Quantitative estimation of insulin sensitivity

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Biomedical Engineering Center and Department of Engineering Sciences, Northwestern University Technological Institute, Evanston, Illinois 60201; and Laboratorio per Ricerche di Dinamica dei Sistemi e di Bioingegneria, Consiglio Nazionale delle Ricerche, 35100 Padova, Italy

Bergman, Richard N., Y. Ziya Ider, Charles R. Bowden, and Claudio Cobelli. Quantitative estimation of insulin sensitivity. Am. J. Physiol., 296(6): E667–E677, 1979 or Am. J. Physiol.: Endocrinol. Metab. Gastrointest. Physiol. 5(6): E667–E677, 1979—We have evaluated the feasibility of using a mathematical model of glucose disappearance to estimate insulin sensitivity. Glucose was injected into conscious dogs at 100, 200, or 300 mg/kg. The measured time course of insulin was regarded as the “input,” and the falling glucose concentration as the “output” of the physiological system storing and using glucose. Seven mathematical models of glucose uptake were compared to identify the representation most capable of simulating glucose disappearance. One specific nonlinear model was superior in that it 1) predicted the time course of glucose after glucose injection, 2) had four parameters that could be precisely estimated, and 3) described individual experiments with similar parameter values. Insulin sensitivity index (SI), defined as the dependence of fractional glucose disappearance on plasma insulin, was the ratio of two parameters of the chosen model and could be estimated with good reproducibility from the 300 mg/kg injection experiments (SI = 7.00 × 10⁻⁴ ± 24% (coefficient of variation) min⁻¹/μU/ml (n = 8)). Thus, from a single glucose injection it is possible to obtain a quantitative index of insulin sensitivity that may have clinical applicability.

Methods

Animal Experiments

Thirteen intravenous glucose tolerance tests (IVGTT) were performed on five mongrel dogs, which weighed between 20.0 and 29.8 kg. Nine experiments on two dogs were used for model comparison; four additional experiments on three other animals were used for estimates of insulin sensitivity (see Results). Under sterile conditions, a polyvinyl chloride catheter was inserted into the right atrium of each dog through the jugular vein. The catheter was filled with sterile heparinized saline and capped. Chronic, indwelling jugular catheters were checked at frequent intervals for patency and were used for injection of glucose and subsequent blood sampling. Dogs were maintained in a controlled kennel environment and were fed Purina dog chow. The animals were fasted overnight before the glucose injections. During the experiments, the animals were conscious and relaxed and were resting on a warm laboratory bench. Experiments consisted of a single injection (over a 1-min period) of a low (100 mg/kg), intermediate (200 mg/kg), or high (300 mg/kg) dose of glucose (α-D-glucose, Mallinkrodt) followed by blood sampling beginning 1.5 min later, at intervals of 1 min or more for a 60-min period. The catheter was flushed with sufficient saline after glucose injection to prevent possible contamination of samples by the injectate. Thirty-two blood samples were collected in each experiment: samples were taken every minute from 1.5 to 17.5 min, every 2.5 min until 50 min, and at 55 and 60 min after injection. Sampling tubes containing
NaF were quickly centrifuged to separate plasma, which was frozen for later measurement of glucose and insulin. Plasma glucose was measured in duplicate on the Beckman glucose analyzer; insulin was measured by radioimmunoassay according to the Herbert technique (17) against a porcine insulin standard. Assay statistics were as follows: coefficients of variation; glucose (± 1.5%), insulin (± 7%).

Data Analysis

A series of distinct mathematical models of utilization was proposed (see MODELS AND RATIONALE) to account for the effect of the changing plasma glucose and insulin on the glucose-disappearance curves. Glucose was represented as the measured value and insulin as the deviation from the preinjection basal value. Parameter values were estimated by using the nonlinear least-squares technique of Marquardt (21). Some models of glucose utilization were insulin dependent. In such cases the insulin data were supplied to the estimation algorithm (together with initial estimates of the parameters) and the time course of glucose concentration was predicted. It was assumed, for purposes of estimation, that the basal values of glucose and insulin were reestablished by 120 min. The goodness-of-fit of a given model was described, as usual, in terms of the sums of squares of the differences between the observed and predicted values (SSR; see Ref. 3). In addition, SSR was compared with the estimated contribution of error in glucose measurement (SSM). Errors in glucose measurement were assumed to be independent and Gaussian, with 0 mean, and with a total measurement error of 2.0%. Errors in insulin measurement were not explicitly considered. The estimation algorithm provided, together with parameter values, an evaluation of parameter precision. (The precision of estimation of an individual parameter for a given model for one experiment is provided by the diagonal elements of the covariance matrix (inverse of the information matrix) that is calculated along with parameter estimation (15).)

