An introduction to the mathematical modeling of insulin secretion

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Lesson 4

M.L. Manca
Department of Clinical
and Experimental Medicine
University of Pisa

What we will learn today?

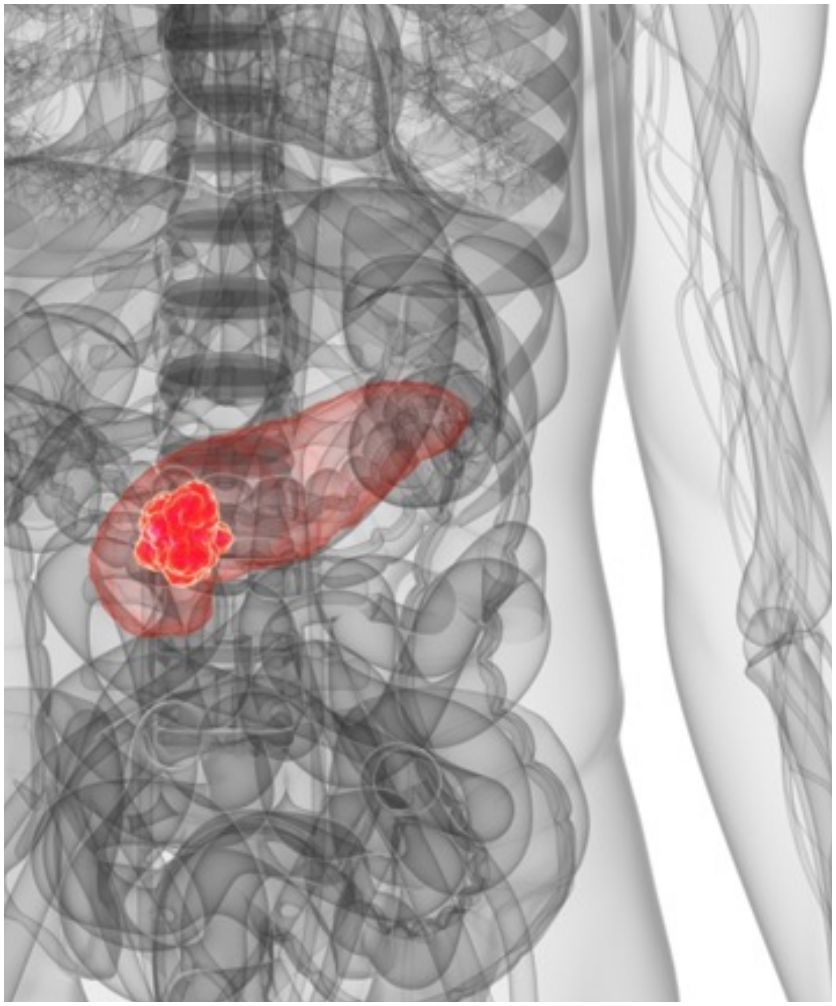
- Insulin
- Derivation of the Grodsky's model for the packet storage of insulin
- Derivation of the Sturis's model for the insulin ultradian oscillations

Pancreas

It is a mixed gland that performs both exocrine and endocrine functions

Pancreas has a role in digestion, metabolism and hormones productions

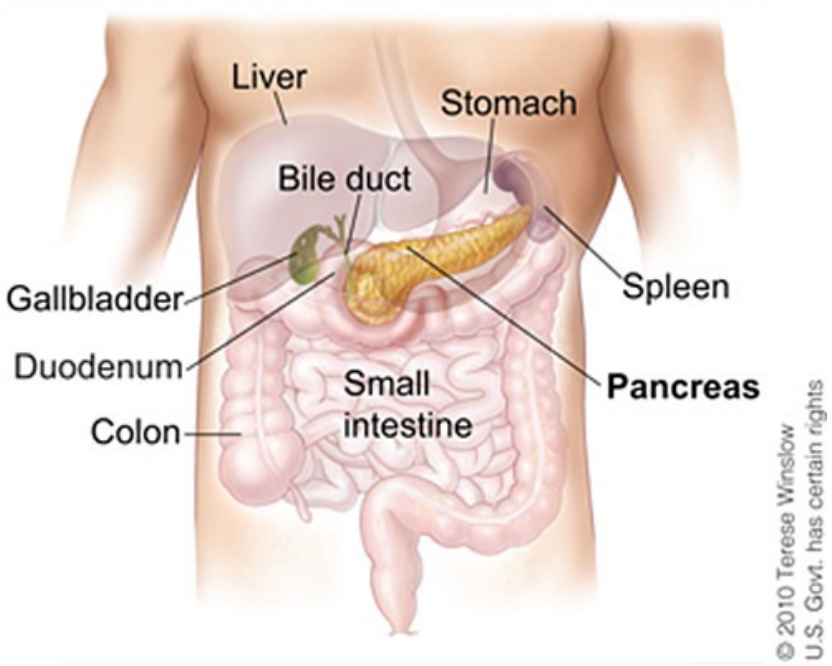
This organ makes enzymes to help digestion and hormones



Pancreas

The endocrine tissues are the smaller part

This part consists of isolated islands called “islets of Langerhans” forming 2% of total pancreatic cells

