# Computer model for mechanisms underlying ultradian oscillations of insulin and glucose

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STURIS, JEPPE, KENNETH S. POLONSKY, ERIK MOSEKILDE, AND EVE VAN CAUTER. *Computer model for mechanisms underlying ultradian oscillations of insulin and glucose.* Am. J. Physiol. 260 (Endocrinol. Metab. 23): E801–E809, 1991.—Oscillations in human insulin secretion have been observed in two distinct period ranges, 10–15 min (i.e., rapid) and 100–150 min (i.e., ultradian). The cause of the ultradian oscillations remains to be elucidated. To determine whether the oscillations could result from the feedback loops between insulin and glucose, a parsimonious mathematical model including the major mechanisms involved in glucose regulation was developed. This model comprises two major negative feedback loops describing the effects of insulin on glucose utilization and glucose production, respectively, and both loops include the stimulatory effect of glucose on insulin secretion. Model formulations and parameters are representative of results from published clinical investigations. The occurrence of sustained insulin and glucose oscillations was found to be dependent on two essential features: *1*) a time delay of 30–45 min for the effect of insulin on glucose production and *2*) a sluggish effect of insulin on glucose utilization, because insulin acts from a compartment remote from plasma. When these characteristics were incorporated in the model, numerical simulations mimicked all experimental findings so far observed for these ultradian oscillations, including *1*) self-sustained oscillations during constant glucose infusion at various rates; *2*) damped oscillations after meal or oral glucose ingestion; *3*) increased amplitude of oscillation after increased stimulation of insulin secretion, without change in frequency; and *4*) slight advance of the glucose oscillation compared with the insulin oscillation. Although these findings do not exclude the existence of an intrapancreatic ultradian pacemaker, they do suggest that the existence and properties of the 100- to 150-min oscillations in insulin secretion and glucose levels observed in normal humans may be entirely accounted for by the major dynamic characteristics of the insulin-glucose feedback system, with no need to postulate the existence of such a pacemaker.

feedback loops; delays; mathematical model; glucose regulation; insulin secretion; nonlinearity

A NUMBER OF STUDIES have established that the dynamics of insulin secretion are complex, involving at least two oscillatory modes with distinctly different periodicities. Oscillations with a period ranging between 8 and 15 min have been most extensively studied (10, 13, 15, 18, 19, 33). However, as early as 1923, Hansen (14), in a series of pioneering studies, observed oscillations in plasma glucose and suggested that these rapid glucose fluctuations were superimposed on larger oscillations of lower frequency. During the past two decades, studies in dogs (5, 20, 22) and in humans (17, 23, 25, 31, 32, 36) have indeed demonstrated the existence of ultradian oscillations in glucose and insulin with periods of 50–200 min.

The rapid 8- to 15-min insulin oscillations have been most clearly observed in monkeys and dogs (10, 15). In humans, they have appeared less consistently, and when detectable, they have been poorly correlated with glucose changes. In these human studies, the amplitude of the insulin oscillations has been small, often averaging only 1–2 $\mu$U/ml (18, 19), whereas average amplitudes of $<1$ mg/dl have been reported for glucose (13, 18, 19). Studies with the isolated perfused canine pancreas (33) have suggested that the rapid oscillations of insulin result from the activity of an intrinsic pancreatic pacemaker.

Large amplitude ultradian oscillations of plasma glucose and insulin levels that occur in humans approximately every 120 min have been observed under a number of physiological conditions: after ingestion of meals (23, 25), after oral glucose (17), during continuous enteral nutrition (32), and during constant intravenous glucose infusion (31, 36). Examples of each of these previous observations are illustrated in Fig. 1. Furthermore, ultradian oscillations with smaller amplitudes have also been observed during fasting (25). Studies by Simon et al. (32), involving sampling at 2-min intervals over an 8-h period, have clearly demonstrated that the ultradian oscillations do not represent an artifact of the 10- to 15-min oscillations due to infrequent sampling. Indeed, the rapid variations of insulin were found to be superimposed on the ultradian oscillations, which are of larger amplitude.

The dynamic properties of the ultradian oscillations so far identified include *1*) the oscillations are self-sustained when the stimulus is presented continuously, such as during constant glucose infusion (31, 36) or continuous enteral nutrition (32); *2*) the oscillations are

 

