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Mathematical Modeling of Glucose Reabsorption in the Renal Tubule

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Abstract In this paper, a mathematical modeling on glucose reabsorption in renal tubule is discussed, and renal diabetes is considered on the basis of the model. The system for glucose reabsorption in renal tubule can be described as nonlinear state equations. Tubular lumen, tubular cell and capillary were set as individual compartments in the model. A homeostasis mechanism of K^+ ion in the tubular cells is added to the model. According to simulation, the rate of glucose reabsorption is affected from the difference of Na^+ ion potentials between in and out of the cells and glucose concentration in the tubular lumen. This model of glucose reabsorption system is consistent with physiological data well.

Following the simulation of the model, the direct reason of renal diabetes is defects of functions of Na^+, K^+-ATPase and glucose-Na^+ ion-symporter. A-type renal diabetes is related to defect of Na^+, K^+-ATPase activity and B-type is to that of glucose-Na^+ ion-symporter activity. Functions of the other carriers have not direct relationships with renal diabetes but affect to state of the tubular cells. In low blood sugar, values of urinary sugar are not different according to symptoms for A-type renal diabetes, but those are markedly different for B-type that.

Key words glucose reabsorption, mathematical modeling, kidney, renal tubule, renal diabetes

Introduction

Glucose absorption is a primary process for nutrition of human beings or animals. The mechanisms of glucose absorption are similar in either small intestine or renal tubule. The glucose absorption process is also responsible for glucose control in human body. Diabetes is due to defects of glucose control in human body. There are two sorts of glucose control in human body; one is active through hormones such as insulin, glucagons and adrenalin, and the other is "passive" which is related to glucose consumption in cells and filtration, reabsorption and excretion in kidney.

Physiological and biochemical researches have widely been carried out for diabetes which is a main metabolic disease so far, and studies of mathematical modeling for glucose tolerance tests and optimal treatment of insulin-dependent diabetes also have been done[1, 3, 5－7, 10, 15]. By the way, since reasons and types of diabetes are various and urinary glucose is closely related to renal functions, now, to evaluate blood glucose and glucose control ability of human body through simple determination of urinary glucose is a difficult problem. Mathematical modeling of glucose reabsorption in the kidney will contribute to estimate glucose concentration of the blood from time series analysis for urinary glucose and to examine the kidney function as well as glucose

control ability of a human body.

Up to now, researches about glucose absorption in microorganisms and animal cells have been done, [2, 4, 8, 12, 13, 16－20] but the modeling of the glucose reabsorption in kidney has remained unsolved until now.

Renal diabetes, in which blood sugar is normal but glucose is excreted in urine because of renal failure, has been known already. However, because there has not been any quantitative analysis of the glucose reabsorption in the kidney, and thus there has not been established any criteria for evaluation of its cause and symptoms.

In the paper, we modeled about the glucose reabsorption in the kidney to establish a comprehensive model of glucose control in human body, and analyzed renal diabetes on the basis of the model.

1. Methods

We formulated the mathematical model describing the glucose reabsorption system that included proximal convoluted tubule and tubular cells as nonlinear simultaneous state equations on the basis known mechanism of glucose reabsorption. For simplification, plasma, tubule (strictly proximal convoluted tubule) and tubule cells were set as individual compartments.

Simulating the state changes in the tubular cells and the curve of glucose titration test with the primary model, we revised and completed the model.

Parameters were estimated by using of genetic algorithm on the basis of human physiological data already known. And the effects of each parameter on the dynamics of the system were examined analytically or with simulation, and identified in connection with the different types of renal diabetes, where the main indices to be considered were the glucose titration curves and the state changes in the tubular cell.

Then, the dynamics of urinary glucose concentration that was significant in clinical practice were simulated. A modified Rayleigh function was used as a test function of blood glucose dynamics.

Simulation was performed with Matlab 7.0 Application.

2. Results and Discussion

2.1. Model formulation

Glucose reabsorption in tubular cells of the kidney can be diagramed as Fig. 1.