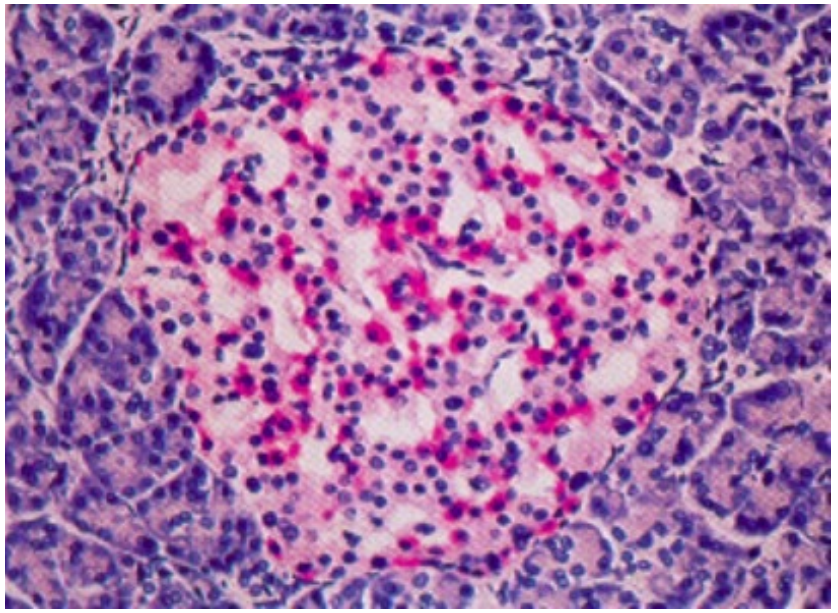


Islets of Langerhans

The Islets of Langerhans are commonly referred to as "islets"

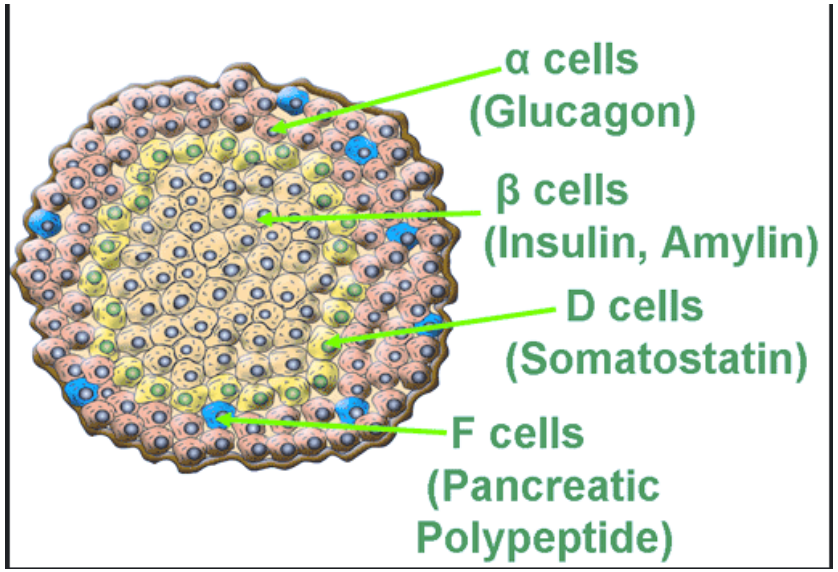
Islets actually are clusters of cells, with each "islet" containing 3,000 to 4,000 cells.

Scientists estimate there are 1 million islets in a healthy, adult pancreas



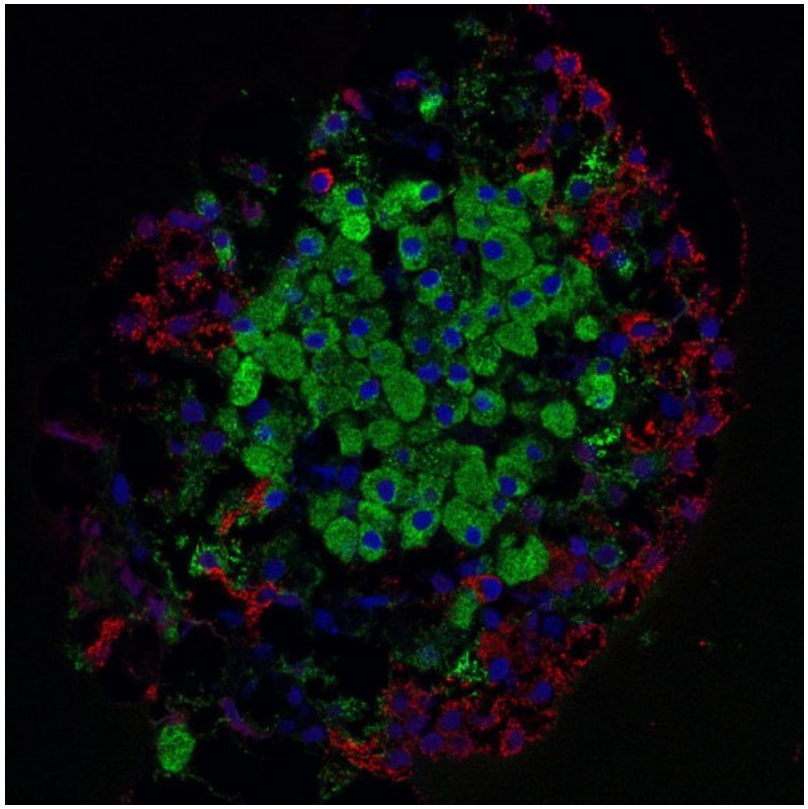
Islets of Langerhans

The islets secrete insulin, glucagon, somatostatin and pancreatic polypeptide: **insulin** and **glucagon**, with major actions on **glucose metabolism** and somatostatin and pancreatic polypeptide, with modulating actions on insulin and glucagon secretion



