A TWO-DIMENSIONAL MATHEMATICAL MODEL OF THE HUMAN BLOOD GLUCOSE REGULATION MECHANISM

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It is well known that processes of sugar oxidation are closely related to energy balance in the organism and disorders of the regulation of these processes cause pathological conditions (2).

Insulin is a main factor regulating blood glucose content. That is why as a first step to qualitative description of the regulatory mechanism it is appropriate to restrict our considerations within a two-dimensional model, i. e. to discuss a model in which two basic variables take part, namely blood glucose level — x, and insulin level — y. These quantities can be measured and managed in clinical practice.

M. J. Davies (3) has proposed a two-dimensional phenomenological model of the blood glucose regulation mechanism. The author has paused on a linear differential model in which a non-zero blood glucose equilibrium level x_0 was accepted. An essential disadvantage of the model was the acceptance of zero insulin equilibrium level $y_0=0$ while it has been experimentally proved in practice that there existed a non-zero one. If we accept that at a given moment system has reached an equilibrium state, i. e., $x=x_0$ and $y=y_0$, Davies' model can not explain the normal functioning of a healthy organism because constant energy consumption by the muscles is realized by means of glucose dissimilation by insulin.

The aim of the present work is to eliminate the disadvantage mentioned above proposing a mathematical model adequately describing real processes. Such a model could enable the comparison between theory and experiment that is not realized by Davies himself (3). Besides the new model proposed renders account of the so-called rapid insulin response of the pancreas in cases of blood glucose increase over its equilibrium level reported by G. M. Grodsky (4).

In our model, equilibrium state of the system is characterized by blood glubcose level on an empty stomach x_0 and non-zero insulin level y_0. When one disturbes the balance of the system as a result from the action of several independent mechanisms the system tends to restore its equilibrium state.

In our model proposed these mechanisms are described by means of a system of two common linear differential equations determining the rate of changing of blood glucose level [1] and that of insulin [2], respectively:

$$\frac{dx}{dt} = -a_1 y + a_2 (x_0 - x)\, \theta (x_0 - x) + a_3 z (t) \qquad [1],$$

where $\theta (x_0 - x)$ is the step function.

In equation [1] the separate terms denote as follows: glucose metabolism by insulin in muscular, adipose and other tissues; liberation of carbohydrate resources from the liver; and, at last, sugar entry by food.

Following Davies' model (3) we accept the function z (t) of the form:

$$z (t) = \begin{cases} 0 & ,t < t_0 \\ ke^{-k(t-t_0)} & ,t \geqslant t_0 \end{cases}$$

where the value of parameter «k» (parameter of retardation) depends on food nature and t_0 is the moment of its taking.

The equation 2 looks like:

$$\frac{dy}{dt} = -b_1 y + b_2(x - x_0)\ \theta(x - x_0) + b_3 f(t)\ \theta(x - x_0) \qquad [2],$$

where the first term ($-b_1 y$) corresponds to free insulin inactivation in alive organism and the rest two terms describe the so-called slow and rapid response of insulin secretion during a more prolonged glucose stimulation (over 0.5÷1 min), respectively (4).

During the first stage (rapid response) about 2 per cent of pancreatic insulin is secreted while during the next one-hour period — another about 20 per cent. The rapid response can be satisfactorily described by means of Gaussian curve, and, therefore, the function f(t) of equation [2], can be written in the form:

$$f(t) = \frac{d}{dt} \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(t-t_1)^2}{2\sigma^2}} \qquad [3]$$

where t_1 is the time interval required by the rapid response to reach its maximal value after the moment of its starting. According to the aforementioned author (4), we accept $t_1=2$ min and $\sigma=t_1/3$ because the main part of the Gaussian curve is limited within the interval $t_1 \pm 3\sigma$.

The method presented above was applied with the description of the experimental results from the standard oral and intravenous glucose tolerance tests (OGTT and IvGTT, respectively) already published elsewhere (1). Numerical procedure after the method «prognosis-correction» (5) was used and realized on microcomputer in order to solve the system of two equations [1] and [2]. It was established that the model fitted best with experimental data in the case of the following parameter values (table 1) which were positive by definition.

In our model, parameter K=0.20 in glucose tolerance tests.

