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研 究 論 文
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Equivalent Circuit Model of Glucose Kinetics

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=Abstract=

The objective of the present study was to develop an equivalent circuit model of glucose kinetics including the hepatic glucose balance functions which were neglected in the previous compartmental models. Using this circuit model, the insulin resistivity parameter and hepatic glucose sensitivity parameter were estimated in optimal fitting of the model based data of glucose and insulin concentration to the reported clinical intravenous glucose tolerance test(IVGTT) data in normal and diabetic subjects. The addition of the hepatic function in the model has improved the overall performance of the simulation. Also, the computed tissue insulin resistivity and the hepatic glucose sensitivity are shown to be significant in distinguishing four clinical groups of normal and diabetic groups.

1. Introduction

The blood glucose level in man is regulated by complex interactions between glucose and insulin. The objective of the present study was to develop an equivalent circuit model of glucose kinetics including the hepatic glucose balance functions which were neglected in the previous compartmental model studies.

In one of the most thorough theoretical study, Cunningham and Heath developed a four compartments model[1] and compared the computed data with Fujita et al.'s clinical results of the intravenous glucose tolerance test(IVGTT) in four clinical groups of normal and diabetic subjects[2]. The glucose quantity in four compartments(arterial, capillary and extravascular volume, venous, and slow glucose pool) was used as state variables of the model, and the venous glucose concentration was computed for various values of capillary-extravascular volume and insulin sensitivity parameter (K_{ins}) to find a good fit to the IVGTT data, where K_{ins} parameter is an index of the mean sensitivity of insulin-dependent tissues to insulin action.

It was shown in the above study that the most important parameter accounting for the differences among four clinical groups is the K_{ins} parameter, as K_{ins} acts as a proportional constant in calculating the insulin-dependent glucose utilization rate by the product of the glucose and insulin concentrations. Furthermore, these investigators have pointed out that the neglect of hepatic uptake in the model

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leads to over-estimation of the K_{ins} parameter. They also showed that K_{ins} was computed differently depending upon whether there were inhibition or maintenance of hepatic output in diabetics after glucose injection.

In the present theoretical study, we have developed an equivalent circuit model of the glucose kinetics including the hepatic regulatory functions, where hepatic functions were simulated using the clinical results by Bergman et al.[3] Using this circuit model, the insulin resistivity parameter and the hepatic glucose sensitivity parameter can be estimated in optimal fitting of the model based data of glucose and insulin concentrations to Fujita et al.'s clinical IVGTT data in normal and diabetic subjects.

2. Computer Simulation

(1) Equivalent Circuit Model

Fig. 1 shows the equivalent circuit model developed for simulation of the changes of glucose concentration during IVGTT. In the model, the compartmental volumes are represented by electrical capacitances(C_i), the glucose quantities in the compartments represented by the charges in the capacitors, and the rate constants represented by electrical resistances (R_i). Then, the glucose volume flow rates between compartments and the concentrations in the compartments are analogous to the electrical currents and voltages of the equivalent circuit, respectively. The concentrations (represented by electrical voltages) are used as state variables in the circuit model instead of the quantities in the compartmental analysis.

Using the above analogous parameters, the circuit model elements of Fig. 1 represent the following physiological functions of glucose

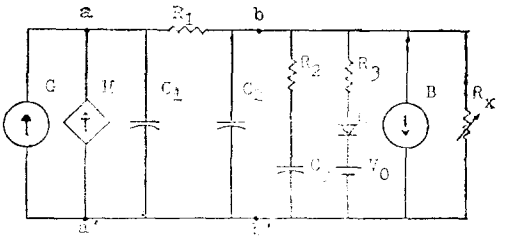

Fig. 1. Equivalent Circuit Model

kinetics as reported by various investigators[4~12].

a. Glucose Pools

Three glucose pools of arterial blood volume, capillary-venous-extravascular volume, and slow pool volume[4] are represented by three capacitors, C_1, C_2, and C_3, respectively.

b. Glucose uptake at the tissue sites

Glucose uptake rate at tissues was known to be proportional to both the glucose concentration and the insulin concentration at the cell surface. Also, it was known that this insulin concentration is the level in the slow insulin pool.[5,6,15] The effect of insulin on glucose utilization rate is different depending upon the insulin resistivity at tissues in normal and diabetics[7,8] In the model, the glucose uptake rate is represented by the currents flowing in the time-varying resistance, R_x, where R_x is related as follows;

$$R_x(t)=\frac{K_r}{I_n(t)} \qquad (1)$$

Where K_r is the insulin resistivity parameter modulating the glucose utilization rate at tissues and $I_n(t)$ is the instantaneous insulin concentration in the slow pool of a insulin kinetic model.