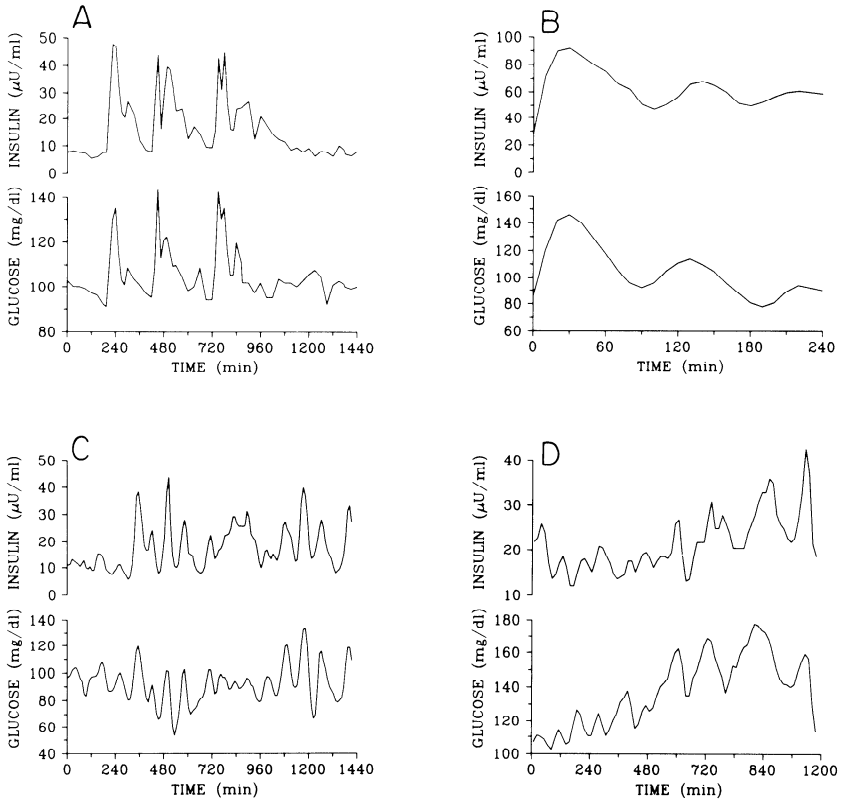


FIG. 1. Oscillations of insulin and glucose observed during ingestion of 3 meals [*A*; from Polonsky et al. (25)], during oral glucose [*B*; adapted from Kraegen et al. (17)], during continuous enteral nutrition [*C*; adapted from Simon et al. (32)], and during constant glucose infusion [*D*; from Shapiro et al. (31)]. These profiles are from 4 different subjects. Data obtained during continuous enteral nutrition and constant glucose infusion were smoothed with 2-point moving average before profiles were plotted.

damped when the stimulus is a single discrete event, such as oral glucose administration (17) or meal ingestion (23, 25); *3*) there is a high correlation between plasma glucose and plasma insulin oscillations (25, 31, 32, 36); *4*) glucose peaks tend to precede insulin peaks by 10–20 min (36); and *5*) an increased stimulus leads to an increase in amplitude of the oscillations, whereas the frequency remains unchanged within detectable limits (36). To the best of our knowledge, none of the models of the insulin-glucose feedback regulation proposed so far can account for the existence and properties of these ultradian oscillations.

Although the origin of the ultradian oscillations is still unknown, a number of possible mechanisms can be ruled out on the basis of experimental observations. First, the oscillations do not result from intermittent nutrient absorption from the gastrointestinal tract, since they persist during constant intravenous glucose infusion. Second, the oscillations are not dependent on the central neurogenic connections of the pancreas, since preliminary studies performed by our group (26) show that the oscillations persist in patients after segmental pancreas transplantation. Finally, analysis of simultaneous cortisol and glucagon changes have failed to show correlations with the insulin and glucose oscillations (31), suggesting that these counterregulatory hormones do not play a role in their genesis. Two major hypothetical mechanisms remain: *1*) the ultradian oscillations originate from an independent intrapancreatic pacemaker, and glucose is passively entrained to oscillate according to the changes in insulin levels; and *2*) the oscillations are a result of the feedback between glucose and insulin, and glucose thus plays an active role in their generation.

In this study, we show that a parsimonious mathematical model of glucose-insulin interactions, incorporating the findings of recent clinical studies, can account for the oscillations and their properties as observed in humans. The purpose of the model is not to predict the exact time course of glucose and insulin in individual subjects but rather to provide a plausible mechanism for the genesis of the oscillations. Our analysis suggests that the ultradian oscillations in insulin secretion and glucose levels could originate from the interactions between glucose and insulin and that it is not necessary to postulate the existence of an intrapancreatic pacemaker to account for their existence.

*Glossary*

| | |
|---|---|
| $E$ | Rate constant for exchange of insulin between plasma and remote compartment, l/min |
| $f_1(z)$ | Insulin secretion, function of glucose |
| $f_2(z)$ | Insulin-independent glucose utilization, function of glucose |
| $f_3(z)$ | Insulin-dependent glucose utilization, function of glucose |
| $f_4(y)$ | Insulin-dependent glucose utilization, function of insulin |
| $f_5(h_3)$ | Glucose production, function of insulin |
| $h_1$, $h_2$, $h_3$ | Variables representing delay process between plasma insulin and glucose production, mU |
| I | Exogenous glucose delivery rate, mg/min |
| $t_1$ | Time constant for plasma insulin degradation, min |
| $t_2$ | Time constant for remote insulin degradation, min |

| | |
|---|---|
| $t_3$ | Delay time between plasma insulin and glucose production, min |
| $V_1$ | Volume of insulin distribution in the plasma, liters |
| $V_2$ | Volume of remote insulin compartment, liters |
| $V_3$ | Volume of glucose space, liters |
| x | Plasma insulin, mU |
| y | Remote insulin, mU |
| z | Glucose, mg |

## METHODS

### *Modeling Procedure*

The general modeling approach we used includes the following steps: *1*) definition of the structure of the model by means of causal loop and flow diagrams, *2*) definition and specification of functions and parameters, *3*) conversion into differential equations, and *4*) numerical simulation of the equations.