As shown in Fig. 1, glucose filtrated firstly through glomerula is reabsorbed into the tubular cell with Na^+ by Na^+-glucose symporter, and then transported by glucose permease while Na^+ ions are transported by Na^+, K^+ ATPase into the capillary. K^+ ions are countertransported into the cells with Na^+ ions. As these processes proceed successively in all cells arranged along the tubule, glucose concentration in the lumen gradually decreases, and glucose, which is not absorbed to the end must be included in urine and excreted.

The glucose concentration in the proximal tubule is continuously deceases along the tubule downward.

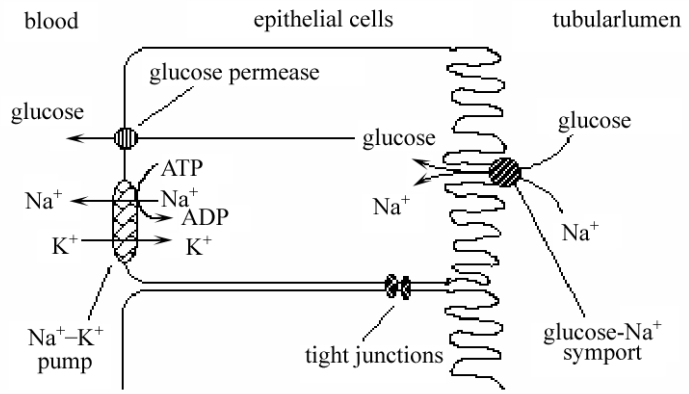

Fig.1. The mechanism of glucose reabsorption in the renal tubule.

Neither it is easy nor does it have a significance to describe these whole processes mathematically in detail. In this case, it is rather convenient to set compartmentation for the simplification.

Therefore, we made a mathematical model, not focusing on the dynamics of glucose concentration in the lumen but on the transport processes by tubular cells within the system that has three distinctive compartments involving lumen, tubular cell, and capillary. In each compartment, concentrations of the main solutes, glucose, Na^+, and K^+ ions, which are related to glucose reabsorption can vary and is also dynamic.

We noticed following characteristics occurred in the glucose reabsorption in the tubule;

Firstly, the concentration of the solutes in the lumen is changeable and external to homeostasis.

Secondly, it is unnecessary to take into account the concentration change of the main solutes in the capillary because blood flows constantly.

Thirdly, the concentration changes the solutes in the cell is of significance in relation to the intracellular homeostasis.

From this viewpoint, we set the concentrations or quantities of the solutes in the lumen and tubular cell as state variables. The concentrations of the solutes in urine are dependent upon these variables.

The variables and parameters of the system are as follows;

GFR: Glomerula filtration rate (mL/min)

P_G: Glucose concentration in the filtrate or plasma (g/dL)

P_S: Na^+ concentration in the filtrate or plasma (mmol/L)

C_G: Glucose concentration in the tubular cell (g/dL)

C_S: Na^+ concentration in the tubular cell (mmol/L)

C_P: K^+ concentration in the tubular cell (mmol/L)

L_G: Glucose concentration in the lumen (g/dL)

L_S: Na^+ concentration in the lumen (mmol/L)

F_G: Rate of glucose filtration in glomerula (g/min)

T_G: Rate of glucose reabsorption in the tubule (g/min)

M_G: Rate of glucose transport from the cell to the capillary (g/min)

F_S: : Rate of Na^+ filtration in glomerula (mmol/min)

T_S: Rate of Na^+ reabsorption in the tubule (mmol/min)

M_S: Rate of Na^+ transport from the cell to the capillary (mmol/min)

T_P: Rate of K^+ transport from the capillary to the cell (mmol/min)

M_P: Rate of K^+ excretion from the cell (mmol/min)

E_G: Rate of glucose excretion through urine (g/min)

E_S: Rate of Na^+ efflux from the proximal tubule (mmol/min)

V_C, V_L; Volumes of tubular cell and tubular lumen (L)

In order to define the kinetic relations between the variables, we assumed as follows.

Each compartment is homogenous.

Delay of solute transport by diffusion is negligent.

The state variables are C_G ,C_S, C_P, L_G, L_S.

The change of glucose concentration in the cells is determined by the rates of reabsorption and transport into the capillary;

$$\frac{dC_G}{dt} = \frac{T_G - M_G}{V_C} \tag{1}$$

Where, V_C is the volume of cells.