Beta-cell

- The beta-cell is one of 4 major types of cells (60%) present in the islets of Langerhans
- The beta-cell synthesizes and secretes the hormone insulin mainly in response to glucose

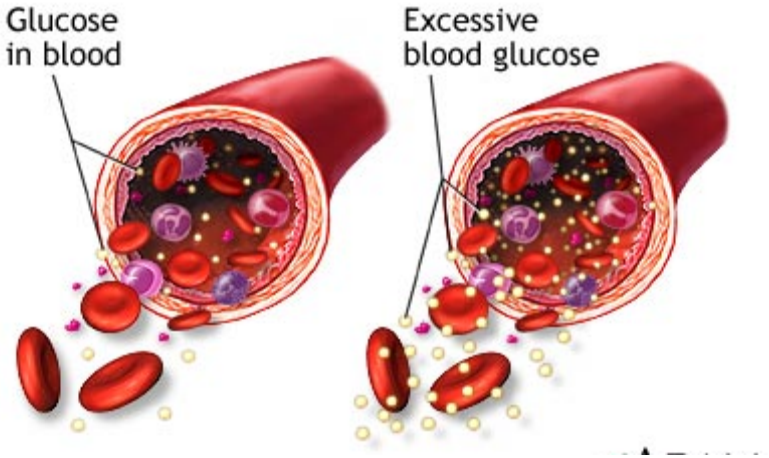


Glucose

The principal product of carbohydrate digestion, and the principal circulating sugar is glucose, that serves as the chief source of energy for the body

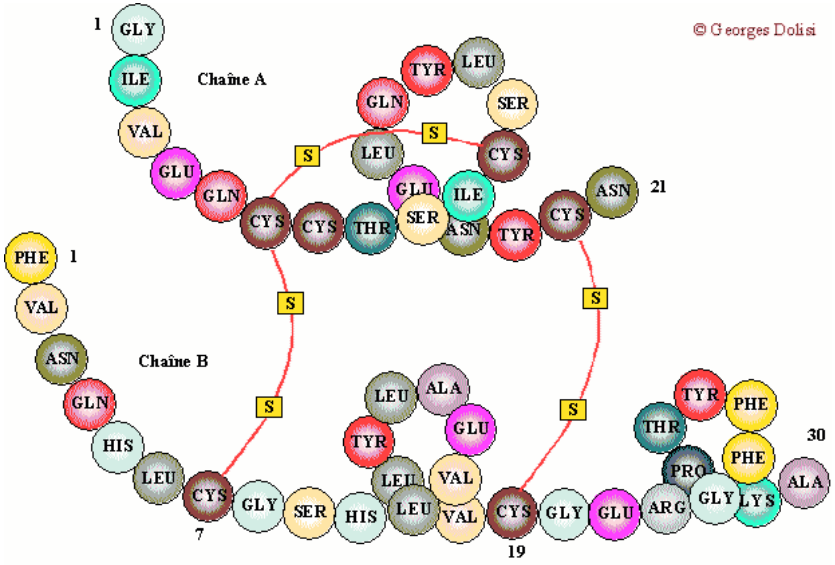
The pancreas and the liver regulate the production of insulin and glucose respectively, in order to keep the glucose level in check

A normal fasting blood sugar level (no food for 8 h) is between 70 and 99 mg/dL, while a normal blood sugar level two hours after eating is less than 140 mg/dL



Insulin

- Between 1914 and 1916, it was the Romanian physiologist Nicolas C. Paulescu who first extracted a pancreatic anti-diabetic agent that treated dogs - but his experiments would be overlooked in favor of work by other scientists
- In 1923 the Nobel Committee awarded Banting and Macleod the Nobel Prize in Physiology or Medicine

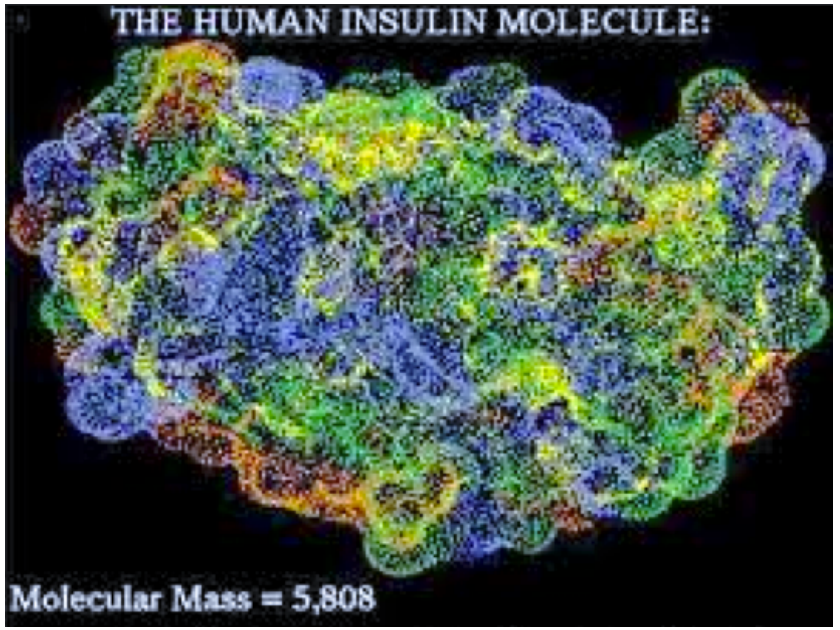


Insulin

It is a peptide hormone consisting of 2 chains with 51 amino acids, and a molecular weight of 5,808 Dalton