*Structure of the model.* It is well known that elevations of blood glucose concentration increase insulin secretion and that insulin enhances glucose uptake and inhibits glucose production. In addition, hyperglycemia per se increases glucose utilization and suppresses glucose production. These interactions can be schematically represented as a causal loop diagram (Fig. 2*A*) consisting of four negative feedback loops. Together these loops regulate the amounts of insulin and glucose in the body toward an equilibrium, which is not necessarily stable. The system contains at least two delays with physiologically important consequences, and negative feedback structures with one or more time delays can exhibit either stable or unstable (i.e., oscillatory) dynamics. One delay is associated with suppression of glucose production by insulin and, conversely, the recovery of this process when insulin decays (8, 27). The other delay relates to the fact that the biological action of insulin is correlated most closely with the concentration of insulin in a slowly equilibrating interstitial compartment rather than with the plasma insulin concentration (3, 38). Figure 2*B* shows a detailed flow diagram of the model. It has three main variables: the amount of glucose in the glucose space, the amount of insulin in the plasma, and the amount of insulin in the interstitial fluid. In addition, there are three other variables representing the delay between insulin and glucose production. Altogether, the model has six state variables. In the following, the relations between the variables and the choice of parameter values are presented.

*Functions and parameters.* INSULIN SECRETION. Although pancreatic insulin secretion is a complex process that is incompletely understood, it is generally accepted that glucose is the most important insulin secretagogue. In response to intravenous glucose, when the plasma glucose concentration increases very rapidly, a typical biphasic secretion pattern can be observed (12). However, under more physiological conditions, the changes in glucose are smoother and the biphasic pattern of secretion disappears (12). In the model, we represent insulin secretion as a sigmoidal function of glucose concentration ($f_1$; Ref. 12; Fig. 3, *top left*). Insulin secretion

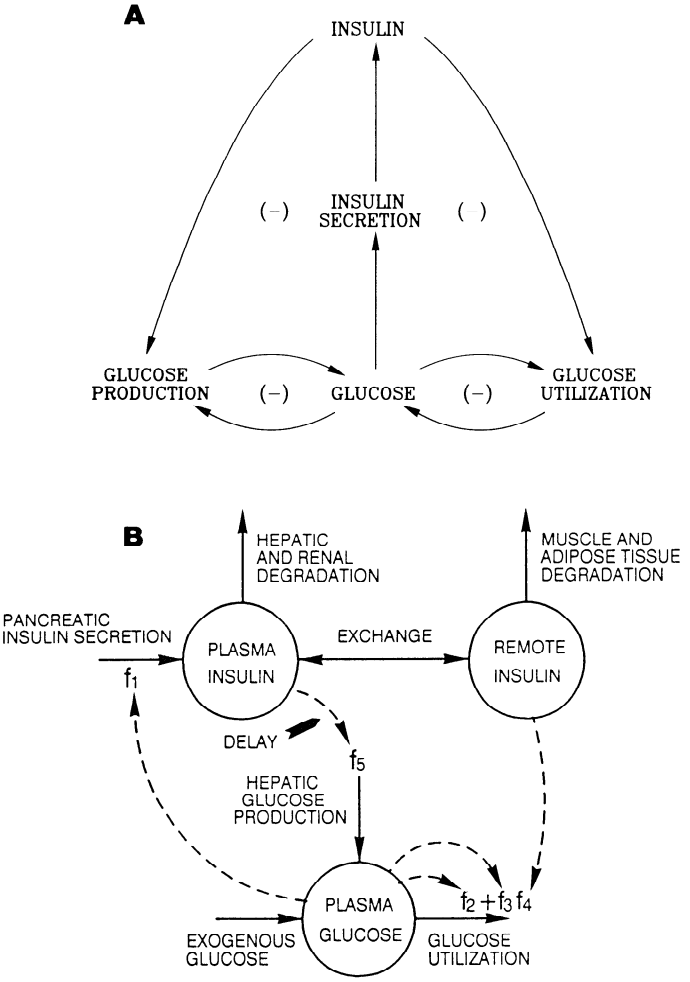


FIG. 2. *A*: causal loop diagram of interactions between glucose and insulin described in model. Four negative feedback loops are involved, namely, *1*) elevated glucose levels stimulate insulin secretion, and elevated insulin levels inhibit glucose production, which in turn lowers glucose levels (top left loop); *2*) elevated glucose levels stimulate insulin secretion, and insulin increases glucose utilization, which in turn diminishes glucose levels (top right loop); *3*) glucose inhibits its own production (bottom left loop); and *4*) glucose stimulates its own utilization (bottom right loop). *B*: flow diagram of model. Circles represent major state variables; solid arrows represent output flows, input flows, and rate of exchange; and dashed arrows denote functional relationships. See *Glossary* for definition of abbreviations.

rates of up to 100 mU/min (700 800 pmol/min) have been reported in nondiabetic subjects in studies involving ingestion of meals (23, 25) or constant glucose infusion (31). The maximum glucose concentrations observed in these studies were 150–200 mg/dl. On the basis of these observations, we assumed a saturating value of ~200 mU/min (1,500 pmol/min) for insulin secretion.