The change of Na^+ concentration in the cells is also determined by the rates of reabsorption and transport into the capillary.

$$\frac{dC_S}{dt} = \frac{T_S - M_S}{V_C} \tag{2}$$

K^+ concentration in the cell increases by Na^+, K^+-ATPase, but K^+ ions has to be excreted from the cell because of its intracellular homeostasis. Therefore, rate of the change of K^+ concentration in the cell is;

$$\frac{dC_P}{dt} = \frac{T_P - M_P}{V_C} \tag{3}$$

Glucose concentration in the lumen is dependent upon rates of glomerula filtration, reabsorption in tubule and excretion through urine;

$$\frac{dL_G}{dt} = \frac{F_G - T_G - E_G}{V_L} \tag{4}$$

Where, V_C is the volume of proximal tubule.

Although the concentration of Na^+ ions in the lumen is relatively higher than that of glucose and is not completely absorbed, it decreases as much as glucose absorption by glucose-Na^+ symporter;

$$\frac{dL_S}{dt} = \frac{F_S - T_S - E_S}{V_L} \tag{5}$$

Then, we defined each rates in the above equations (1)－(5).

In general, the concentration of Na^+ ions in the cell is much lower than that in the plasma, and their difference determines the Na^+ reabsorption. If the rate of Na^+ reabsorption is simply proportional to the difference, it follows that;

$$T_S = k_1(L_S - C_S) \tag{6}$$

Where, k_1 is a coefficient dependent upon the activity and distribution density of glucose-Na^+ion-symporters in the cellular membrane of the tubule.

As glucose reabsorption couples with that of Na^+ ions in the proximal tubule, the glucose reabsorption rate is also proportional to T_S. If a symbol n stands for the coupling ratio of Na^+ and glucose, then

$$T_G = 0.018 \times n \times T_S = 0.018 \cdot k_1(L_S - C_S) \tag{7}$$

Where, the number 0.018 was set to match the concentration units of Na^+ and glucose.

As glucose transport by uniporter(permease) at capillary-side membrane seems to be the single enzymatic reaction[2], it can be formulated like Michaelis-Menten equation.

$$M_G = k_2 \cdot \frac{C_G}{K_{mG} + C_G} \tag{8}$$

Where, k_2 is the transport rate of glucose when its concentration is much higher than $K_{mG,}$ which is the glucose concentration when M_G is a half of the maximal transport rate. Because the transport of glucose is also active, the glucose concentration in plasma is not contained in equation (8), and the quantity of ATP in cells can also affects to k_2.

As Na^+, K^+-ATPase in the membrane on the capillary side carries Na^+ in the opposite to the direction of K^+, the transport rate is dependent upon the concentration of these ions in the case that the concentration of them is not so much high as to reach the saturated transport rate. Since the concentrations of Na^+, K^+ ions in the plasma are constant and their transports are active, their transport rates are dependent on only the intracellular concentrations of them. Therefore it follows that;

$$M_S = k_3 \cdot \frac{C_S}{C_P} \tag{9}$$

Where, k_3 is a coefficient dependent upon the activity of Na^+, K^+-ATPase. In (9), it is assumed that the transport rate of Na^+ ions into the capillary is inversely proportional to K^+ concentration in the cell. And the direct effect of ATP concentration on the transport rate was negligent even though the transport of these ions is accompanied with consumption of ATP. But, their constraint influences were ignored here.

As Na^+ exchanges with K^+ in proportion of 3 : 2, the transport rate of K^+ ions from the capillary into the cell can be defined like;

$$T_P = \frac{2}{3} M_S = \frac{2}{3} k_3 \cdot \frac{C_S}{C_P} \tag{10}$$

As it is difficult to imply the mechanism of K^+ efflux uniquely, we assumed that the efflux rate of K^+ ions from the cell simply depends on the K^+ ion concentration in the cell;

$$M_P = k_4 C_P \tag{11}$$

In equation (4), F_G, the rate of glucose filtration through glomerula is directly determined by glucose concentration in blood and glomerula filtration rate;

$$F_G = P_G \times \frac{GFR}{100} \tag{12}$$

Where, the number 100 was set to match the concentration units.