Table 1

Parameter values of the model fitness

Sensitivity of the gradient to	designation	value
A. glucose to:		
— insulin presence in muscular, adipose and other tissues	a_1	0.309×10^{-1}
— low blood glucose level	a_2	0.600×10^{3}
— food intake	a_3	0.438 ± 10^{2}
B. insulin to:		
— insulin level	b_1	0.240×10^{1}
— high blood glucose level (delayed response)	b_2	0.271×10^{3}
— high blood glucose level (rapid response)	b_3	0.359×10^{-1}

Both figures 1 and 2 show theoretical curves obtained (with dense lines) concerning OGTT and IvGTT, respectively. Straight lines parallel to x-axes correspond to equilibrium levels $x_0=4$ mmol/l and $y_0=50$ pmol/l of blood glucose and insulin, respectively.

Our data demonstrate that the two-dimensional model described above agrees well with experimental results not only qualitatively, but also quantitatively, indeed.

We can conclude that by means of parameter changing this model can describe pathological conditions (e. g. diabetes mellitus), too. Besides by adding of an additive term into equation [2] one can optimize therapeutic regimen by insulin injections.

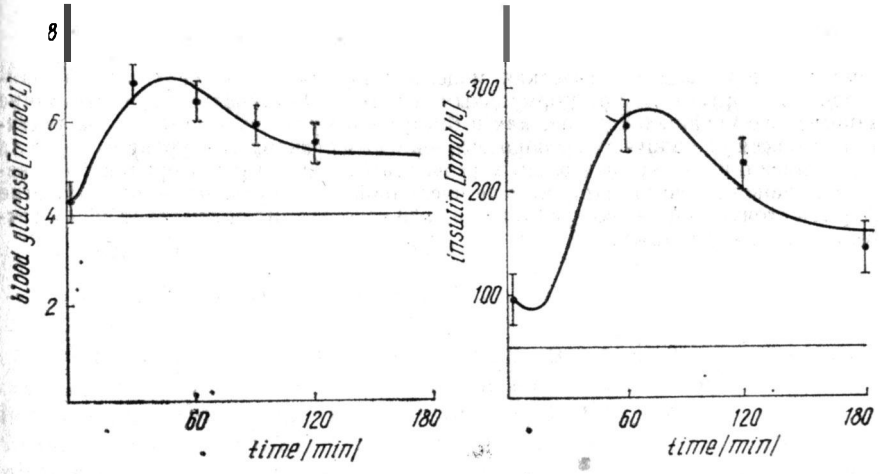

Fig. 1.

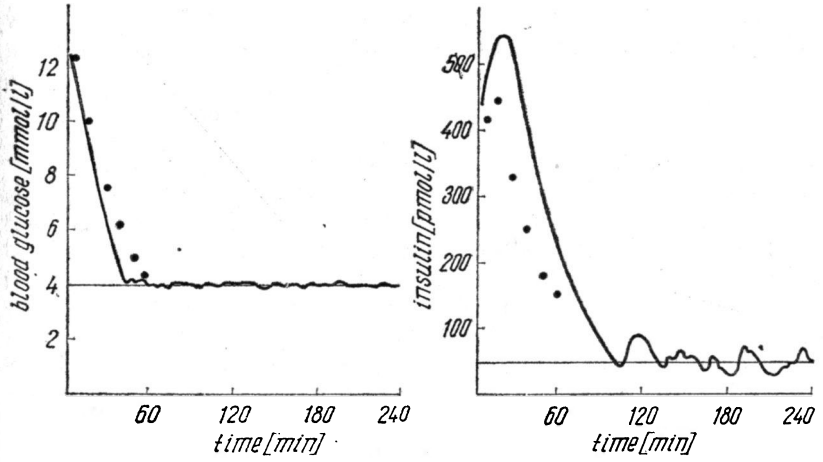

Fig. 2.

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ДВУХМЕРНАЯ МАТЕМАТИЧЕСКАЯ МОДЕЛЬ РЕГУЛЯЦИОННОГО МЕХАНИЗМА ГЛЮКОЗЫ КРОВИ У ЧЕЛОВЕКА

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РЕЗЮМЕ

Предложена двухмерная математическая модель регуляционного механизма кровяной глюкозы в здоровом организме при нормальных условиях. Установлены существование ненулевого равновесного уровня инсулина, как и быстрый инсулиновый ответ поджелудочной железы при повышении количества глюкозы крови над равновесном уровнем. Модель применялась при описании экспериментальных результатов стандартного орального и венозного глюкозотолерансных тестов. При помощи численной процедуры на микрокомпьютре был сделан отбор тех стоимостей параметров модели, при которых она оптимально согласуется с экспериментальными данными.