From the above analysis, the glucose uptake rate in R_x can be varied by the three factors; the voltage(glucose concentration) across R_x, insulin resistivity parameter, and insulin concentration in the slow insulin pool.

c. Glucose uptake at the brain

As glucose uptake at the brain was known to be relatively constant and independent of glucose and insulin concentrations[9,10], it is represented by a current sink, B, separately from the glucose uptake at tissues.

d. Hepatic balance

The hepatic glucose balance(uptake or output) is represented by a voltage-controlled current source, H, in eq. (2), where this equation is based upon Bergman et al.'s experimental result[3].

$$H=H_0+H_1(V_2-V_{20}) \qquad (2)$$

Where

H_0 is the net hepatic glucose output at basal level, H_1 is the hepatic sensitivity relating the net hepatic glucose balance to the changes of the glucose concentration, V_2 is the glucose concentration in capillary-venous space(voltage across capacitor C_2) in the model, and V_{20} is V_2 at basal level.

e. Renal excretion

The renal glucose excretion rate(I_r) occuring at a high glucose concentration is represented by a diode(D), a resistance(R_3), and a constant voltage source(V_0), and computed as follows, using McPhaul et al.'s clinical data[11];

$$Ir=0 \quad \text{when } V_2<V_0$$
$$Ir=(V_2-V_0)/R_3 \quad \text{when } V_2>V_0 \qquad (3)$$

where $V_0=220(\text{mg/dl})$, $R_3=0.79(1/\text{dl})$

f. Rate constants

The resistance R_1 representing a rate constant of glucose flow between arterial and venous blood pool is computed as follows, using McQuire et al.'s data;

$$R_1=(A-V)_B/H_0 \qquad (4)$$

Where $(A-V)_B$ is the difference of glucose concentrations between arterial and venous blood at basal level, and was reported to be $3.1\pm0.6(\text{mg/dl})$ by McQuire et al.[12]. The resistance R_2 value of $0.24(1/\text{dl})$ was used for computation, based upon Long et al.'s results[4], where it shows the rate constant between the venous space and the slow pool.

(2) State Equations

The voltages across the capacitors representing the glucose concentrations in the three compartments are used as the state variables in the following equations (5) and (6). Either equation is used depending upon the magnitude of the computed hepatic glucose balance function, H. When the liver uptakes glucose with negative values of H, it uptakes from the venous space(C_2), while the liver produces glucose into the arterial space C_1 with positive values of H. Thus, the circuit branch location of the hepatic balance function is changed from a-a' to b-b' in Fig. 1, as H becomes negative during IVGTT. Equation(5) represents the hepatic output state when H is positive, and the hepatic uptake state is represented by equation(6) with negative values of H.

a. In the hepatic output condition(H>0);

$$\frac{dV_1}{dt}=-\frac{V_1}{R_1C_1}+\left(H_1+\frac{1}{R_1}\right)\frac{V_2}{C_1}+(G-I_r+H_0-H_1V_{20})\frac{1}{C_1}$$

$$\frac{dV_2}{dt}=\frac{V_1}{R_1C_2}-\left(\frac{1}{R_1}+\frac{1}{R_2}+\frac{1}{R_x}\right)\frac{V_2}{C_2}+\frac{1}{R_2C_2}V_3-\frac{B}{C_2}$$

$$\frac{dV_3}{dt}=\frac{V_2}{R_2C_3}-\frac{1}{R_2C_3}V_3 \qquad (5)$$

b. In the hepatic uptake condition(H>0);

$$\frac{dV_1}{dt}=-\frac{V_1}{R_1C_1}+\frac{V_2}{R_1C_1}+(G-I_r)\frac{1}{C_1}$$

$$\frac{dV_2}{dt}=\frac{V_1}{R_1C_2}+\left(H_1-\frac{1}{R_1}-\frac{1}{R_2}-\frac{1}{R_x}\right)\frac{V_2}{C_2}+\frac{V_3}{R_2C_2}-(B-H_0+H_1V_{20})\frac{1}{C_2}$$

$$\frac{dV_3}{dt}=\frac{V_2}{R_2C_3}-\frac{V_3}{R_2C_3} \qquad (6)$$

where

V_i; the glucose concentration(mg/dl) in the i-th compartment(voltage across capacitor)

