GLUCOSE TOLERANCE CURVES IN GENETICALLY DIABETIC KK-CA^y MICE: THE PHARMACOKINETIC ANALYSIS FOR HUMPING EFFECT

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(Received July 17, 1980)

Pharmacokinetic analysis on glucose tolerance curves in genetically diabetic KK-CA^y mice treated with hypoglycemics was investigated using an analog computer. The glucose tolerance curves in KK-CA^y mice showed humping phenomena. They could not be simulated by a simple compartmental model, but might be fitted to the model containing the non-linear function. "Compartment-H" model was contrived by adding the H-factor between glucose and insulin compartments. All the glucose tolerance curves in the KK-CA^y mice could be simulated reasonably by this model and some suggestions on the humping effect were obtained from the analysis of H-factor. The H-factor was observed to be influenced by adrenergic α -blocker. This pharmacokinetic approach was indicated to be useful for the pharmacological research.

Keywords—pharmacokinetic approach; glucose tolerance curve; hypoglycemics; KK-CA^y mice; analog computer analysis; humping effect; Compartment-H model

INTRODUCTION

Studies of the glucose tolerance curves in genetically diabetic KK-CA^y mice reported previously¹⁾ are useful for the classification of the mechanisms of action of antidiabetics in addition to a bioassay of their effects. On the glucose tolerance curve in this paper, the authors dealt with a humping phenomena, reported by Takeuchi *et al.*,²⁾ to analyze the pattern of the response curve induced by drugs. Recently it has been recognized that the blood glucose is controlled by the level of blood insulin. According to Atkins' study,³⁾ the plasma insulin level is indispensable in the analysis of glucose tolerance curve. The humping effect observed in the glucose tolerance curve of KK-CA^y mice might depend on the reflection of insulin effect. In this investigation, the "Compartment-H" model was proposed to regard the H-factor as the humping factor. The H-factor means the hyperglycemic effect caused by the reflecting effect of the secreted insulin in this model.

The glucose tolerance curves have been generally expressed by several equations; for example, $y = ae^{-kt}$ by Greville,⁴⁾ $y = Ae^{-\alpha t} + Be^{-\beta t}$ by Hirata,⁵⁾ and

$$y = \frac{a}{k_2 - k_1} \{k_2 e^{-k_1 t} - k_1 e^{-k_2 t}\} + C$$

by Fukushima.⁶⁾ The last equation expresses an atypical curve which explained the humping curve obtained from their experimental results in dogs⁷⁾ and in alloxan diabetic rabbits.⁸⁾ This humping curve consists of an exponential curve and a transient rising curve. In the humping effect, however, Fukushima *et al.* did not accept the factor controlled by the level of blood insulin. On the other hand, system models which include the parameters of hormones dynamics in blood have been reported by Srinivasan *et al.*⁹⁾ and Carson *et al.*¹⁰⁾ In addition to the evaluation of these equations and models, experiments in the present study were specifically designed to elucidate the H-factor. It is the aim of this investigation to show a methodological attempt of estimating the

TABLE I. The Mathematical Models and the Values of Parameters for the Analysis of Glucose Tolerance Curve (1)

- (A) i) Two-compartment model $y = Ae^{-\alpha t} + Be^{-\beta t}$
 ii) Three-compartment model $y = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$
 (B) i) Humping model (I) $y_1 = Ae^{-\alpha t}$
 $y_2 = B \cdot \beta / (\alpha - \beta) \{ e^{-\beta(t-T)} - e^{-\alpha(t-T)} \} \quad (t \geq T)$
 ii) Humping model (II) $y_1 = Ae^{-\alpha t} + Be^{-\beta t}$
 $y_2 = a \cdot k / (k - \beta) \{ e^{-\beta(t-T)} - e^{-k(t-T)} \} \quad (t \geq T)$

Model	Mice	A	B	C	a	α	β	γ	k	T	SS
		(mg/dl)				(min ⁻¹)				(min)	
A-i	KK	375	207	—	—	.126	.0083	—	—	—	231
	KK-CA ^y	475	243	—	—	.199	.0039	—	—	—	1777
A-ii	KK	531	245	283	—	.0999	.0396	.0096	—	—	224
	KK-CA ^y	790	516	364	—	.0923	.0404	.0057	—	—	772
B-i	KK	512	394	—	—	.0347	.0264	—	—	43	1049
	KK-CA ^y	584	1428	—	—	.0402	.0070	—	—	31	923
B-ii	KK	383	177	—	11	.093	.0078	—	.484	60	770
	KK-CA ^y	585	252	—	63	.302	.0056	—	.410	52	1753

The values of parameters were calculated by FACOM 230-45S OS2 computer using FORTRAN. SS: sum of squares.