We considered a parameter to be nonidentifiable if the fractional standard deviation of the parameter estimates (when fitting a single experiment) exceeded 100%.

Along with other criteria for comparing models, we applied the criterion of Akaike (4) to compare the ability of three linear models to simulate the glucose data (I, IV, V; see MODELS AND RATIONALE). This criterion simultaneously takes into account the relative contributions of goodness-of-fit and the number of parameters in evaluating the worth of competing model structures. For a given model and a single experiment, this criterion is calculated as

$$\frac{1}{2}AIC = (N/2) \ln SS_R + n$$

where \(N\) is the number of data points, \(n\) is the number of estimated parameters, and \(\frac{1}{2}AIC\) is the variable of Akaike (4).

RESULTS

Glucose Injection

Nine experiments were used for model evaluation: four at the highest dose, two at the intermediate, and three at the low dose (Table 1). Glucose and insulin values (for 7 experiments only; animal 1) are shown in Fig. 1. At each dose, the glucose values are plotted on the upper panel; for comparison, the insulin curves, which differed markedly from each other, are plotted below. At the initial sampling time, 1.5 min after the injection, the glucose values were maximal: 259 ± 11, 236 ± 8, and 171 ± 10 (SE) mg/dl at the three doses (Table 1). At 5.5 min after the beginning of injection, glucose had fallen to 200 ± 6, 158 ± 1, and 125 ± 5 mg/dl, respectively, values at or near the renal threshold (26). 1 There was an average 38 ± 4 mg/100 ml increase in plasma glucose at 5.5 min, per 100 mg/kg injected, and the dose-response relationship was approximately linear (\(r = 0.96\)).

Following the initial peak, glucose concentration fell rapidly, reaching the basal value by 27.5 min. In two experiments (7 and 9) no undershoot in the glucose concentration was observed.

In contrast to the rather similar and well-behaved nature of the glucose response, insulin responses were extremely variable (Fig. 1) although the well-known "early peak" (12) was usually observed. However, multiple peaks in insulin were frequently observed, particularly at the high and intermediate doses of glucose. In no case did the first peak in plasma insulin occur before 2.5

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1 Although urine glucose was not measured, it was assumed that significant glucose would not spill during the short period glucose exceeded the expected \(T_{max}\) (at the highest dose) after 5.5 min, and disappearance of glucose via renal excretion was not included in any of the 7 models evaluated.
FIG. 1. Responses of plasma glucose and insulin to 3 glucose doses in a single dog: injection was begun at 4.5 min and lasted about 1 min. Glucose samples at 1, 2, and 3 min were not used for analysis; all insulin values were used. Insulin is plotted below as it is viewed as input to system producing and utilizing plasma glucose.

TABLE 2. Models of glucose utilization

<table>
<thead>
<tr>
<th>Model</th>
<th>Insulin Dependence</th>
<th>Compartments</th>
<th>Linear</th>
<th>Total Parameters</th>
</tr>
</thead>
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<tr>
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<td>1</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>V</td>
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<td>VI</td>
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<tr>
<td>VII</td>
<td>+</td>
<td>1</td>
<td>2</td>
<td>No</td>
</tr>
</tbody>
</table>

Seven distinct models of glucose uptake were proposed to account for the observed glucose kinetics (Table 2, Figs. 2 and 3). The structures were carefully chosen to allow for comparison between classical models and alternative propositions and to establish the limitations of the systems-identification approach in quantifying physiological parameters of glucose regulation.

To evaluate the importance of insulin as a factor in determining the kinetics of glucose disappearance, we examined three models in which glucose disappearance was dependent on glucose only. The results from these models could then be compared with the remaining four models (IV-VII) that assume explicit relationships between insulin, glucose, and glucose fluxes. Thus, for estimating parameters for models IV-VII, the (measured) time course of insulin was supplied as a model input.

