above. It is known that cells of central nervous system are irreversibly damaged above 41 °C. It may be concluded that the present model describes the temperature regulation system of a rat quite adequately and provides a better understanding of physiological tempera-

ture regulation by applying a simple analysis to some of the available physiological data on rats.

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