Note that the simulation of the linear model (A-i, A-ii) in KK mice may have good agreement, whereas all the model can not fit and the rate constant β (A-i, B-i) or γ (A-ii) were smaller in the KK-CA^y mice.

TABLE II. The Mathematical Model and the Values of Parameters for the Analysis of Glucose Tolerance Curve (2)

- (C) Non-linear model using a function generator

$$dX_1/dt = -(k_1 + k_3)X_1 + k_2X_2$$

$$dX_2/dt = K(t) + k_1X_1 - k_2X_2$$

Mice	X_1^0	X_2^0	k_1	k_2	k_3	K	$(0 \leq t \leq 20)$
	(mg/dl)		(min ⁻¹)			(mg/dl/min)	
KK							
Control	750	258	.0272	.0209	.0269	2.698	
Insulin 100 mU/kg	663	289	.1304	.0512	.0243	2.286	
Insulin 200 mU/kg	763	478	.1372	.0351	.0353	3.432	
KK-CA ^y							
Control	810	186	.0805	.0791	.0140	1.089	
Insulin 100 mU/kg	771	204	.0883	.0757	.0155	1.241	
Insulin 400 mU/kg	818	453	.1035	.0410	.0286	3.752	

X_1^0 , X_2^0 : the concentrations of glucose compartment 1 and 2 immediately after glucose injection.

k_1 , k_2 , k_3 : the rate constants. K: variable input as the rate.

The parameters for the analog computer analysis were calculated by FACOM 230-45S OS2 computer using the least squares method, assuming that the rate, K, was invariant for 20 min immediately after injection.

drugs dependent on the H-factor by a pharmacokinetic approach.

MATERIALS AND METHODS

Animals — All adult male mice, KK-CA^y (A^ya, BB, Cc) and KK (aa, BB, cc) as controls used in the present study were derived from the closed mouse colony maintained in our laboratory. The fed blood glucose levels of KK-CA^y mice (15 — 25 weeks old) used were more than 300 mg/100 ml. Further detailed references have been given

in the previous paper.¹⁾

Glucose Tolerance Test — Glucose (2 g/kg) in a 20% (w/v) solution was intravenously given through the tail vein of mice fasted overnight or nonfasted. Bleeding was made from the orbital vein plexus immediately before and after the glucose administration (at 3, 20, 40, 60, 80, 120, 160 min). Blood glucose was determined by the Momose's method.¹¹⁾ The drugs were administered by dissolving them in the glucose solution. In the control experiment, the same mice were

FIG. 1. The Simulation by the Function Generator Model (Model C) using an Analog Computer for the Glucose Tolerance Curves

Solid circles show data of blood glucose level obtained from the average of three to six mice. Simulation of the data are shown in the upper part in each panel (A-F). K values are shown in the lower part in each panel (A-F). A—C: KK mice, D—F: KK-CA^y mice. A and D are represented in the ratio to the values shown in Table II. A and D show the data of control by the injection of 2 g/kg glucose alone. B and E: with 100 mU/kg insulin, C: with 200 mU/kg insulin, F: with 400 mU/kg insulin.

FIG. 2. The Diagram of Compartment-*H* Model and the Model of Interaction between Plasma Glucose and Plasma Insulin reported by Atkins (Ref. 3)

used repeatedly at intervals of about 10 days.

Drugs — Beef crystalline insulin (Novo industries, Copenhagen; 1 mg = 24.3 I.U.), Tolbutamide (Toyama Chemical Industries) and Phentolamine (Regitine[®], Ciba-Geigy) were used.

Computer Analysis — An analog computer (Hitachi ALS 505E) and a X-Y recorder (Watanabe WX 432) were used for performing the simulation of the glucose tolerance curve to a mathematical model.