The seven models depicted in Figs. 2 and 3 and summarized in Table 2 are described as follows.

**Insulin-Independent Models**

*Model I.* It is assumed in this model that glucose production is constant, that glucose distributes in a single compartment, and that the rate of glucose utilization is a linear function of the plasma glucose concentration. Thus, the parameter $k_1$ in this model (Fig. 2) represents the classical diagnostic glucose disappearance term KG, which is obtained from a semilogarithmic plot of glucose disappearance kinetics. The success of this model is therefore related to the acceptability of KG as a measure of the glucose disappearance rate.

*Model II.* This model is identical to model I, except that glucose utilization is a saturable process that obeys Michaelis-Menten kinetics and depends on the plasma glucose concentration.

*Model III.* The third model assumes two-compartment glucose distribution. Disappearance from either compartment is linearly dependent on glucose concentration in that compartment. Glucose production is constant. Multicompartmental glucose distribution has been widely suggested (cf. Refs. 19 and 23).
Insulin-Dependent Models

Model IV. Glucose disappearance in this model is linearly dependent on both the plasma glucose and insulin concentrations. Glucose distributes in a single compartment, and the production is assumed constant. The relationships among insulin, glucose, and glucose disappearance used in this model were first proposed by Bolle (10), and have been assumed in a substantial fraction of those studies that have used system identification to analyze glucose kinetics for clinical purposes (1, 2, 10, 13, 14, 25). The extent of success of model IV to account for disappearance relates to the potential applicability of the Bolle (10) model (and its descendants) for purposes of diagnosis.

Model V. This model assumes that glucose uptake is directly dependent on the concentration of insulin, not in plasma, but in a second compartment of insulin distribution remote from plasma. This proposition is based on the studies of Insel and his colleagues (19, 28) and is consistent with the existence of a remote receptor pool that is intimately involved in the action of insulin (30). In this model insulin (I(t)) enters the remote compartment (I'), and I' increases glucose disappearance in a linear, independent fashion. Glucose also accelerates its own disappearance independent of insulin, and glucose production is constant.

In models I through V glucose production was assumed to be constant at all times. Because it has long been known that insulin inhibits glucose production, we introduced models VI and VII (see below), in which this interaction was included. Two approaches were used. In VI, glucose production and hepatic glucose uptake were lumped together as net hepatic glucose balance. In model VII an alternative approach was used, i.e., hepatic and peripheral glucose utilization were lumped together, and absolute glucose production (R) (cf. Ref. 18) was represented explicitly.

Model VI. In this model, the rate of change of glucose is the difference between the net hepatic glucose balance, B (which may take on positive (production) or negative (uptake) values), and the disappearance of glucose into peripheral tissues only (U_p). We have previously shown that hepatic glucose balance varies according to a relation of the form (8):

\[ B = B_0 - (k_5 + k_6)G \]

where B is net glucose balance; and B_0 is the net balance expected when plasma glucose concentration is extrapolated to 0 (see Fig. 5, Ref. 8). It is assumed that the insulin acts from a remote compartment, as in model V.

For glucose utilization we may write a similar expression

\[ U_p = (k_1 + k_4)G \]

where “remote” insulin is envisioned to increase the mobility of glucose across the cell membrane, and this motility potentiates glucose disappearance.

Model VII. In this model, we explicitly represented “absolute” hepatic glucose production (R_a) and the inhibition of this rate by remote insulin. Utilization (which, in this case, includes hepatic and peripheral) is described by a similar nonlinear function as in model VI.

Comparison of Models I–VII

Criterion 1: Identifiability

Each of the seven models was individually fitted to the
nine experiments by using parameter estimation as described in METHODS. Parameters of models II and VII were clearly not identifiable (Table 3) as indicated by the great uncertainty in the estimates of the parameters. All three characteristic parameters of model II and three of the five characteristic parameters of model VII could not be estimated within 100% of the parameter value. These models were therefore eliminated from further consideration. One parameter of model III was not identifiable (\( p_5 \)); however, because the remaining parameters of model III could be estimated, this model was not removed from consideration at this stage. The mean estimates of the parameters for the five remaining models for all nine experiments are given in Table 4.