Insulin is cleared (“eliminated”) from the circulation in 10-15 minutes

The insulin release is not continuous even after a meal but oscillates



Insulin and metabolism

- Metabolism is a set of chemical transformations within the cells
- The main relevant action is the **conversion of food in energy** to run cellular processes
- **Insulin** is involved in **metabolism of carbohydrates** and lipids

Insulin and carbohydrate metabolism

- Insulin maintains blood glucose homeostasis
- It is the only hormone capable of lowering the glucose level
- Thanks to insulin, nearly all cells (80%) increase glucose uptake

Insulin and carbohydrate metabolism

The effects of insulin vary depending on the target tissue:

Muscle

Uptake (utilization) of glucose and immediate use (exercise)

Liver

Uptake of glucose and storage as glycogen

Adipose Tissue

Promotes glucose uptake and conversion to glycerol for fat production

Insulin and carbohydrate metabolism

The main 2 important effects are:

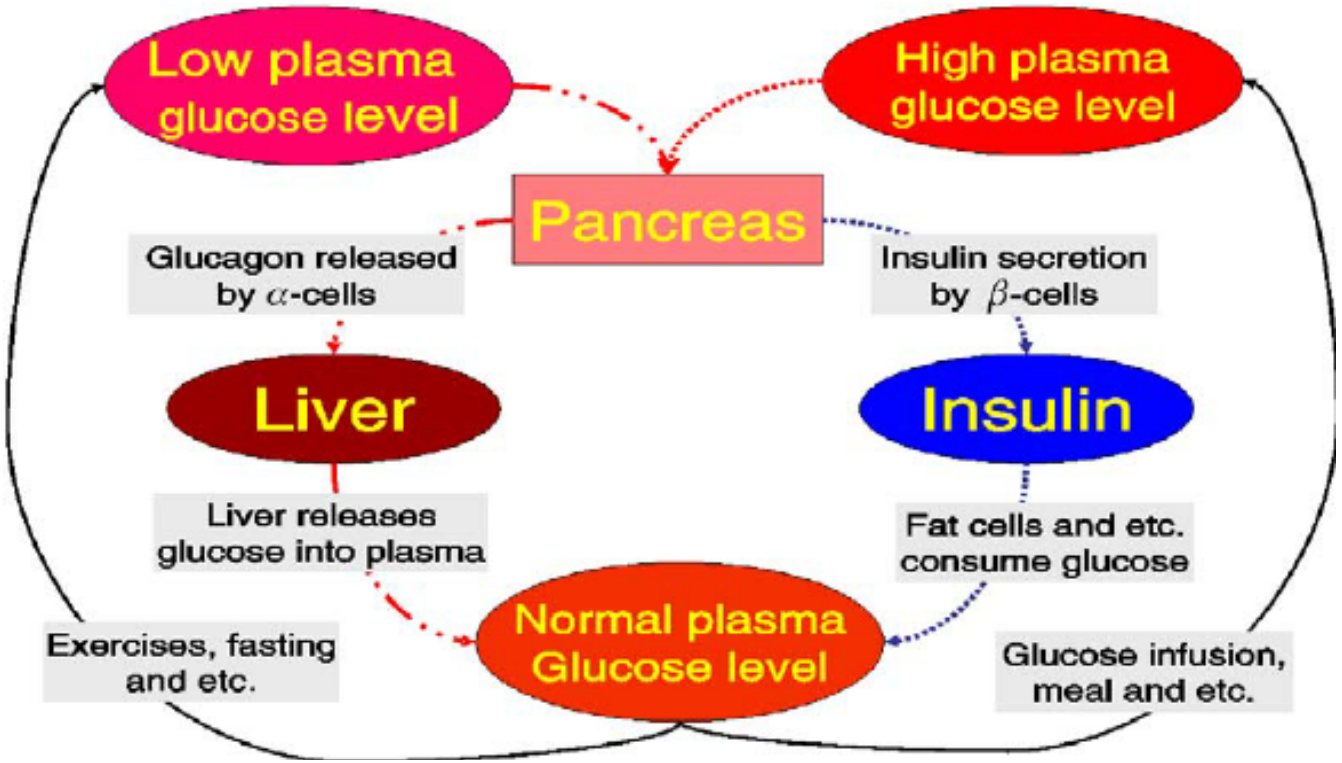
- Insulin facilitates entry of glucose into muscle, adipose and several other tissues

- Insulin stimulates the liver to store glucose in the form of glycogen

So, **the main effect of insulin is to decrease the concentration of glucose in blood**

As blood glucose concentrations fall, insulin secretion ceases

The glucose-insulin regulatory system



Diabetes is a dysfunction of the equilibrium in the regulation of glucose

This is caused by an autoimmune attack on beta cells (Type I diabetes) or by the inadequate supply or function of β-cells in counteracting the fluctuations of blood glucose(Type II diabetes)

The model of Grodsky (1972)

- After a glucose load, the insulin secretion (i.e. the velocity of release of insulin) has a multiphase pattern
- The underlying mechanisms long remained unresolved, but pioneering modeling work (for example Grodsky) established a 2-compartment model