INSULIN DISTRIBUTION AND DEGRADATION. In the model, equilibration of insulin between plasma and interstitial fluid is assumed to be a passive diffusion process governed by the difference between insulin concentrations in the two kinetic compartments. We have chosen a transfer rate ($E$) between plasma and interstitial fluid of 0.2 l/min and set the plasma volume ($V_1$) at 3 liters. This is consistent with previous experimental data from our laboratory (24). The volume of the extravascular space ($V_2$) is estimated at 11 liters, and the removal of insulin from this space is assumed to follow first-order

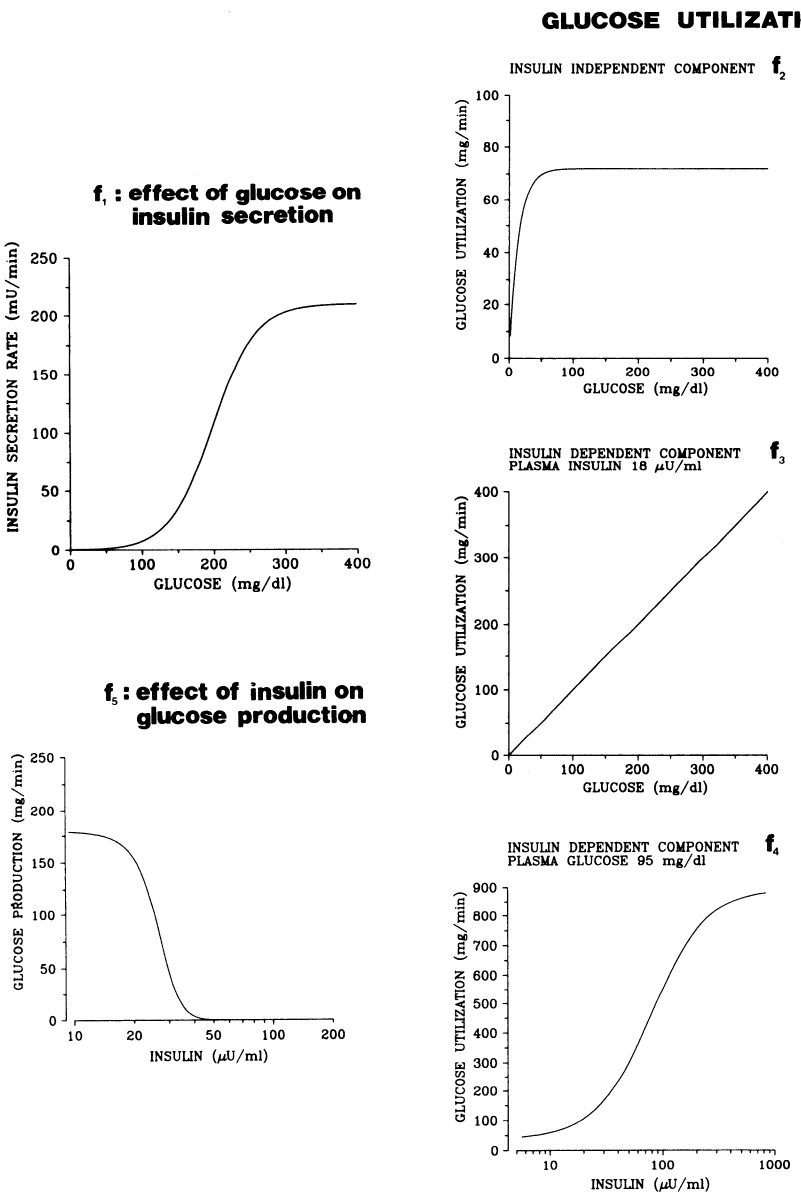


FIG. 3. Functional relationships used in model. See *Glossary* for definition of abbreviations.

kinetics with a half-life of 69 min ($t_2$ is the corresponding time constant), as suggested by Mosekilde et al. (21). For plasma insulin degradation, a single exponential decay with a half-life of 4 min ($t_1$, time constant) is used (24). These values imply the existence of a 3:2 gradient of insulin concentration between the plasma compartment and the interstitial compartment at equilibrium. The magnitude of this concentration gradient is in excellent agreement with experimental results (3, 38).

GLUCOSE DISTRIBUTION. Several different configurations have been suggested for the distribution of glucose (2, 3, 9, 35). For simplicity, and in agreement with other contemporary models (2, 3, 35), we chose to represent the glucose space as a single compartment. The volume of distribution ($V_3$) was assumed to be 10 liters. This estimation is in close concordance with values used in the Steele (34) equations.