**Criterion 2: Meaning of Parameters**

It was important to consider whether the estimated parameters of the remaining models could be interpreted in a physiologically meaningful way. Close comparison of the estimates shown in Table 4, with the definition of parameters in Figs. 2 and 3, shows that in the case of model III the estimated value of one parameter is physiologically absurd. Parameter \( p_2 \) of model III was negative for all nine experiments, and its value \((-1.25 \pm 0.44 \times 10^{-2})\) was significantly less than 0 (df = 8; \( t = -2.85; p < 0.025 \)). A negative \( p_2 \) implies that, as glucose increases in the remote compartment, it will decrease the mass flux from \( G_2 \) to \( G_1 \), in violation of the law of mass action. This paradoxical prediction of model III results from the fact that the role of insulin was ignored in this model, and the inverse dependence on \( G_2 \) of \( G_1 \) flux compensates for the absence of consideration of the time-dependent insulin effects on glucose utilization.

**TABLE 3. Accuracy of parameter estimates**

<table>
<thead>
<tr>
<th>Model</th>
<th>Identifiability</th>
<th>( p_1 )</th>
<th>( p_2 )</th>
<th>( p_3 )</th>
<th>( p_4 )</th>
<th>( p_5 )</th>
<th>( p_6 )</th>
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<tr>
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<td>16†</td>
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</tr>
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</table>

* Average for 9 experiments. † Represents initial condition (G(0)); not a characteristic parameter of the model.

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**FIG. 3.** Four proposed insulin-dependent models of glucose metabolism. \( I(t) \), time course of plasma insulin supplied to model; \( I' \), concentration of insulin in a compartment remote from plasma. Equations for model VI are derived as described in text. \( G_0 \), extrapolated hepatic glucose production at 0 glucose concentration.
The inconclusive positiveness of this parameter.

crease glucose uptake. Because \( p_z \) is not significantly greater than 0 at the \( P < 0.05 \) level (df = 8; \( t = 0.92 \), \( P > 0.1 \)), we do not reject model IV at this stage because of the inconclusive positiveness of this parameter.

A second paradox is the positive sign of \( p_2 \) in model IV. This implies that an increase in insulin should decrease glucose uptake. Because \( p_2 \) is not significantly greater than 0 at the \( P < 0.05 \) level (df = 8; \( t = 0.92 \), \( P > 0.1 \)), we do not reject model IV at this stage because of the inconclusive positiveness of this parameter.
model VII) includes insulin inhibition of liver glucose production (represented as glucose balance), whereas model V assumes (incorrectly) constant production in the face of elevated insulin. We therefore selected model VI, of all seven models considered, as the best, in that it has acceptable properties from the identification point of view and it is consistent in broad terms with the known physiology of glucose metabolism.

The ability of model VI to describe glucose data from three typical experiments with high, medium, and low doses of injected glucose is shown in Fig. 4. Also shown are the predicted time courses of the variable designated X, which is proportional to the concentration of insulin in the remote compartment.

**INSULIN SENSITIVITY**

It is our goal to define insulin sensitivity formally, in mathematical terms, and estimate it using the parameters of model VI.

**Definition**

Glucose effectiveness (E) is defined as the quantitative enhancement of glucose disappearance due to an increase in the plasma glucose concentration

$$E = -\frac{\partial G}{\partial t}$$

(4)

where $\dot{G}$ is the time rate of change of the plasma glucose concentration $[G]$.

Insulin sensitivity is then defined (in steady state (SS)) as the quantitative influence of insulin to increase the enhancement of glucose of its own disappearance

$$S_I \equiv -\frac{\partial E_{SS}}{\partial I_{SS}}$$

(5)

**Insulin Sensitivity Index**

It is of interest to estimate insulin sensitivity from the parameters of model VI because 1) model VI appears to be a reasonable representation of glucose kinetics, and 2) the parameters of model VI can be readily determined from the insulin and glucose response to a single glucose injection. Applying the definitions of Eqs. 4 and 5 to model VI (see APPENDIX) yields the insulin sensitivity index ($S_I$)

$$S_I = \frac{p_3}{p_2}$$

(6)

where $p_3$ and $p_2$ are parameters of model VI defined in Fig. 3, with mean values (for dogs) listed in Table 4. $S_I$ is expressed as min⁻¹/(µU/ml) (fractional glucose disappearance per insulin concentration unit).