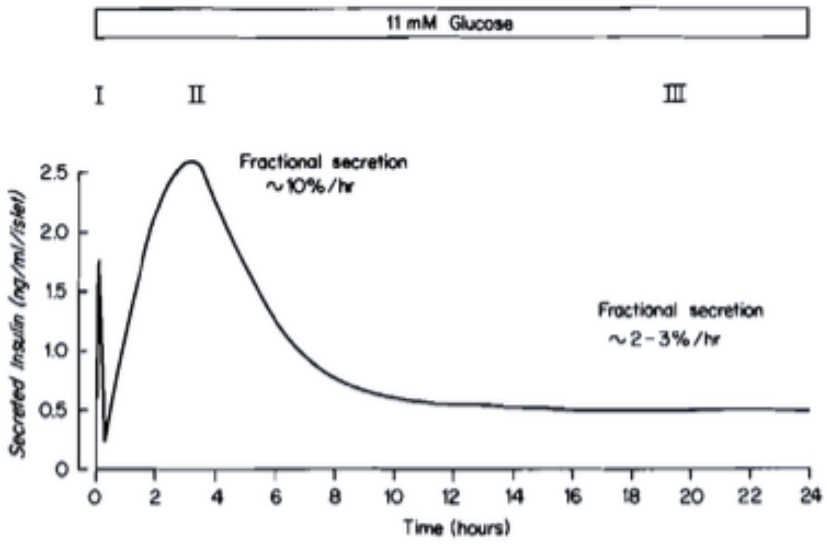


FIG. 1. Schematic representation of characteristic 3 phases of insulin secretion during 24-h constant stimulation of islets with glucose. Defined medium: HANA HB104. (From Bolaffi et al. [24]. © by The Endocrine Society.)

The model of Grodsky

Observational experimentation:

- the pancreas responds to constant stimulation with a multiphase pattern of insulin release

- the pattern is related to the modality of glucose increase (for example single step or staircase), the level of glucose and the duration of the stimulus

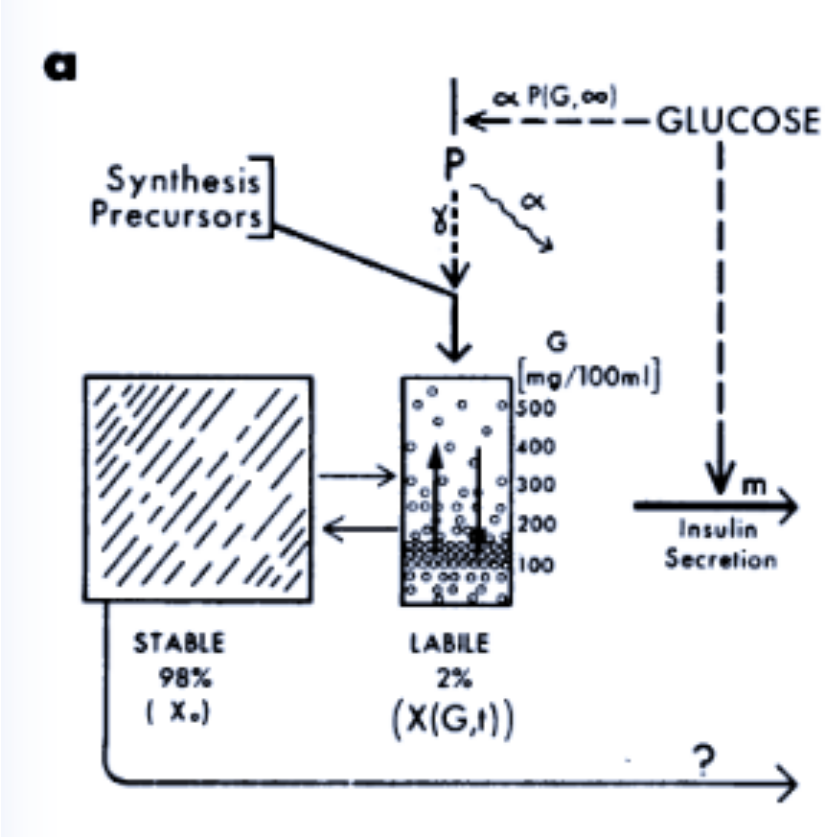
The aim of Grodsky's model is to mimic the biphasic behavior of pancreatic insulin secretion in response to a stimulus of glucose

The model refers to the rat pancreas

The 2-compartment model

This model is a 2-compartment model in which a small labile insulin compartment (2% of insulin) is assumed to exchange insulin with a large storage compartment (98% of insulin)

The rate at which insulin flows from the stable into the labile compartment is regulated by a **"provisional" factor P(G,t)**, where G is the glucose and t the time