GLUCOSE UTILIZATION. *Insulin-independent component.* In general, glucose utilization depends on both the concentration of glucose and insulin (3, 7–9, 11, 27, 29, 37, 38). However, brain utilization of glucose is independent of insulin (37). Except during hypoglycemia, this uptake is also independent of glucose levels. We used a function similar to that proposed by Turner et al. (35) to describe this component in the total utilization of glucose ($f_2$; Fig. 3, *top right*).

*Insulin-dependent component.* Verdonk et al. (37) have shown that there is a linear relationship between total glucose utilization and the glucose concentration over the normal physiological range. When brain glucose uptake is subtracted, this function passes through the origin, indicating that, over a range of insulin concentrations, insulin-dependent glucose uptake is proportional to glucose concentration. Figure 3, *middle right*, illustrates the function ($f_3$) used in the model to describe this relationship.

As shown by Rizza et al. (29), the dependence of glucose utilization on insulin concentration at steady state is a sigmoidal function with a logarithmic $x$-axis. In the present model, insulin-dependent glucose uptake was assumed to be a function of insulin in the extravascular space, as suggested by Bergman (3) and Yang et al.

(38). To account for the concentration gradient between the two compartments, this function has been adjusted so that at steady state it matches the relationship between plasma insulin and glucose utilization reported by Rizza et al. ($f_4$; Ref. 29; Fig. 3, *bottom right*). Brain glucose uptake has also been subtracted from this function. Several studies have investigated in vivo uptake of glucose at various insulin and/or glucose levels (6, 7, 11, 27, 29, 37). Those results indicate that the dependence of total insulin-dependent glucose utilization can be approximated by multiplying the functions describing the dependence on glucose and the dependence on insulin, respectively (i.e., $f_3$ and $f_4$ in Fig. 3). In our model, total glucose utilization thus consists of this product plus insulin-independent glucose utilization ($f_2$ in Fig. 3).

GLUCOSE PRODUCTION. Glucose may enter the circulation either by exogenous ingestion followed by absorption or by endogenous glucose production in the liver.

The regulation of hepatic glucose production is complex. It is known, however, that this process is regulated predominantly by the concentrations of insulin and glucagon. We did not include the glucagon concentration in the model as a separate parameter, since available data have failed to define a significant role for glucagon in generating the ultradian oscillations (31). On the basis of the findings by Rizza et al. (29), the function ($f_5$) illustrated in Fig. 3, *bottom left*, was selected to represent the effect of insulin on glucose production. This relationship implies that high insulin concentrations inhibit glucose production completely. At lower insulin concentrations, glucose output increases. As previously mentioned, the effect of insulin on glucose production is not immediate but involves a substantial time delay (8, 27). This delay was assumed to be of third order, implying that a chain of three intermediate variables links plasma insulin to glucose production. Introduction of state variables to represent delay processes is a commonly used mathematical modeling technique (16). The conceptual difference between instantaneous action and a third-order delay is illustrated in Fig. 4. Ideally, the actual biological processes that take place and that are responsible for the delay should be modeled, but the exact pathway of this insulin effect is unknown (28). It has been suggested (28, 38) that the effect of insulin is both direct and indirect and that insulin in part acts from the remote insulin compartment (38). Because this is still a somewhat open question, we settled for an empirical description that does not claim any particular pathway of the delay.

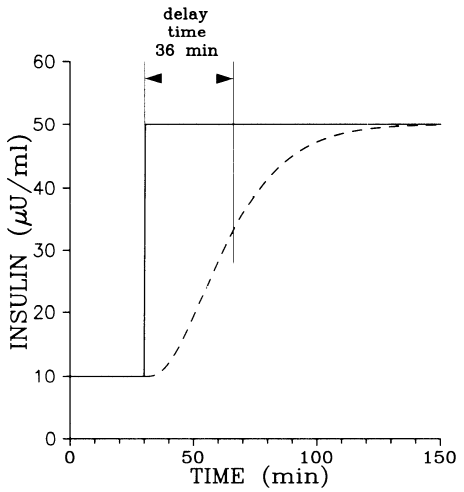


FIG. 4. Response to step increase in insulin level when third-order delay is used. Solid line, actual change in plasma insulin; dashed line, signal on which liver reacts. In this example, corresponding delay time is 36 min. Delay time of order $n$ is defined as $n$ times the transfer rate constant between $n$ compartments used to model delay.

On the basis of experimental findings by Prager et al. (27), a delay time of 36 min was chosen. When insulin is infused at three different rates under euglycemic conditions, this value of the delay time led to simulated times for half-deactivation and half-activation of glucose production that were, on average, within 12% of the reported experimental values (27).

Studies by Bergman and Bucolo (4) have indicated that glucose also plays an important role in determining net hepatic glucose balance by inhibiting its own hepatic production. We tested a version of the model in which the effect of glucose on hepatic glucose production is omitted as well as a version that includes this effect. When the absolute glucose level was assumed to play a role in glucose production, the dynamic properties of the model were similar to those observed when this effect of glucose was omitted. All subsequent simulations are based on the version of the model that does not include the effect of glucose.