Table 8 lists the calculated values of $S_I$ for the (grouped) low- and intermediate-dose experiments and for the high-dose (300 mg/kg) experiments. In addition, glucose at the 300 mg/kg dose was administered in four experiments in three additional animals, and the calcu-

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**TABLE 7. Criteria for acceptability of models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Identifiability</th>
<th>Parameter Absurdity</th>
<th>Goodness-of-Fit</th>
<th>Acceptance</th>
</tr>
</thead>
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<tr>
<td>II</td>
<td>NA</td>
<td>Not considered</td>
<td>Not considered</td>
<td>No</td>
</tr>
<tr>
<td>III</td>
<td>?</td>
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<td>Not considered</td>
<td>No</td>
</tr>
<tr>
<td>IV</td>
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<td>?</td>
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</tr>
<tr>
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<td>OK</td>
<td>OK</td>
<td>Yes</td>
</tr>
<tr>
<td>VI</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
<td>Yes</td>
</tr>
<tr>
<td>VII</td>
<td>NA</td>
<td>Not considered</td>
<td>Not considered</td>
<td>No</td>
</tr>
</tbody>
</table>

NA, not acceptable.

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**FIG. 4. Ability of model VI to predict falling plasma glucose concentration for 3 sample experiments. Closed circles represent fit of model with best parameter values for each experiment, open circles represent measured glucose data beginning at 4 min. Bottom curves are time course of insulin in a compartment remote from plasma that represents time course of insulin action. Glucose concentration at 120 min was assumed to be same as preinjection basal glucose.**
lateral results are included in Table 8. With the high dose, \( S_I \) could be calculated with a high degree of reproducibility (\( S_I = 7.0 \times 10^{-4} \) min\(^{-1}\)/\( \mu U/ml \); coefficient of variation = 24%). On the other hand, the reproducibility of the \( S_I \) estimate for the lower groups was much worse (coefficient of variation = 86%) although the estimate of \( S_I \) from the combined lower-dose group was not different from the \( S_I \) value estimated from the high-dose group (df = 11; \( P > 0.06 \)). It is clear from the variation in the estimates of the individual parameters, \( p_3 \) and \( p_4 \), that the variation in the \( S_I \) estimate for the lower-dose group resulted from a wide variation in the estimate of parameter \( p_3 \) from the dynamic response to lower doses of glucose. The estimate of this parameter (equal to the disappearance parameter \( k_0 \)) for insulin in the remote compartment (\( I' \), Fig. 3) is very sensitive to the “undershoot” dynamics of glucose (Table 1); and the greater prevalence of this undershoot is presumably responsible for the more reproducible estimate of \( p_3 \) in the high-dose experiments.

Thus, it is possible to obtain a precise estimate of the insulin sensitivity index from parameters of model VII, identified from the dynamic data obtained from an intravenous 300 mg/kg glucose injection.

**DISCUSSION**

Numerous approaches have been suggested for more effectively delineating the specific tissue changes responsible for glucose intolerance. In particular, it could be of great benefit to quantitatively differentiate in a given pathological situation the extent to which \( \beta \) cell insensitivity to glucose or peripheral insulin insensitivity (“resistance”) is responsible for the inability to dispose of a glucose load. These studies attempt to quantify insulin sensitivity by employing a simple dynamic perturbation, i.e., intravenous glucose injection, and by using the observed system dynamics to identify the parameters of a model of glucose metabolism.

Many workers have proposed simple models of the system regulating the blood glucose concentration (1, 2, 5, 10, 13, 14, 25) and have attempted to relate the model parameters to insulin secretory function and insulin action. Such attempts have frequently been confounded by the inherent difficulty in representing the nonlinear process of insulin secretion. Glucose-stimulated insulin secretion is difficult to model and requires multiple parameters (9, 11, 16, 20), and if the response to several secretagogues or prolonged stimulation is to be modeled, even more complex, nonlinear, and multiparametric models are required (7).