RESULTS

Fitness of a Mathematical Model to Glucose Tolerance Curve

Glucose tolerance curves have been generally dealt with the following equations; $y = ae^{-kt}$, $y = Ae^{-\alpha t} + Be^{-\beta t}$ (Model A) and

$$y = \frac{a}{k_2 - k_1} \{k_2 e^{-k_1 t} - k_1 e^{-k_2 t}\} + C$$
 (Model B). These equations and their modified

FIG. 3. The Block Diagram of Compartment-*H* Model for the Program of an Analog Computer

equations were examined by the digital computer on the data of genetically diabetic KK-CA^y mice and KK mice. The results in Table I showed that two-compartment model as well as three-compartment model could have good agreement in the KK mice when examined in the values of sum of squares, whereas all the model was unfitting in the KK-CA^y mice. This indicated that the simple compartment model could not be adopted for the data of the KK-CA^y mice and that the model representing the atypical curve, at least as the humping model, might be necessary to be fitted to them. As shown in Table II (Model C), hence, the maintained input factor as the variable rate, K , was given into the second compartment. This input factor was generated by the function generator using an analog computer and a better

fitness was obtained from the simulation of the data on some drugs (Fig. 1). In this model, however, each parameter does not always convey the biological meaning.

On the other hand, the system models with multihormonal control, reported by Srinivasan *et al.*⁹⁾ and Carson *et al.*,¹⁰⁾ have been devised from the knowledge of the biological and physiological unit process behaviour in the metabolism and of the system science or their regulation. These non-linear system models were examined by the digital computer. Good fitness failed to be obtained by those models in spite of changing flexibly the set of values of parameters.

The Compartment-H Model and a Humping Curve
Atkins' model³⁾ as shown in the lower part of Fig. 2 was summarized as follows;

TABLE III. *Compartment-H Model and the Values of Parameters using an Analog Computer for the Analysis of Glucose Tolerance Curve*

Mice	k_1	k_2	k_3	k_5	k_6	V
	(min ⁻¹)			(mg/dl/min)		
Fasted KK						
Control	.159	.536	.093	.329	.052	1.00
Insulin 100 mU/kg	.159	.536	.093	.329	.081	.253
Insulin 400 mU/kg	.159	.536	.093	.329	.073	.283
Tolbutamide 20 mg/kg	.196	.536	.100	.329	.053	.328
Fasted KK-CA ^y						
Control	.184	.342	.100	.218	.096	.223
Insulin 400 mU/kg	.184	.436	.100	.218	.086	.305
Nonfasted KK						
Control	.110	.536	.095	.509	.038	.248
Insulin 100 mU/kg	.141	.536	.095	.329	.074	.356
Nonfasted KK-CA ^y						
Control	.091	.284	.075	.218	.134	.463
Insulin 400 mU/kg	.135	.321	.093	.218	.098	.305

Among the parameters, k_4 (the rate of insulin degradation, 0.2 min⁻¹, according to Carson¹⁰⁾), G^* (the threshold of insulin release, 250 mg/100 ml, corresponding to nonfasted blood glucose level in KK-CA^y mice) and G_∞ (basal blood glucose level experimentally obtained, 94 (KK) and 132 (KK-CA^y) mg/100 ml) and K (in working term, 40 mg/100 ml) were fixed.

Note that increase in k_6 and/or decrease in V (both increase in H-factor) are shown in both fasted and nonfasted KK-CA^y mice compared with the parameters in KK mice, and also k_2 (glucose utilization by insulin) and k_5 (inhibition of glucose production by insulin) decrease in the KK-CA^y mice.

FIG. 4. Compartment-H Model and the Values of Parameters for the Glucose Tolerance Curves of the Fasted KK and KK-CA^y Mice

Solid circles show experimental data of blood glucose levels obtained from the average of three to six mice and solid lines are theoretical values of glucose (G), insulin (I) and H-factor (H). I-curves represent the values of endogenous insulin as the ratio to the basal levels. The values are estimated by subtraction of the added insulin from the total insulin. Shaded parts under H-curves represent the area of H-factor after the time point at which the values of I-curve have a maximum. Note that the shaded part is increased dose-dependently in the KK mice by the insulin treatment and in the KK-CA^y mice it is enhanced by 400 mU/kg insulin.

$$\frac{dx_1}{dt} = k_{10} + k_{13}X_3 - (k_{01} + k_{31})X_1, \frac{dX_2}{dt} = k_{20} - k_{02}X_2, \frac{dX_3}{dt} = k_{31}X_1 - (k_{13} + k_{03})X_3.$$

This model is considered to be characterized by the interacted control between plasma glucose level (compartment 1 and 3) and plasma insulin level (compartment 2). This system may be much more reasonable to express the blood glucose regulation in a physiological sense. Since it was necessary to set up an additive factor for the data fitting in the KK-CA^y mice, "Compartment-H" model was proposed by adding the H-factor compartment between glucose and insulin compartments (Fig. 2).