Glucose unabsorbed in the proximal tubule is included into urine and water absorption does not occur in the proximal tubule, so the rate of glucose excretion through urine is;

$$E_G = L_G \times \frac{GFR}{100} \tag{13}$$

In equation (5), F_S, the rate of Na^+ filtration through glomerula is similar with F_G of (12) while E_S the rate of Na^+ excretion, is similar with E_G of (13);

$$F_S = P_S \times \frac{GFR}{100} \tag{14}$$

$$E_S = L_S \times \frac{GFR}{1\,000} \tag{15}$$

Where, the number 1 000 was also set to match the concentration units.

From the equations (1)－(15), we set the equations system representing the dynamics of the solutes in tubule cell and of glucose concentration in the lumen as follows.

$$\frac{dC_G}{dt} = \left[0.018 \cdot nk_1 (L_S - C_S) - k_2 \frac{C_G}{K_{mG} + C_G} \right] \Big/ V_C \tag{16}$$

$$\frac{dC_S}{dt} = \left[k_1 (L_S - C_S) - k_3 \frac{C_S}{C_G} \right] \Big/ V_C \tag{17}$$

$$\frac{dC_P}{dt} = \left[\frac{2}{3} k_3 \frac{C_S}{C_P} - k_4 C_P \right] \Big/ V_C \tag{18}$$

$$\frac{dL_G}{dt} = \left[(P_G - L_G) \times \frac{GFR}{100} - 0.018 \cdot nk_1 (L_S - C_S) \right] \Big/ V_L \tag{19}$$

$$\frac{dL_S}{dt} = \left[(P_S - L_S) \times \frac{GFR}{1\,000} - k_1 (L_S - C_S) \right] \Big/ V_L \tag{20}$$

The measurable output variables are urinary glucose concentration and the rate of glucose excretion through urine. Those variables become functions of state variables.

2.2. Validation and revision of the model

One of the most important criteria in validating the model is its stability. We examined the stability of the system with the equations (16)－(20).

Since this system is nonlinear, general methods of stability judgment for linear systems can be applied to it. We observed the stability of the system by simulating its dynamical behavior programmatically.

The system model has several unknown parameters. For simulation, the values of these parameters must be given. We settled them adequately, artificially because clear characteristic data of individual transporters have not been reported yet.

In the normal human body, GFR=125mL/min, P_G=0.1g/dL, and we set C_G, C_S, C_P .as 0.02, 14, 140 respectively on the basis of physiological data. We set remainder parameters as positive values within the range of 0 to 30, and simulated time changes of state variables (The results not shown).

According to the results, state variables showed stabilization processes relatively but final values of them, especially the value of K^+ ion concentration did not reach to physiologically normal values. This implies that the assumption that K^+ ion decreases with its concentration passively is incorrect. We deduced that additional mechanism for homeostasis of K^+ ion concentration in addition to transport of the ion exists, and modified the expression (18) as following;

$$\frac{dC_P}{dt}=\left[\frac{2}{3}k_3\frac{C_S}{C_P}-k_4(C_P-140)\right]\Big/V_C \tag{21}$$

Using this expression, when the value of k_4 is not smaller than some number, not only K^+ ion concentration in cells, but also Na^+ ion concentration which is related to the former were stabilized with time.

Then, we investigated the characteristics of glucose transference in the glucose reabsorption system. For that, we observed changes of glucose transference quantities in steady-states when glucose concentration in glomerula filtrates i.e. that in plasma varied in the range of 0～0.8%. The results are shown in Fig. 2.

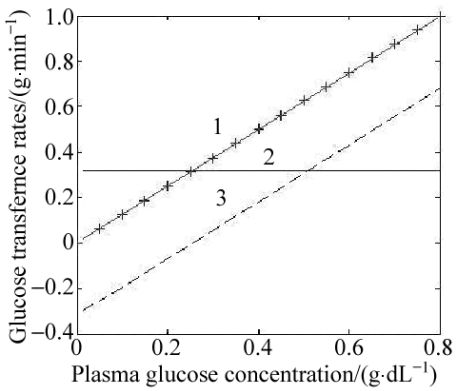

Fig. 2. Changes of glucose transference rates with plasma glucose concentration in the glucose reabsorption system
k_1=1, k_2=30, k_3=10, k_4=0.025, K_{mG}=0.8, V_C=1, V_L=1; 1－filtration rate at glomerula, 2－reabsorption rate of glucose, 3－excretion rate of glucose

As shown in Fig. 2, all graphs are linear. What is characteristic in those is that the quantities of glucose reabsorption are uniform irrelevantly to filtration quantities. Therefore, even negative quantities of glucose excretion exist. That is inconsistent to reality. This implies that our model has some defects.