The novelty of the present study is that we circumvented the difficulty of modeling the \( \beta \)-cell response by treating the measured time course of insulin concentration as a model input. This approach allowed us to treat the system as “open-loop” and analyze the interactive effects of insulin and glucose on glucose disappearance without having to simultaneously analyze insulin secretion and without suppressing insulin secretion or manually controlling the blood glucose concentration by variable infusion. It was hoped that a quantitative measure of insulin sensitivity would emerge from this modeling effort because the ability to estimate insulin sensitivity by a simple dynamic perturbation of the system would certainly simplify the study of the physiological regulation of insulin sensitivity in vivo and should be useful in clinical studies.

We systematically investigated seven distinct physiologically based models of glucose disappearance to identify the one or more models that were able to describe the experimental data well with the smallest set of identifiable and meaningful parameters.

Five models (I, II, III, IV, and VII) were judged unacceptable by the criterion of parameter identification. The first three models failed to perform well, presumably because they included the erroneous implicit assumption that glucose disappearance is independent of insulin. Thus identification may be difficult when flagrantly incorrect assumptions are incorporated into the model structure.

The failure of model IV is of particular interest because it includes the dependence of glucose disappearance on plasma insulin. The formulation of glucose disappearance in model IV (i.e., disappearance as a linear function of plasma insulin and glucose) was first introduced by Bolin (10) and has since been implemented by various groups who have identified the parameters of glucose metabolism for clinical purposes. The introduction of a remote compartment for insulin action (I) into those earlier models might have improved their ability to describe the available data.
**Model VII**, a reasonable representation of glucose kinetics, was not identifiable from the available data, indicating the difficulty of separately quantitating (from glucose-tolerance test data) insulin inhibition of glucose production on the one hand and the potentiation of hepatic and peripheral glucose uptake on the other. Nevertheless, we were able to include insulin inhibition of glucose production as a component of net hepatic glucose balance in model VI.

The improvement in identifiability between model IV on the one hand and models V and VI on the other came about by the introduction of an insulin compartment (I') remote from plasma on which glucose disappearance is dependent. This dependence was first demonstrated by Insel, Sherwin, and their colleagues (19) in their kinetic analysis of glucose clamp studies. Our studies strongly confirm the earlier analyses; this agreement with their studies illustrates that artificially maintaining a constant glucose concentration is not required to deduce the steady-state relationship between insulin and glucose uptake. The glucose-clamp studies clarified the effect of insulin on glucose disappearance when glucose was constant and close to a normal fasting level; the present technique extends beyond that limited objective by distinguishing between possible alternative quantitative representations of the interactive effects of glucose and insulin on disappearance while both signals are elevated and changing with time.

The choice of model VI over V for estimating sensitivity was made because VI is the more realistic model physiologically in that it includes the insulin inhibition of hepatic glucose balance. Thus, we were able to define the insulin sensitivity index, SI, and estimate it from model VI as a function of system parameters that are representative of the sensitivity of both the liver and the periphery to insulin.

We have formulated an unambiguous, mathematically precise definition of insulin sensitivity. In model VI, SI is independent of glucose and insulin, and equal to \((-p_3/p_2)\). By definition of \(p_1\) and \(p_2\) therefore (Fig. 3), SI is equal to \((k_2/k_3)(k_4 + k_5)\), and I' (or X) is representative of the time course of insulin action. Thus, it is possible to suggest that the remote insulin compartment, I', represents a receptor “pool” for insulin bound to peripheral tissues (30), for which the forward binding constant times the number of binding sites is related to \(k_3\), the dissociation constant is \(k_4\), and the “effectiveness” of the insulin-receptor complex is related to both \(k_4\) and \(k_5\). If this suggestion were valid, SI would represent a composite measure of the amount of receptor-bound insulin and the combined effectiveness of bound insulin on glucose efflux and hepatic glucose balance.