In the Compartment-H model, blood glucose

is designed to eliminate in two ways, affected and unaffected by insulin. The reflecting effect of secreted insulin was added as the H-factor compartment expressed by the non-linear equation. Fig. 3 shows the program of an analog computer for the analysis of Compartment-H model. The details should be referred to Appendix. The terms of drug effects are also included in this model (Fig. 2 and 3). The data on the glucose tolerance curves in the KK and KK-CA^y mice were reasonably simulated by this mathematical model, and the parameters were summarized in Table III.

In the analysis of the analog computer, the effect of humping on the glucose tolerance curve can be represented as the shaded area as shown in

FIG. 5. Glucose Tolerance Curves treated with Insulin in the Fasted KK and KK-CA^y Mice

Plotted points are mean $\pm$ S.E. of blood glucose levels of mice (numbers shown in parentheses). Note that the curves in KK-CA^y mice showed the humping, not in KK mice. The curves in KK mice treated with insulin showed the humping after the drastic falling dose-dependently, and in KK-CA^y mice the humping was intensified by the treatment with 400 mU/kg insulin compared with that in non-treated control.

Fig. 4. This area is surrounded by the compartment-H curve on the right side of the line crossed with the time axis at the maximum value of compartment-I curve which indicated the increase in insulin secretion stimulated by glucose. The integrated area indicates the H-factor caused by the reflecting effect of insulin in this model. Although the H-factor was little observed in the control experiment of the KK mice, increase in

the H-factor by insulin was dose-dependent, and tolbutamide, one of the insulin releasers, also induced this effect.

A Humping Effect of the Glucose Tolerance Curve in Genetically Diabetic KK-CA^y Mice

As can be seen on the characteristic pattern of the curves in Fig. 5, the glucose tolerance of the KK-CA^y mice in fasting humped markedly compared with that of the KK mice. In the KK mice,

FIG. 6. *Compartment-H Model and the Values of Parameters for the Glucose Tolerance Curves of the Non-fasted KK and KK-CA^y Mice*

Symbols and methods of analysis are the same as Fig. 4. The data of blood glucose levels were obtained from the average of three to eight mice. Note that H-factor was observed in both KK and KK-CA^y mice and increased by the treatment with insulin.

the curves were observed to return to the level before glucose loading after 160 min and to decrease drastically by insulin in the early phase, but this is not so in the KK-CA^y mice. The pattern of curve of the KK mice was altered to the humping pattern by 100 mU/kg insulin, whereas that of the KK-CA^y mice could not be influenced by the same dose of insulin. These observations imply that insulin sensitivity decreased in the KK-CA^y mice.

In the nonfasting state, on the other hand, the humping effect in the curves of the KK mice as well as the KK-CA^y mice was observed by a pharmacokinetic analysis as shown in Fig. 6. The humping effect in the KK-CA^y mice was not influenced by feeding, indicating that the H-factor of the KK-CA^y mice may be essential for the diabetic abnormality. Insulin administration, of

course, resulted in the potentiation of the humping effect.

On the H-factor, the effect of the adrenergic α -blocker was studied preliminary on the glucose tolerance curves in both the KK and KK-CA^y mice. As shown in Fig. 7, the pretreatment with phentolamine influenced the control curve of the KK mice in the early phase. The humping phenomena of the KK mice induced by added insulin and of the KK-CA^y mice were completely abolished by phentolamine. Fig. 8 shows the result of simulation of the data in Fig. 7 by Compartment-H model. The abolishment of the humping in the KK-CA^y mice was indicated by the decrease in the H-factor.

DISCUSSION

Out of the models used by workers mentioned

FIG. 7. Effects of Phentolamine on the Glucose Tolerance Curves in the KK and KK-CA^y Mice

Phentolamine (10 mg/kg) was given intraperitoneally 30 minutes before glucose injection. In the experiments designed with or without pretreatment of phentolamine, the same mice were used repeatedly. Each point indicates a mean $\pm$ S.E. of blood glucose levels of mice (numbers shown in parentheses). Note that phentolamine decreased the blood glucose level in the KK mice drastically without the reflex rise (A) and abolished the humping effects in the KK mice treated with insulin (B) and in the KK-CA^y mice (C).

in the introduction, both the simple compartmental model and the Fukushima's model⁶⁾ can not simulate the experimental curves in this investigation. Although the H-factor compartment may be

regarded to resemble the second compartment in Carson's model,¹⁰⁾ the system models can not fit the humping curves in KK-CA^y mice. The glucose tolerance curves with the humping