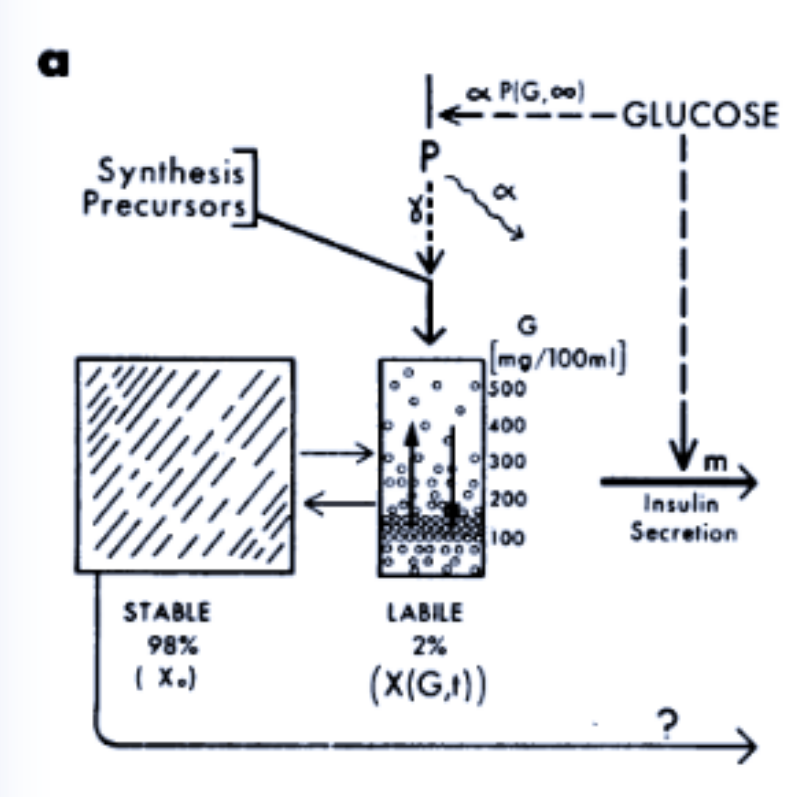
The 2-compartment model

A compartment is usually considered homogeneous but 2 homogeneous compartments were not able to reproduce the insulin pattern (Grodsky, 1970)

So Grodsky presumed that the labile stored form of insulin is "**nonhomogeneous**", consisting of elementary packets of insulin distributed in a bell-shaped function as to their glucose thresholds

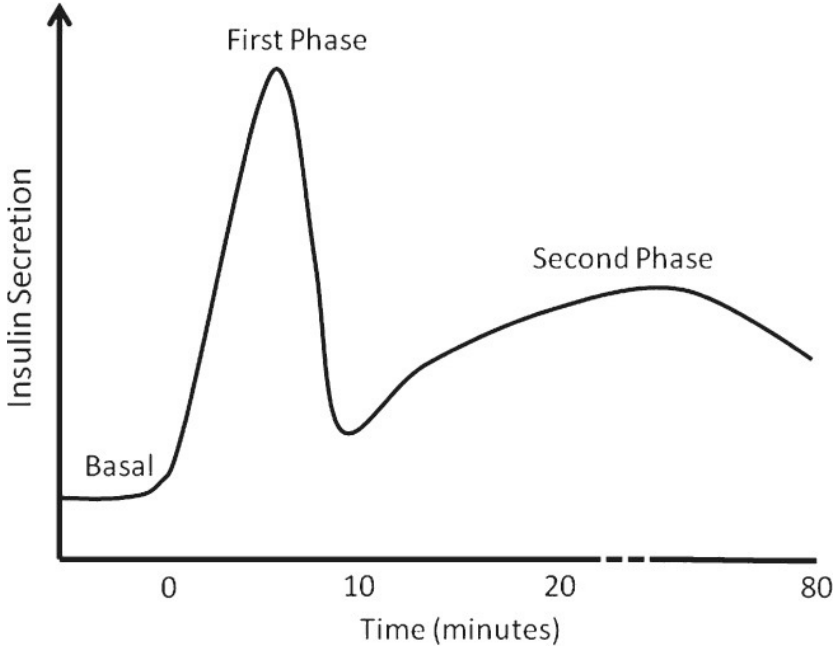
Since similar spike pattern of release have been observed for other endocrine system, the **threshold distribution hypothesis** may apply to system other that the beta-cells (it is a "general" model)

- The labile compartment consists of packets (beta cells) of insulin whose threshold sensitivity to glucose varies according to a bell-shaped function
- The function is represented by the vertical density of circles (packets)
- These packets rapidly release insulin when their thresholds are reached
- After any changes from original steady state, the packets slowly re-equilibrate to their original distribution



The 2-compartment model

- The model provides a mathematical description of the pancreas biphasic response to a glucose stimulus
- **The first phase** insulin release is caused by an instantaneous increase in the glucose followed by a rapid increase in its inhibitor (**insulin in the labile compartment**)
- **The second phase** release (approximately 50 min) results from the direct dependence of the insulin secretion rate on the glucose stimulus and the **gradual increase in the level of the factor P**



The factor P

- The second phase overlaps with the transfer of insulin from the stable into the labile compartment, modulated by the factor P
- P is a hypothetic “provisionary” or “potentiation” factor which mediates the new synthesis of insulin and/or controls the transport of insulin from the stable to the labile compartment
- In any case, **P has the function of provision of insulin** to the more labile storage state
- The production of P is assumed to be dependent upon the instantaneous glucose concentration

The initial situation

At time t = 0, the glucose G = G(0) is into the basal range

Xs(G,t=0) is the amount of insulin in the stable compartment, X(G,t=0) in the labile compartment

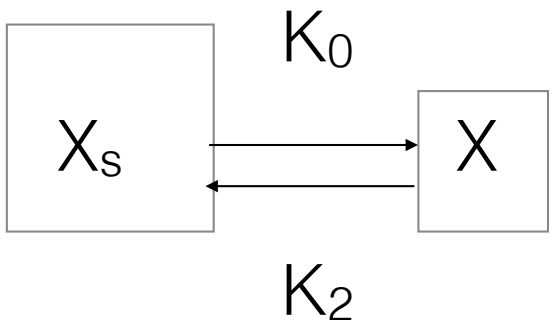
K_0 is the (slow) constant velocity of exchange from Xs to X, K_2 from X to Xs