C_i; the i-th compartment volume(ml) (Capacitance)

R_i; the inverse of the product of the rate constant and the compartment volume (1/dl) (resistances)

H_0; the basal hepatic output rate(mg/min)

H_1; the hepatic sensitivity to glucose level (dl/min)

I_r; the rate of the renal glucose loss(mg/min)

G; the glucose infusion rate(mg/min)

B; the brain uptake rate(mg/min)

V_{20}; the basal glucose concentration across C_2(mg/dl)

(3) Simulation Methods

Fujita et al. 's clinical data in IVGTT were used as reference to test the present network model. Also, the insulin concentration in the slow insulin pool was estimated from the reported plasma insulin concentration of IVGTT using the models of Insel et al.[5] and Frost et al.[13] These estimated insulin concentrations were used in the computation of equation(5) and(6).

The following reported constants were used for the simulation;

Total blood volume per body weight; 75.6 ml/kg

Slow pool volume as given by Long et al.[4]; 100 ml/kg

Glucose uptake at the brain; 1.06 mg/min/kg

Net hepatic glucose output at basal level 2 mg/min/kg

Glucose infusion rate; 250 mg/min/kg in 2 min. IVGTT, 100 mg/min/kg in 5 min. IVGTT

Also, we assume initially that the arterial volume(C_1) is approximately one third of the total blood volume and finally set at the value of 25(ml/kg) during iterative computation.

In calculating glucose space and glycouria, the glucose space of blood was taken as 0.86 $l/1l$ of blood and mean body weight of 60 kg was assumed.

Three parameters (C_2, K_r, and H_1) were varied iteratively to provide the condition of the minimum squared error difference between the computed and the measured venous glucose concentrations of Fujita et al.. The accuracy of fitting was compared by the following residual mean squares;

$$E^2=\sum_{i=1}^{n} W_i\, D_i^2/DF$$

where

E^2 is the residual mean square

D_i is the difference between the computed and the measured data at the i-th sample point

W_i is the weighting factor for the i-th sample, as calculated by the inverse of the square of the standard deviation of the measured data at the i-th sample

n is the number of data points

DF is the degree of freedom, i.e., n.

All computations and simulations were carried out using a Digital Equipment Corporation MINC-11 computer and a Hewlett Packard HP 9872 A Plotter

3. Results

Evaluations of the present equivalent circuit model were performed using Fujita et al.'s IVGTT results of four clinical groups(nonobese normal, nonobese mild diabetics, obese

mild diabetics, and nonobese moderate diabetics).

In Fig. 2,3 it is shown that changes of glucose concentration after intravenous injection are closely simulated by the model for normal subjects and nonobese moderate diabetics in two minute infusion period. These best fitted graphs are obtained when the residual mean square of the glucose concentrations (E^2) has the minimum value. Only the three parameters of K_r, H_1, and C_2 are used as variables, since the variation of the other parameters does not contribute any significant changes in E^2 within the physiological ranges. This result is comparable to Cunningham's model study where only two parameters, capillary-extravascular volume and K_{ins} were shown as significant variables. Since the present model does not include the delay effects of the glucose distribution from an injection site to a measuring site, we do not include the first one minute of data for analysis.

We have studied the differences of the above three parameters among four clinical groups for the data of both two minute and five minute glucose infusion. In the computations, we used two insulin models(Insel et al.'s and Frost et al.'s) in converting the reported plasma insulin level to the slow pool insulin level used in the computation of the model study.

Table 1 summarizes the best fitted data of K_r, H_1 and C_2 for normal subjects. The estimated values of K_r and H_1 are different depending upon which insulin models were used, since the slow pool insulin is different for the same plasma insulin level in the two insulin models. However, there is no significant changes in K_r and H_1 values as the infusion period varies from 2 to 5 minutes.