*Differential equations.* From the flow diagram and the functions and parameters just delineated, a set of six nonlinear ordinary differential equations were derived. They are presented in the APPENDIX. Because of their nonlinear nature, the equations cannot be solved analytically, but by means of computer simulation, solutions can be obtained.

*Numerical simulations.* The set of differential equations was solved numerically using a sixth-order Runge-Kutta integration algorithm. In-house software was written in Pascal.

## RESULTS

### *Simulation of Constant Intravenous Glucose Infusion*

During constant glucose infusion, it has been demonstrated that the amplitude of the oscillations of insulin secretion is larger with higher rates of glucose infusion, while their frequency remains virtually constant (36). Figure 5 shows the results of two simulations with an infusion rate (I) of 108 and 216 mg/min, respectively. It can be seen that doubling the rate of glucose infusion almost doubles the amplitude of the insulin oscillations in accordance with the experimental results. Furthermore, the period remains essentially identical for the two glucose infusion rates (110–120 min/cycle), and its duration is also in agreement with experimental results. A third concordance with experimental data is the observation that peaks of glucose on are, on average, 10–20 min ahead of peaks of insulin.

### *Simulation of Oral Glucose Intake*

To simulate the response to meals or oral glucose loads, we mimicked the absorption of glucose from the gastroin-

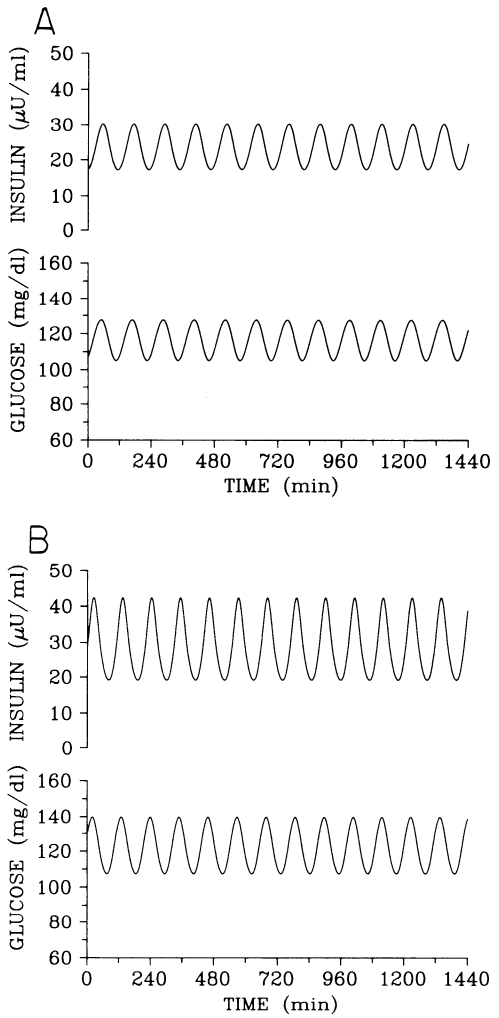


FIG. 5. Simulations with constant glucose infusion at rates of 108 (*A*) and 216 mg/min (*B*).

testinal tract. A similar approach has previously been used (1). The glucose uptake increases rapidly toward a plateau during oral ingestion and decays slowly with a time constant of ~2 h. Introduction of this type of exogenous intake three times over a 24-h period (i.e., simulating meal ingestion) or as a single dose (i.e., simulating an oral glucose load) leads to the results shown in Fig. 6. The observed patterns are similar to those seen in various human studies (17, 23, 25) in that both simulated and experimental results show damped oscillations (cf. Fig. 6 with Fig. 1).

### *Dependence of Oscillatory Behavior on Model Structure and Parameters*

Extensive simulations were performed to identify the features of the model that are essential for the occurrence of ultradian oscillations. The occurrence of oscillations was found to be critically dependent on the existence of a delay between increments in insulin concentrations and subsequent effects of the hormone on glucose production. If the delay is omitted, the model does not exhibit oscillatory behavior. The oscillations become damped if the delay is very short (<25 min) or very long (>50 min). In the range 25–50 min, sustained oscillations with periods of 95–140 min occurred if constant glucose infusion was simulated and if the delay was of at least third order.

The two-compartmental distribution of insulin was also found to be necessary for oscillations to occur, since simulations performed using only one compartment showed stable dynamics. We simulated the model using a wide range of parameter combinations, and we found that the existence of oscillations is not crucially dependent on the parameter values we chose; oscillations persist over a wide range of parameter values. Because of the relatively large number of parameters in the model, it is very difficult to perform a complete parameter sensitivity analysis. We performed a partial analysis by varying one parameter at a time while keeping the other parameters at base case values. For each parameter, we thus obtained a range (not necessarily the maximum range) within which the oscillations are self-sustained. The results are summarized in Table 1. In addition to the parameters listed in Table 1, we also tested the sensitivity of the oscillations to the shape of the functional relationships $f_1$–$f_5$, and we found that there was some sensitivity to the steepness of $f_1$ and $f_5$. If the slope in the point of symmetry of either of these functions is reduced by 10–20%, the oscillations also become damped.