FIG. 8. *Compartment-H Model and Analysis for the Glucose Tolerance Curves of α -Adrenergic Blocker-treated KK and KK-CA^y Mice*

Symbols and methods of analysis are the same as Fig. 4. The data used were obtained from Fig. 7. Note that the H-factor observed in the KK-CA^y mice is markedly decreased when treated with phentolamine.

phenomena in the KK-CA^y mice might be simulated quite well by the Compartment-H model. The Compartment-H model in the present study is characterized by the design of the intermediate compartment for the H-factor between the pharmacokinetic phase and the pharmacodynamic phase. By the H-factor, the phenomenon of humping has been dealt with semiquantitatively. Recently the other workers^{12,13} proposed that the kinetics of both glucose and insulin in blood were useful to analyze the glucose tolerance curve. Their proposals were supported also by the investigation in this paper. The pharmacokinetic analysis of the H-factor gave a clue to the pharmacological analysis of the humping effect, and might offer, we believe, a new approach in the pharmacological research.

On the H-factor as can be seen in Fig. 4, the humping effect in the fasted state was greater in the KK-CA^y mice than in the KK mice. The smaller H-factor in the KK mice was markedly increased by the administration of insulin or tolbutamide known as insulin releaser. In the non-fasted state, however, the humping effect in the KK as well as KK-CA^y mice was scarcely influenced by the insulin-administration as shown in Fig. 6. This observation could be interpreted to state that the diabetic abnormality in the KK-CA^y mice might be dependent on the H-factor. Tobe *et al.*¹⁴ reported that the pretreatment with α -adrenergic blocking agents abolished the humping effect and led the humping curve to the exponential curve of Greville.⁴ From these observations, Takeuchi *et al.*² reported that the sympathetico-adrenal system might be one of the possible major control systems for blood glucose level. Our results, using phentolamine, supported that the α -adrenergic effect may be related to the humping effect (Fig. 7). As reported previously,¹¹ however, hyperglucagonemia was also observed in the KK-CA^y mice. The glucagon level in plasma is considered to be the other possible factor for humping. Recently the adrenergic modulation of pancreatic secretory mechanisms, particularly the existence of α -adrenergic receptor on A cells, was reported.¹⁵ The cause of the

humping effect in the KK-CA^y mice must be studied in the future.

APPENDIX

For the analysis of an analog computer, equations shown in Fig. 2 were reformulated as follows (drug effect term was also included):

$$dG/dt = K_1 - k_a \cdot I + k_g \cdot V \cdot H / (K + H) - k_b \cdot G - k_c \cdot I \cdot G \quad \text{Eq. 1}$$

$$dI/dt = K_2 + k_d |G - G^*| - k_e \cdot I + R \cdot C \quad \text{Eq. 2}$$

$$dH/dt = k_f (I - I_\infty) - V \cdot H / (K + H)$$

K_1 = basal glucose output into blood

K_2 = basal insulin output into blood

k_a = rate of glucose output inhibited by insulin

k_b = rate of glucose elimination

k_c = rate of glucose utilization by insulin

k_d = rate of insulin secretion by glucose

k_e = rate of insulin elimination

k_f = rate of H-factor output by insulin

k_g = rate of glucose output by H-factor

G^* = threshold of glucose level for insulin secretion

R = rate of insulin secretion induced by drugs

C = concentration of drugs

I_∞ = basal insulin level in blood

$V \cdot H / (K + H)$ = elimination rate of H-factor (working term)

At steady state, Eq. 1 and Eq. 2 are reduced to Eq. 4 and Eq. 5.

$$0 = K_1 - k_a \cdot I_\infty - k_b \cdot G_\infty - k_c \cdot I_\infty \cdot G_\infty \quad \text{Eq. 4}$$

$$0 = K_2 + k_d |G_\infty - G^*| - k_e \cdot I_\infty \quad \text{Eq. 5}$$

It follows from Eq. 1 that:

$$dG/dt = K_1 - K_a \cdot I + k_g \cdot V \cdot H / (K + H) - k_b \cdot G - k_c \cdot I \cdot G + k_c \cdot I_\infty \cdot G - k_c \cdot I_\infty \cdot G \quad \text{Eq. 1'}$$

Subtracting Eq. 4 from Eq. 1' and reformulizing, Eq. 6 is finally obtained.