It is important to compare the insulin sensitivity index, estimated by our technique, with the insulin effectiveness parameter previously introduced by Insel et al. (19). Their technique involves the identification of 12 parameters of a combined glucose (“hot” and “cold”) and insulin model. It was necessary to perform three separate experiments on a single subject to determine the parameters for that single individual: 1) the pulse injection of insulin to identify a three-compartment model of insulin kinetics, 2) the primed continuous infusion or pulse injection of \(^{14}C\)glucose for determination of the transfer coefficients of a three-compartment glucose model, and 3) the “clamping” of the plasma glucose concentration by variable glucose infusion to clarify the relationship between the insulin concentration in three compartments and the rate of disappearance of glucose. They defined the insulin effectiveness as the derivative of glucose utilization with respect to the insulin concentration in a compartment remote from plasma because evidence was presented showing that utilization was dynamically differentiated from plasma insulin and the temporal pattern of utilization bore some resemblance to the time course of remote insulin. Obviously, the technique presented here is sufficiently simple to be performed on a routine basis as it requires only the performance of an intravenous glucose-tolerance test and the accurate identification of a five-parameter model. We may therefore compare the sensitivity estimates of the Insel technique with our own. By a simple conversion of their effectiveness definition to ours, one may calculate that they report an average sensitivity index of \(12 \pm 7 \times 10^{-4} (\pm SD) \min^{-1}/(\mu U/ml)\), for six human subjects, surprisingly close to the average \(7.0 \pm 1.7 \times 10^{-4} (\pm SD) \min^{-1}/(\mu U/ml)\), which we found for dogs using 300 mg/kg glucose (Table 8). Therefore, it appears possible to obtain a reasonable estimate of insulin sensitivity with a much simpler experimental protocol and a model greatly reduced in size.

Despite the similarity of these estimates, it is important to recognize a fundamental difference between the insulin effectiveness of Insel et al. (19) and the sensitivity index proposed in our study. In their experiments, sensitivity is limited to the lumped effect of insulin on glucose uptake by periphery and liver because hepatic glucose production during glucose clamping and insulin infusion is at a constant level below the fasting value. Our index includes the effect of insulin not only to augment glucose uptake by periphery and liver, but also to inhibit hepatic glucose production. The similarity of the sensitivity estimates of the two groups may indicate that the sensitivity index estimate is dominated by the effect of insulin on glucose uptake.

SI is attractive in that it is normalized to body size, is independent of the plasma glucose concentration, and is based on glucose disappearance as a function of insulin in plasma. Thus, this has the potential for comparing individuals of varying size, weight, and body composition. In fact, due to the generosity of Drs. Ferrannini, Navalesi, and Pilol of the University of Pisa, Italy, we have been able to obtain plasma glucose and insulin measurements on normal human subjects whose blood was sampled frequently after intravenous glucose injections (330 mg/kg body wt). SI for this group of normal subjects was 6.5 ± 3.9 (SD) \(\times 10^{-4} \min^{-1}/(\mu U/ml)\), and the SI value for normal human subjects appears to be similar to the estimated value in normal dogs, given a similar intravenous glucose load.

The meaning of SI can be illustrated by the following example. A sensitivity index of 0.00070 min\(^{-1}\)/(\mu U/ml) by assuming sensitivity equal to B in Eq. 7 of Ref. 19; assuming \(L/L_i = 2\) (Fig. 2, Ref. 19) and \(M_i = 5\) g (Table 3, Ref. 19).
fractional glucose disappearance. Of course, it must be understood that i) this index may only apply over a limited range of glucose and insulin concentration, and ii) glucose disappearance in this sense refers to all the combined effects of glucose to lower the plasma glucose concentration (i.e., inhibition of production, and augmentation of uptake by liver and periphery).

Thus, using model VI, it appears possible to estimate insulin sensitivity with good precision, from the response to a simple intravenous glucose injection. The estimated value of $S_0$ appears to characterize the responses to different glucose doses and may be characteristic of a normal population of animals. Future experimental studies, in which insulin sensitivity is simultaneously estimated in different ways, are required to validate the proposed technique and to determine whether this technique is sufficiently sensitive to be of use in monitoring changes in insulin sensitivity (possibly receptor number) that may occur in altered metabolic states, such as starvation (6), exercise (29), and (in man) maturity-onset diabetes mellitus.

**APPENDIX**

**Estimation of Insulin Sensitivity for Model VI**

Applying the definition of $S$ to model VI (Eq. 5, Fig. 3), we can say that, because

$$G = (p_1 - X)G + p_1$$

then (by Eq. 4)

$$E = X - p_1$$

Also (by Fig. 3), at steady state

$$X_{ss} = \frac{p_3}{p_1} I_{ss}$$

so that

$$E_{ss} = \frac{p_3}{p_1} I_{ss} - p_1$$

Therefore, by Eq. 5, we define the insulin sensitivity index

$$S_t = \frac{p_3}{p_1}$$

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