We deduced that inconsistency between the model and real system was due to incorrect analysis about the mechanism of glucose symport. In previous literatures, it is explained that the reabsorption rate of glucose depends on only differences of Na^+ ion potentials between in lumen and in cells, so we expressed reabsorption rates of glucose and Na^+ ions expressions (6) and (7) above. The action of symporter at the membrane of tubular cells might depend on the glucose concentration because it is symporter so as its name. Therefore, we deduced that glucose reabsorption rate depends not only on the difference of Na^+ ion concentrations between in and out of cells but also on glucose concentration in tubular

cells. We assumed that the rate is proportional to a product of them, modified expression (7) as below expression (22) and corrected related expressions correspondingly.

$$T_{\mathrm{G}} = 0.018 \cdot k_1 (L_{\mathrm{S}} - C_{\mathrm{S}}) \cdot L_{\mathrm{G}} \tag{22}$$

We considered the behaviors of glucose transference rates as in Fig. 3 in this conditions,. Seeing the results, their tendencies were consistent to physiological processes well.

Finally, the whole model of glucose reabsorption in renal tubule is as follows;

$$\begin{cases} \dfrac{dC_{\mathrm{G}}}{dt} = \left[0.018 \cdot nk_1 (L_{\mathrm{S}} - C_{\mathrm{S}}) \cdot L_{\mathrm{G}} - k_2 \dfrac{C_{\mathrm{G}}}{K_{\mathrm{mG}} + C_{\mathrm{G}}} \right] \Big/ V_{\mathrm{C}} \\ \dfrac{dC_{\mathrm{S}}}{dt} = \left[k_1 (L_{\mathrm{S}} - C_{\mathrm{S}}) \cdot L_{\mathrm{G}} - k_3 \dfrac{C_{\mathrm{S}}}{C_{\mathrm{P}}} \right] \Big/ V_{\mathrm{C}} \\ \dfrac{dC_{\mathrm{P}}}{dt} = \left[\dfrac{2}{3} k_3 \dfrac{C_{\mathrm{S}}}{C_{\mathrm{P}}} - k_4 (C_{\mathrm{P}} - 140) \right] \Big/ V_{\mathrm{C}} \\ \dfrac{dL_{\mathrm{G}}}{dt} = \left[(P_{\mathrm{G}} - L_{\mathrm{G}}) \times \dfrac{GFR}{100} - 0.018 \cdot nk_1 (L_{\mathrm{S}} - C_{\mathrm{S}}) \cdot L_{\mathrm{G}} \right] \Big/ V_{\mathrm{L}} \\ \dfrac{dL_{\mathrm{S}}}{dt} = \left[(P_{\mathrm{S}} - L_{\mathrm{S}}) \times \dfrac{GFR}{1\,000} - k_1 (L_{\mathrm{S}} - C_{\mathrm{S}}) \cdot L_{\mathrm{G}} \right] \Big/ V_{\mathrm{L}} \end{cases} \tag{23}$$

2.3. Identification of parameters

To identify the system's parameters, we used below physiological variables as standards. The rate of glomerula filtration in kidney is 125mL/min at average, the daily quantity of urine is 1.5 ~2L/d and the volume of filtrate decreases to one hundredth by water absorption when it becomes to urine. The rate of glucose excretion through urine is no greater than 0.25mg/min. The concentration of glucose in plasma at which glucose begin to be detected i.e. glucose efflux is detected is 0.2 ~0.3g/dL. Though there is some difference between man and woman, the concentration of glucose in plasma at which glucose reabsorption rate is saturated is about 350mg/dL. The concentrations of glucose in cells are greatly different according to the states of cells and vary in a range of 0 ~20mg/dL.

The concentration of Na^+ ion in plasma is about 142mmol/L and that in cells is not higher than its one tenth. The concentration of K^+ ion is about 140mmol/L and that in plasma is also not higher than its one tenth.