$$\begin{aligned} dG/dt &= -k_a(I - I_\infty) + k_g \cdot V \cdot H / (K + H) \\ &\quad - k_b(G - G_\infty) - k_c(I - I_\infty)G \\ &\quad - k_c \cdot I_\infty(G - G_\infty) \\ &= -k_a(I - I_\infty) + k_g \cdot V \cdot H / (K + H) \\ &\quad - k_b(G - G_\infty) - k_c(I - I_\infty)G \\ &\quad - k_c \cdot I_\infty(G - G_\infty) + k_c(I - I_\infty)G_\infty \end{aligned}$$

$$\begin{aligned}
& -k_c(I - I_\infty)G_\infty \\
& = -(k_a + k_c \cdot G_\infty)(I - I_\infty) \\
& \quad + k_g \cdot V \cdot H / (K + H) \\
& \quad - (k_b + k_c \cdot I_\infty)(G - G_\infty) \\
& \quad - k_c(I - I_\infty)(G - G_\infty) \\
& = -I^*(k_a + k_c \cdot G_\infty) \{ (I - I_\infty) / I^* \} \\
& \quad + k_g \cdot V \cdot H / (K + H) \\
& \quad - (k_b + k_c \cdot I_\infty)(G - G_\infty) \\
& \quad - k_c \cdot I^* \{ (I - I_\infty) / I^* \} (G - G_\infty)
\end{aligned}$$

Eq. 6

I^* means the assumptive standard value of changes in the insulin level for the program of an analog computer, and its dimension must be related with that of the blood glucose level, resulting in that the dimension of I-factor can be represented by that of the blood glucose level.

Eq. 6 is rearranged by substituting $k_b + k_c \cdot I_\infty = k_1$, $k_c \cdot I^* = k_2$, $I^*(k_a + k_c \cdot G_\infty) = k_5$, $k_g = k_6$, and Eq. I is obtained.

$$d(\Delta G)/dt = -k_5(\Delta I) + k_6 \cdot V \cdot H / (K + H) - k_1(\Delta G) - k_2(\Delta I)(\Delta G)$$

Eq. I

In practice, a limiting value, H^* , was presumed for $V \cdot H / (K + H)$ term. Subtracting Eq. 5 from Eq. 2, Eq. 7 is obtained,

$$dI/dt = k_d |\Delta G - G^{**}| - k_e(I - I_\infty) + R \cdot C$$

Eq. 7

where G^{**} is the mathematically composed threshold value.

Dividing Eq. 7 by I^* , Eq. 8 is obtained.

$$(1/I^*)d(I - I_\infty)/dt = (k_d/I^*)|\Delta G - G^{**}| - k_e\{(I - I_\infty)/I^*\} + R \cdot C/I^*$$

Eq. 8

Insulin releaser (tolbutamide) is eliminated by the first order rate step. This is expressed as Eq. 9.

$$dC/dt = -k_h \cdot C$$

Eq. 9

It follows: $d(R \cdot C/I^*)dt = -k_h(R \cdot C/I^*)$.

$$\text{Substituting } R \cdot C/I^* = C', \quad dC'/dt = -k_h \cdot C'$$

Eq. 10

k_h is substituted by k_7 in the program of an analog computer (Fig. 3).

Eq. 8 is rearranged by substituting $k_d/I^* = k_3$, $k_e = k_4$, and Eq. II is obtained.

$$d(\Delta I)/dt = k_3 |\Delta G - G^{**}| - k_4(\Delta I) + C'$$

Eq. II

Eq. 3 is reformulized as Eq. 11, and Eq. 11 is

transformed into Eq. 12.

$$dH/dt = k_f \cdot I^* \{ (I - I_\infty) / I^* \} - V \cdot H / (K + H)$$

Eq. 11

$$d\{H/(k_f \cdot I^*)\}/dt = (I - I_\infty)/I^* - \{V/(k_f \cdot I^*)\} \{H/(k_f \cdot I^*)\} / \{K/(k_f \cdot I^*) + H/(k_f \cdot I^*)\}$$

Eq. 12

Eq. 12 is rearranged by substituting $H/(k_f \cdot I^*) = H'$, $V/(k_f \cdot I^*) = V'$, $K/(k_f \cdot I^*) = K'$, and Eq. III is obtained.

$$dH'/dt = (\Delta I) - V' \cdot H' / (K' + H')$$

Eq. III

The dimension of H-factor in the program for an analog computer also can be represented by that of the blood glucose level for the same reason as mentioned above on that of I-factor.

Eq. I, Eq. II and Eq. III are used for the program of an analog computer shown in Fig. 3, and symbols with Δ denote the difference from the basal levels.

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