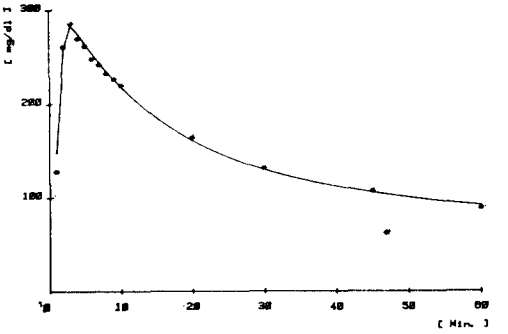

Fig. 2. Comparison of clinical data(*) and simulation(—) in nonobese normal subjects

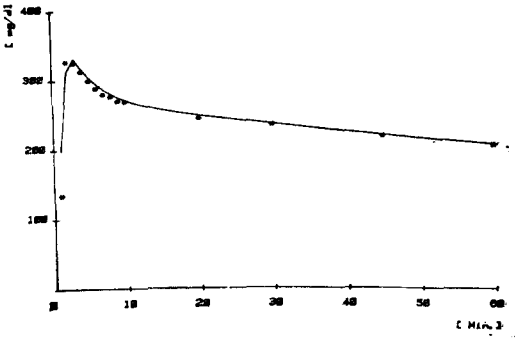

Fig. 3. Comparison of clinical data(*) and simulation(—) in nonobese moderate diabetics

Table 2 summarizes the K_r, C_2, and H_1 values for three diabetic groups, as estimated for the data of 2 min. IVGTT using the Frost et al.'s insulin kinetics model. In the obese mild diabetic subjects, K_r has the highest values, showing that this group has the maximum insulin resistance at tissue sites. Also, this group has zero H_1 value showing that there is no hepatic glucose inhibition during IVGTT test. In the nonobese group, K_r value is higher in the moderate diabetics group than in the mild diabetics group and in the normal group. On the other hand, H_1 is lower in the moderate group. As compared with these variations of K_r and H_1, C_2 is relatively constant for all three groups except the obese mild

Table 1. Estimated values of K_r (min. μU/dl), H_1(dl/min.), and C_2(dl/kg) in the normal subjects.

Infusion period	Insulin model	K_r	H_1	C_2	E^2
2	Frost	17.5	−1.50	183.3	0.08
	Insel	12.8	−1.90	180.0	0.05
5	Frost	17.0	−1.60	193.3	0.54
	Insel	11.3	−1.95	195.8	0.35

Table 2. Estimated values of K_r(min.μU/dl), H_1(dl/min.), and C_2(dl/kg) in the diabetic groups.

Group	K_r	H_1	C_2	E^2
nonobese mild diabetics	26.0	−0.95	183.3	0.90
nonobese moderate diabetics	29.4	−0.90	192.7	0.41
obese mild diabetics	39.5	0	166.7	0.23

diabetics group which has a smaller value of C_2.

Fig. 4 shows the changes of the total hepatic glucose output after glucose infusion in four groups. As the degree of diabetics becomes more severe, the responses of hepatic glucose balance is shown to become smaller up to zero response in the obese mild diabetics group.

4. Discussion

In simulating interactions between glucose and insulin during intravenous glucose infusion test, the present study has the following two difference as compared with the other previous investigations. One difference is the usage of the equivalent electrical circuit analysis instead of the compartmental model analysis. The other difference is the addition of the hepatic glucose balance functions in the model.

Once a circuit model is developed for simulation, many well-developed techniques of analysis, synthesis, and optimization of electrical science can be utilized. As an example, the development and the optimal operation of a closed-loop artificial pancreas will be greatly assisted by the use of the equivalent circuit model.

Addition of the hepatic balance function in the model has caused a difference in the computed values of the insulin resistivity parameter, K_r, and the hepatic sensitivity parameter, H_1, in the four clinical groups.

Fig. 4 shows that the responses of the hepatic output are different among the four clinical groups. This theoretical estimation agrees with other clinical reports[14] in which the changes of hepatic output were shown to be smaller in the more severe diabetic patients. This difference in the responses affects the computation of glucose kinetics in all the elements of the model. Among the three significant parameters, only the hepatic sensitivity parameter, H_1, was not considered in Cunningham's model while the effects of K_r and C_2 are included in their model. Thus, the improved overall fitting of the model in the present study could be caused by the inclusion of the effects of the hepatic balance function. By evaluating the insulin sensitivity, K_{ins}, as an inverse of the resistivity, K_r, we may validate Cunningham's suggestion that the neglect of the effects of the hepatic balance function