## DISCUSSION

Two discrete temporal patterns of oscillatory behavior have been demonstrated experimentally in studies of

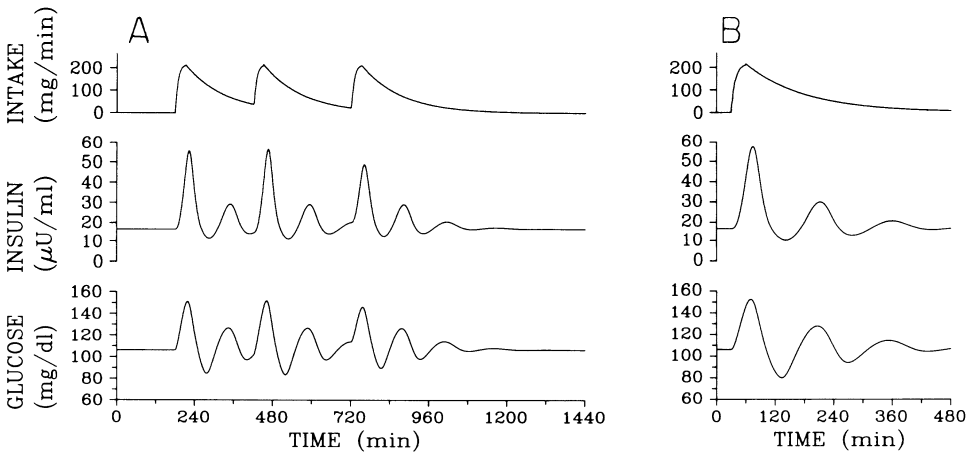


FIG. 6. Simulation of ingestion of 3 mixed meals over 24-h period (*A*) and oral glucose administration (*B*). Top profiles represent assumed patterns of glucose absorption, middle profiles show insulin changes, and bottom profiles depict resulting plasma glucose fluctuations.

TABLE 1. *Parameter sensitivity analysis*

| Parameters | Base Case Value | Range Checked |
|---|---|---|
| $t_1$, min | 6 | 4–8 |
| $t_2$, min | 100 | 60–140 |
| $t_3$, min | 36 | 25–50 |
| $E$, l/min | 0.2 | 0.1–0.3 |
| $V_1$, liters | 3 | 2–4 |
| $V_2$, liters | 11 | 7–15 |
| $V_3$, liters | 10 | 7–13 |

See *Glossary* for definitions of abbreviations.

insulin secretion from the β-cell. Small-amplitude secretory pulses that occur every 10–15 min have been observed in monkeys, dogs, and humans. The persistence of these pulses in isolated islets suggests that they originate from an endogenous islet pacemaker. These small rapid oscillations are superimposed on slower larger amplitude oscillations that occur approximately every 120 min. The mechanisms causing these oscillations are unknown. The aim of the present study was to determine whether these slow oscillations of insulin secretion and glucose levels could reflect the dynamic properties of the insulin-glucose regulation or whether it is necessary to postulate the existence of an ultradian pancreatic pacemaker to account for their occurrence. Our approach was to develop a parsimonious mathematical model of the two major negative feedback loops between insulin and glucose production and utilization, respectively, including the stimulatory effect of glucose on insulin secretion. Numerical simulations of this simple model mimicked all experimental findings so far observed for these ultradian oscillations, including *1*) self-sustained oscillations in the 100- to 150-min range during constant glucose infusion; *2*) damped oscillations after mixed meal or oral glucose ingestion; *3*) increased amplitude of oscillation in the presence of increased stimulation; and *4*) slight advance of the glucose oscillation compared with the insulin oscillation. These results show that the occurrence and properties of the ultradian oscillations of insulin secretion and glucose levels may be entirely accounted for by the major dynamic characteristics of glucose regulation, with no need to postulate the existence of an intrapancreatic ultradian pacemaker.

Our approach differs from most previous modeling efforts (1, 3, 12, 30) in the area of glucose regulation in that rather than quantitatively fitting parameters to match specific data sets, we have chosen representative parameters from data published in the literature. Indeed, for a nonlinear system, such as the insulin-glucose feedback system, with dynamic behaviors as complex as those illustrated in Fig. 1, the possibility of satisfactorily fitting parameters to the data is essentially excluded.

By modifying key aspects of the model, we were able to dissect the components that are essential in the genesis of the oscillations of insulin secretion. The occurrence and properties of the oscillations were found to be critically dependent on the existence and size of a delay between the insulin concentration and the subsequent effect on glucose production. The oscillations of insulin secretion also disappeared if the distribution of insulin was assumed to occur in a single compartment instead