From experimental data:

$K_0 = 0{,}0002\ (\text{min}^{-1})$

$K_2 = 0{,}01\ (\text{min}^{-1})$

$P(G,0) = 0$



The system and the insulin equations

$K_1(G,t)$ is the velocity of exchange between the 2 compartments, when G increases (min^{-1})

K_2 is the constant velocity from X to X_s

$m = 0{,}622\ min^{-1}$ represents the rate coefficient of insulin release from the labile compartment, approximately constant and independent to G

$$\frac{dX}{dt} = K_1(G,t)X_s(G,t) - (K_2 + m)X(G,t)$$

$$\frac{dX_s}{dt} = K_2X(G,t) - K_1(G,t)X_s(G,t)$$

The system and the P(G,t) equation

p(G,t=0) = 0

The product aP(G,oo) is, for any glucose concentration G, the steady-state production rate of the factor P

a = a(G) is a disappearance rate coefficient, possibly a function of glucose concentration

The disappearance constant a is small so that P is dissipated slowly

P(G,oo) is the steady state of P(G,t) minus a definite function of glucose concentration

$$\begin{cases} \frac{dP(G,t)}{dt} = \alpha(P[G,\infty] - P[G,t]) \\ \frac{dX}{dt} = K_1(G,t)X_s(G,t) - (K_2 + m)X(G,t) \\ \frac{dX_s}{dt} = K_2X(G,t) - K_1(G,t)X_s(G,t) \end{cases}$$

What about the insulin secretion SR?
For the first phase (without P)

$\xi(\vartheta,t)d\vartheta$ represents the amount of insulin in the labile compartment with a threshold between ϑ and $\vartheta + d\vartheta$. when the level of glucose is G

So, the releasable insulin for the level G is: $X(G,t) = \int_0^{G(t)} \xi(\vartheta,t)\,dt$

SR(G,t) has been considered proportional to X(G,t):

$$SR(G,t) = mX(G,t) = m\int_0^{G(t)} \xi(\vartheta,t)dt$$

where m(G) is the rate coefficient of insulin release; m(G) = m = 0,622 min^{-1}

For the second phase, the expression of SR is more complicated

Results of the simulations

Insulin secretion during staircase stimulations with 50mg/100ml increments of glucose

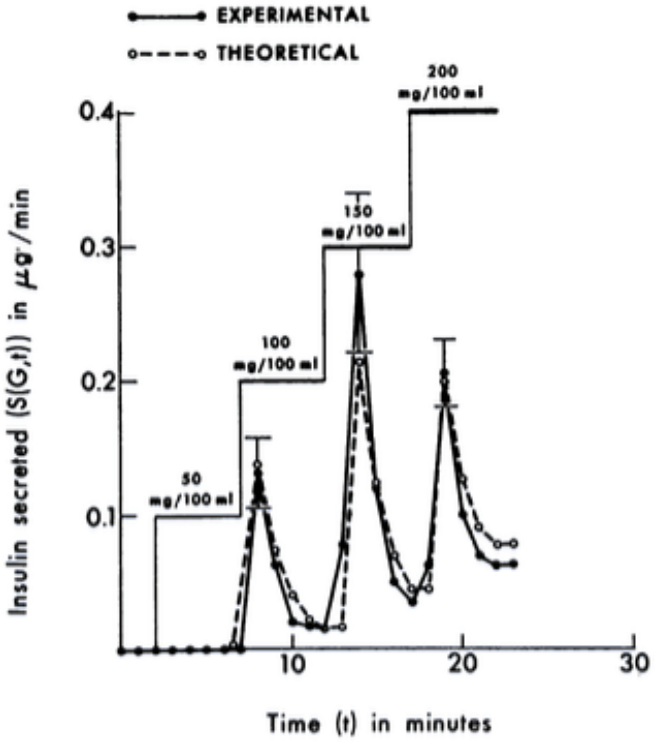


FIGURE 1 Insulin secretion during staircase stimulations with 50 mg/100 ml increments of glucose. Values in mg/100 ml refer to glucose concentration at each 5 min step. Solid line shows experimental results; $\bar{x}$ is mean ±SE., n = 7. Broken line shows results of computer simulation (equation 12 and 13) based on the model in Fig. 6 and the data from Fig. 2.

Results of the simulations

Insulin secretion during single-step continuous infusion with glucose at different concentrations, for 1 hr

Insulin secretion was not detectable when glucose concentrations were maintained at 50 mg/100 ml