Parameters of the system were identified by using genetic algorithm. Since values of parameters to be identified must be positive, each parameter was encoded as binary code sets of 10 bits, and chromosomes-individuals were constituted by linking those code sets. The accuracy of the parameters was evaluated the difference (evaluating function) between the simulating data for the glucose titration curve and experimentally measured data of that. Assuming n=1, estimated approximate values of the model parameters are as follows; k_1=300, k_2= 7.7, k_3=900, k_4=0.81, K_{mG}=0.83.

According to results of several simulation experiments, other parameters do nearly not change

but only the values of k_1 can vary in a wide range from 177 to 500, and the values of L_G can change thereby. For example, if values of k_1 are smaller than 177 in P_G=0.1, then the value of L_G exceeds 0.000 3, and if the former are greater than 600, then the latter become smaller than 0.000 1. This indicates that k_1 affects definitive effect to urinary sugar because L_G value is related to urinary sugar directly. If glucose concentration is diluted 100-folds by absorption of water after the proximal convoluted tubule, when the value of k_1 change in the above range, the concentration of urinary glucose may vary in the range of 0.01～0.03mg/dL.

In the condition of V_C=V_L=1, the glucose titration curves(simulation) are shown in below Fig.3.

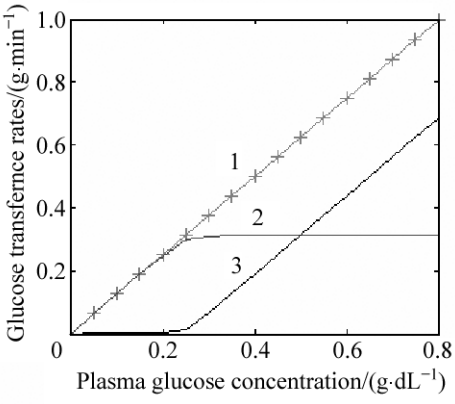

Fig. 3. Rates of glucose transport with glucose concentration in plasma glucose titration curve(simulation)
1－filtration of glucose, 2－reabsorption of glucose, 3－excreation of glucose

The results in Fig. 3 are well consistent with data for the physiological system. This implies that the constructed mathematical model satisfy human physiological process for glucose reabsorption in renal tubule relatively good. Since the glucose absorption in small intestine proceeds in the nearly same mechanism as in kidney, this model can be used in consideration for digestion and absorption of nutrients. Furthermore, the model can give valuable data in constructing universal model about glucose metabolism in human body and in diagnosis and treatment of various diseases connected to sugar metabolism.

In current model, values of some parameter were defined artificially, so those values would be further modified with addition of experimental physiological data. And effects which other factors including hormones have on the glucose reabsorption would be added to the model.

2.4. Consideration about renal diabetes on the basis of the mathematical model

Since renal diabetes is mainly related to genetic characteristics, our aim is to explain what those parameters affect to the blood sugar-urinary sugar relationship.

2.4.1. Roles of V_C, V_L in glucose reabsorption

Normally glomerula filtration rate-*GFR* is about 125mL/min and blood sugar often changes in dimension of hour. Therefore, we can assume steady-state in short time intervals such as about one minute.

In steady-state, all left sides of model (1) are zero, and if rearranged in this situation, both V_C and V_L are eliminated. This implies that values of V_C and V_L have any effects on the stationary values of state variables of the system. Namely, these parameters play only roles as time-constants, but cannot be factors of renal diabetes. Therefore parameters; volumes of cell and lumen are excluded in consideration for reason of renal diabetes.

2.4.2. A-type renal diabetes

In the A-type renal diabetes patient, the maximal reabsorption rate(T_{mG}) is lower than that in

normal person (about 350m%).

We investigated which parameter of k_1, k_2, k_3, k_4, K_{mG} affects definitive effect to the maximal reabsorption rate, through the glucose titration curve. According to the results, that parameter was k_3, which reflects the transport ability of Na^+, K^+-ATPase. The other parameters have not direct effect to that. Effects of k_3 values on the rate of glucose reabsorption are shown in Fig. 4 in a shape of glucose titration curve.