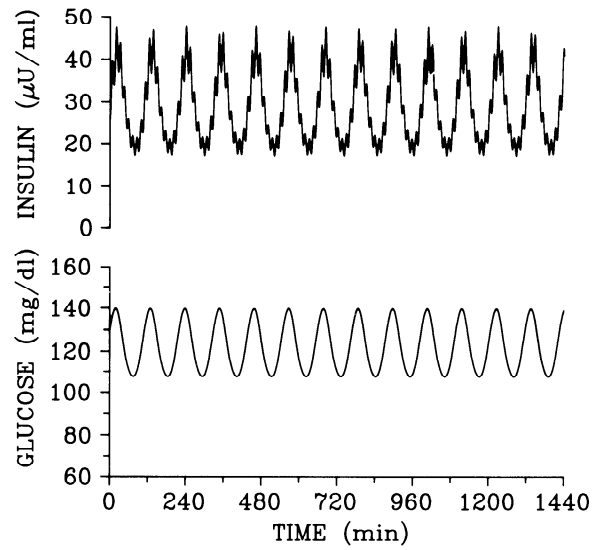


FIG. 7. Simulation in which rapid pulsations of insulin secretion have been assumed to originate from a putative intrapancreatic pacemaker functioning independently of glucose. Insulin secretion is now modified by factor of $[1 + 0.33\sin(2\pi t/13)]$, representing rapid oscillations. Note that oscillations in insulin levels are clearly apparent, whereas amplitude of glucose changes is too low to be detectable.

of in two distinct compartments. This observation is consistent with the recent findings of Yang et al. (38), which have demonstrated that measures of insulin action are more closely correlated with the concentration of the hormone in the lymph than with the plasma levels. Our simulations further suggest that the slow equilibration of insulin in this interstitial compartment is partly responsible for the oscillatory nature of insulin secretion. In addition, the shapes of the functional relationships in the model are of importance to the existence of oscillations.

Although our model is able to highlight and provide insight into certain aspects of in vivo insulin secretion and to mimic all properties of ultradian oscillations identified so far, there is an obvious difference between the simulation results and the experimental in vivo data. Indeed, the simulated oscillations are completely regular, whereas the experimentally observed oscillations show considerable irregularity both in amplitude and in frequency. A number of possible explanations for these differences exist. First, the simulations are based on unvarying parameter values. However, each of the model parameters constitutes an empirical description of complex biochemical processes that are unlikely to operate at rates reflected by strictly constant parameter values. In theory, temporal fluctuations of any parameter can affect the properties of the ongoing oscillation. In particular, if the time delay between changes in insulin and effects on glucose production is not constant, then both the frequency and the amplitude of the oscillations will vary. Second, glucose and insulin levels may be influenced by factors that have not been included in the model, such as counterregulatory hormones and physical activity. A third likely source of irregularity in the experimentally observed ultradian oscillations is the existence of rapid 10- to 15-min pulsations in insulin secretion. Figure 7 illustrates the results of a simulation

showing how rapid pulsations of insulin secretion originating from a putative intrapancreatic pacemaker could affect the insulin and glucose oscillations. Because glucose utilization depends on insulin in a remote compartment and because equilibration of insulin between the plasma and remote compartments is relatively slow, rapid oscillations of the plasma glucose concentration are not visible. This is in agreement with the fact that rapid plasma glucose oscillations have been observed inconsistently in humans.

In summary, the present modeling approach supports the hypothesis that the ultradian oscillations observed in humans during continuous enteral nutrition, after meal ingestion, and during constant glucose infusion have their origin in the feedback structure between glucose and insulin. Although we cannot exclude the existence of an ultradian pancreatic pacemaker, the hypothesis supported by our analysis implies that glucose plays an active role in the generation of the oscillations and suggests that conditions of glucose intolerance may be associated with abnormal ultradian oscillations of insulin secretion.

## APPENDIX

The model equations are

$$dx/dt = f_1(z) - E(x/V_1 - y/V_2) - x/t_1 \quad \text{(mU/min)}$$

$$dy/dt = E(x/V_1 - y/V_2) - y/t_2 \quad \text{(mU/min)}$$

$$dz/dt = f_5(h_3) + I - f_2(z) - f_3(z)f_4(y) \quad \text{(mg/min)}$$

$$dh_1/dt = 3(x - h_1)/t_3$$

$$dh_2/dt = 3(h_1 - h_2)/t_3$$

$$dh_3/dt = 3(h_2 - h_3)/t_3$$

Here, x denotes the amount of plasma insulin, y is the amount of insulin in the interstitial fluid, and z is the amount of glucose in the glucose space. The variables $h_1$, $h_2$, and $h_3$ all represent the delay process between insulin and glucose production described in the text.

The exact equations of the functions in the base run (as presented in Fig. 3) are

$$f_1(z) = 209/\{1 + \exp[-z/(300V_3) + 6.6]\}$$

$$f_2(z) = 72[1 - \exp(-z/144V_3)]$$

$$f_3(z) = 0.01z/V_3$$

$$f_4(y) = 90/[1 + \exp(-1.772 \log\{y[1/V_2 + 1/(Et_2)]\} + 7.76)] + 4$$

$$f_5(h_3) = 180/[1 + \exp(0.29h_3/V_1 - 7.5)]$$

Base run parameter values are I = 216 mg/min, $t_1$ = 6 min, $t_2$ = 100 min, $t_3$ = 36 min, $E$ = 0.2 l/min, $V_1$ = 3 liters, $V_2$ = 11 liters, and $V_3$ = 10 liters.

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