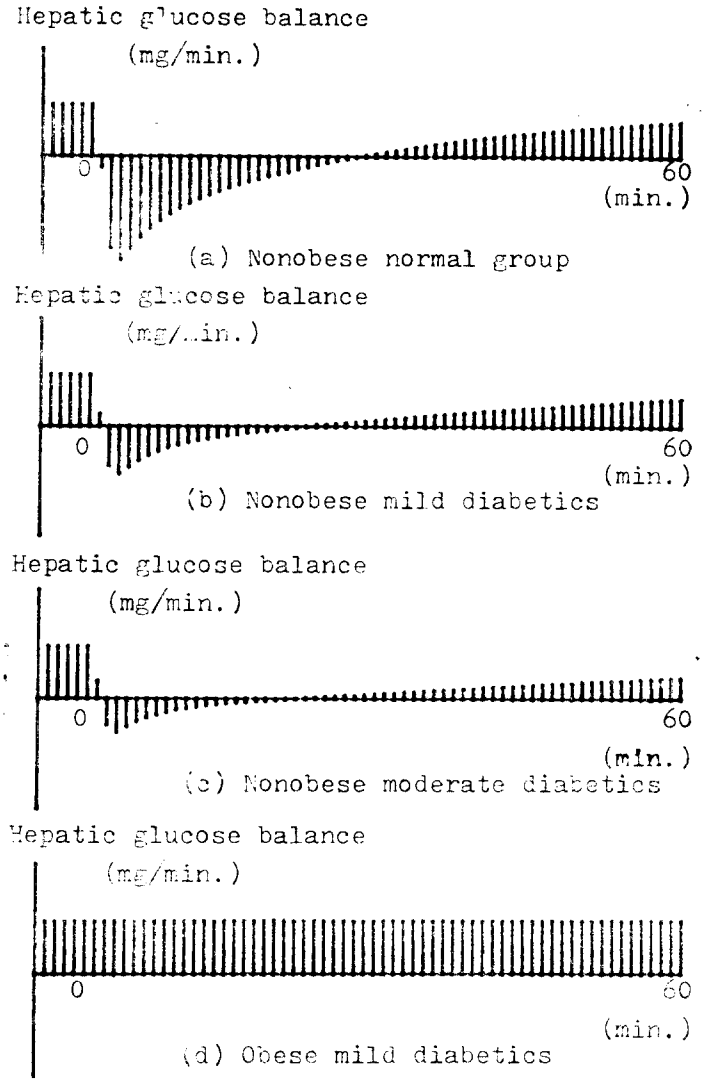

Fig. 4. Hepatic glucose balance during IVGTT in four clinical groups. (positive values for glucose output and negative for glucose uptake)

may cause overestimations in K_{ins} values. As an example, in the nonobese normal, K_{ins} is shown to become greater when we recompute K_{ins} under the assumption of zero hepatic output after glucose infusion.

In conclusion, the addition of the hepatic function in the model has improved the overall performance of the simulation. Also, the computed tissue insulin resistivity and the hepatic glucose sensitivity are shown to be significant in distinguishing four clinical groups of normal and diabetic subjects.

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□ 국문초록 □

生體內 葡萄糖動態의 等價回路 모델

尹長鉉 · 閔丙九 · 金宗相

본 연구에서는 과거의 생체 모델들에서 고려하지 않았던 간에서의 포도당의 조절기능을 포함하여 생체내의 포도당 동태에 대한 새로운 등가 회로 모델을 고안하였다.

본 모델을 사용하여 정상인과 당뇨병 환자들의 IVGTT(정맥당 부하시험) 자료를 시뮬레이션 하였다. 본방법에서는 모델에 의하여 추정된 혈당농도 변화와 임상 자료간에 최소 자승오차를 나타내는 인슐린 저항성 조변수와 간의 포도당 농도에 대한 민감성 조변수를 구하였다.

모델내의 간의 기능을 추가함으로써 시뮬레이션 결과를 과거의 모델에 비교하여 향상 시킬수 있었으며 인체조직에서의 인슐린 저항성과 간의 포도당 농도에 대한 민감성이 정상그룹과 당뇨병의 정도에 따른 세개의 임상그룹들을 구별하는데 중요한 조변수임이 밝혀졌다.