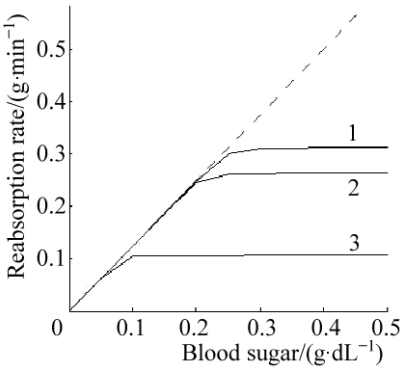

Fig. 4. Effects of k_3 values on the rate of glucose reabsorption
1－k_3=900, 2－k_3=90, 3－k_3=9,
Dashed line represents glucose filtration rate.

As shown in Fig. 4, the value of T_{mG} decreases as k_3 value decreases. On the other hand, when considered at the values same as above, the values of state variables in tubular cells changed greatly (data not shown). This implies that the reason of A-type renal diabetes is ascribed to functional defect of Na^+, K^+-ATPase.

2.4.3. B-type renal diabetes

In the case of B-type renal diabetes, the maximal reabsorption rate of glucose is normal but the "renal threshold" i.e. the value of blood sugar at which glucose can be detected in urine is small.

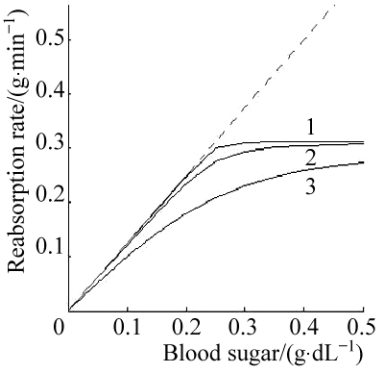

Fig. 5. Effects of k_1 values on the rate of glucose reabsorption
1－k_1=300, 2－k_1=30, 3－k_1=3,
Dashed line represents glucose filtration rate

We tried finding parameters that affect to renal threshold by simulation method as above. According to the result, the factor that affected to renal threshold was coefficient k_1, which was related to the ability of glucose-Na^+-symporter and the other parameters did not affect to that directly. Rates of glucose reabsorption in tubule with several k_1 values are shown in Fig. 5.

As shown in Fig. 5, when values of k_1 are small, the differences between filtration rate and absorption of glucose are obvious, so that glucose might excrete through urine. And the maximal glucose reabsorption rates are similar to the normal level which is the representative characteristics of B-type renal diabetes. Thus, we can conclude that the main reason of B-type renal diabetes is ascribed to decrease of k_1 value i.e. functional defect of glucose-Na^+-symporter.

2.4.4. Roles of k_2, k_4, K_{mG} in the glucose reabsorption system

We investigated changes occurring in states of tubular cell when values of k_2, k_4 vary. According to simulation results, the change of k_2 value has great effects on the glucose concentration in cell, but it does not change concentrations of Na^+ and K^+ ions (data not shown).

On the other hand, when value of k_4 decreases, the concentration of K^+ ion in the cell increases greatly, and in the condition of $k_4 \leq 0.01$, it shows instability. In addition, in that condition, the concentration of Na^+ ion tended to change toward values lower than its normal value, but the

concentration of glucose did not change (data not shown).

As shown in expression (23), the value of K_{mG} is concerned to that of k_2. Therefore, when we changed this value, changes corresponding to that of k_2 values occurred (data not shown). Nevertheless, these three parameters did not affect significant effects to renal diabetes.

As shown above, reasons of renal diabetes are ascribed to functional defects of two transporters; Na^+, K^+-ATPase and glucose-Na^+symporter. Total functions of transporter proteins are related to the products of distribution densities and activities of the proteins at their transport positions. And individual transport ability of a protein can be either its characteristic parameter or a result of regulation by any external factor.

The change of distribution densities of transporter proteins is related to expression extent of corresponding genes, and decrease in their intrinsic transport capabilities implies that those genes were varied. On the other hand, functions of those proteins might be decreased by materials which inhibit the proteins. Experimental data for this are very poor but there have been reported some studies.

For example, reference [9] confirmed experimentally that renal diabetes is related to the inhibition of Na^+, K^+-ATPase gene expression, and reference [11] described that the activities of renal Na^+, K^+-ATPase are inhibited by leptin which is secreted from fatty tissues in rat. Literature [14] showed that the activity of inhibitor for this transporter protein increased in a hypertensional diabetes patient. But the relation between glucose-Na^+-symporter and renal diabetes have not been reported and experimental data explaining reasons of disease-types have also not been given in previous studies. Our calculating experiments with the model explained that functions of these transporter proteins are directly related to types of renal diabetes.

We shall show that urinary sugar changes greatly even though the changes of parameter's values are not so great below.

2.4.5. Dependence of urinary sugar on blood sugar at renal diabetes

We considered blood sugar-urinary sugar relationship, which is the diagnosis factor at two kinds of renal diabetes from the mathematical model on the glucose reabsorption. In order to make blood sugar to change so as, for example, after saccharide uptake or at glucose tolerance test, we used Rayleigh function as a test function. The function was modified as following;

$$P_G = \text{raylpdf}([0:0.1:4], 1.0) \times 0.12 + 0.08 \tag{24}$$

and used as input to the system.

Equation (24) is described in Matlab language. In this equation, P_G is the value of blood sugar and "raylpdf" is a function name, which expresses Rayleigh function in Matlab language. According to this equation, blood sugar changes in a range of 0.08～0.15mg/dL and is shown in below Fig. 6. Fig 6 shows results of considering changes of urinary suger corresponding to changes of parameters k_3, k_1. In this Fig., dashed curve is plot of Rayleigh function described as the equation (24) i.e. plot of blood sugar and the others are plots of urinary sugars which are calculated assuming that urinary sugar is 100 folds of glucose concentration in the lumen.

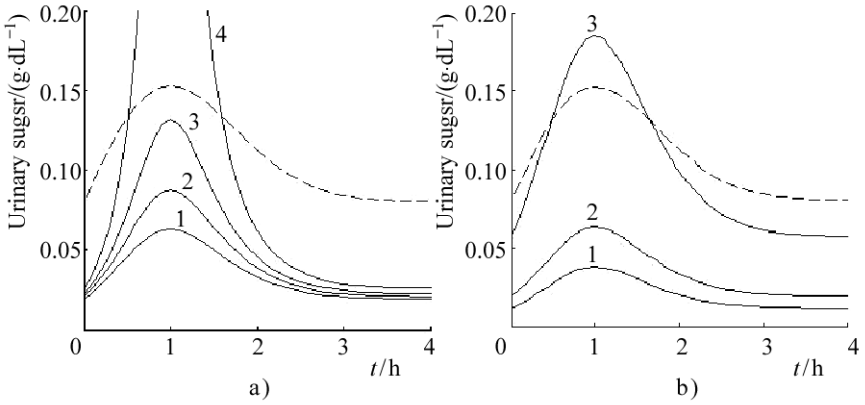

Fig. 6. Time change of urinary sugar to blood sugar at renal diabetes.
a) A-type renal diabetes: 1－k_3=900, 2－k_3=90, 3－k_3=50, 4－k_3=30;
b) B-type renal diabetes: 1－k_1=500, 2－k_1=300, 3－k_1=100;
Dashed line represents curve of blood sugar

In Fig. 6, changes of urinary sugar to that of blood sugar show similar morphological characteristics each other, but there exist important differences between them. Firstly, at the time t=1h, the sensitivities of urinary sugar to corresponding parameters in the case of B-type renal diabetes is greater than in the case of the A-type. For example in the range of k_3=90～900, the sensitivity of urinary sugar is about $(0.08\sim0.06)/(90\sim900)\approx -2.47\cdot10^{-5}$, but in the range of k_1=100～300, sensitivity of urinary sugar is about $(0.06\sim0.18)/(100\sim300)=-6.0\cdot10^{-4}$. Another important difference is in the absolute values of urinary glucose. In low blood sugar, values of urinary sugar are not different according to symptoms for A-type renal diabetes, but those are markedly different for B-type renal diabetes.

Such data can be a good basis for classification of disease types of renal diabetes and evaluation of symptoms of them.

Thus, the presented model can be used in diagnosis and treatment of diseases connected to sugar metabolism. Furthermore, it can give valuable data for constructing universal model about glucose dynamics in human body.

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