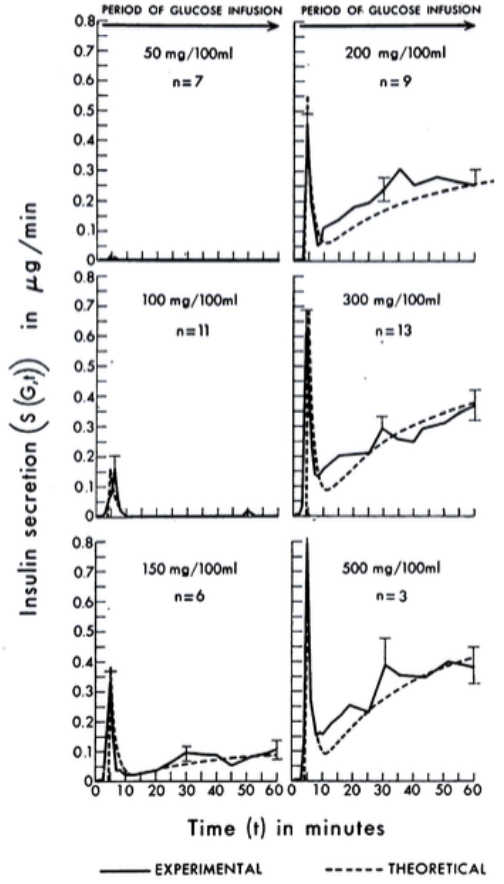


FIGURE 2 Insulin secretion during single-step continuous perfusion with glucose. Solid lines show experimental results; I is mean ±SE. Broken line shows results of computer simulations (equations 12 and 13).

Results of the simulations

Insulin secretion during single-step infusion with glucose at high concentrations (300mg/100ml)

Stimulation was interrupted during at rest period from minutes 60 to 65

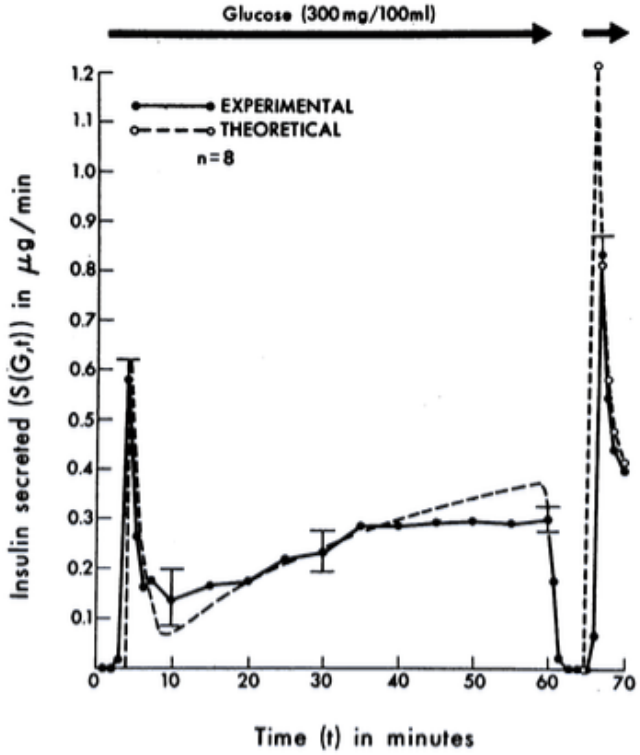


FIGURE 3 Insulin secretion during single-step perfusion with glucose (300 mg/100 ml). Stimulation was interrupted during a rest period from minutes 60 through 65. Solid line shows experimental results; $\bar{x}$ is mean ±SE. Broken line shows results of computer simulation (equations 12 and 13).

Insulin oscillations

- To add a further level of complexity to the study of insulin, experimental studies have interpreted the biphasic curve of the insulin secretion as constituted by rapid (first phase) and **ultradian** (second phase) nature

- As you can remember from sleep lesson (REM-nonREM cycle), the ultradian oscillations are defined as cycles which are repeated throughout a 24 h day

- To understand the effects of insulin on glucose utilization and production, and vice versa, Sturis and colleague proposed a model illustrating the ultradian oscillations of insulin secretion

Oscillations of insulin secretion in humans

In addition to the rapid insulin pulses that recur every 5 - 15 min, slow and large ultradian oscillations of insulin secretion with a period range of 50 - 120 min have been described

They are closely associated with similar oscillations of plasma glucose concentration

These ultradian oscillations have been studied in a variety of ways and can better be seen during **glucose infusion** than meals

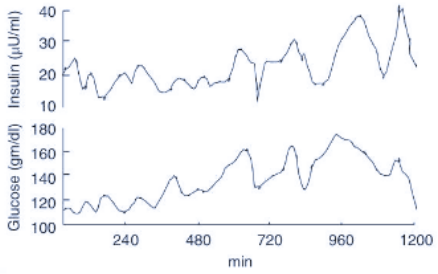


Figure 2.1: Graphical representation of the ultradian oscillations of insulin and glucose under conditions of constant glucose infusion. Adaption taken from Li et al (2006).

Mechanisms of ultradian insulin oscillations

Since 1923, some researchers have showed the existence of ultradian oscillations in insulin and glucose

However, the mechanisms that generate the ultradian insulin oscillations are not fully understood

In particular, it is not well established whether the glucose oscillations have an active role in the origin of the insulin oscillations or whether the latter are independently generated by an intra-pancreatic pacemaker

Sturis's model (1991)

- Sturis and co-workers developed a 6 dimensional differential equations system to model the ultradian oscillations
- 3-compartment model
- The model separates **insulin** stock into **2 distinct compartments** and contains a **time delay** of insulin effectiveness and **1 glucose compartment** (for simplicity)

modeling methodology forum

Computer model for mechanisms underlying ultradian oscillations of insulin and glucose

JEPPE STURIS, KENNETH S. POLONSKY, ERIK MOSEKILDE, AND EVE VAN CAUTER
Department of Medicine, University of Chicago, Pritzker School of Medicine, Chicago, Illinois 60637; and Physics Laboratory III, Technical University of Denmark, DK-2800 Lyngby, Denmark

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 100–180 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

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 μU/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.

Structure of the model

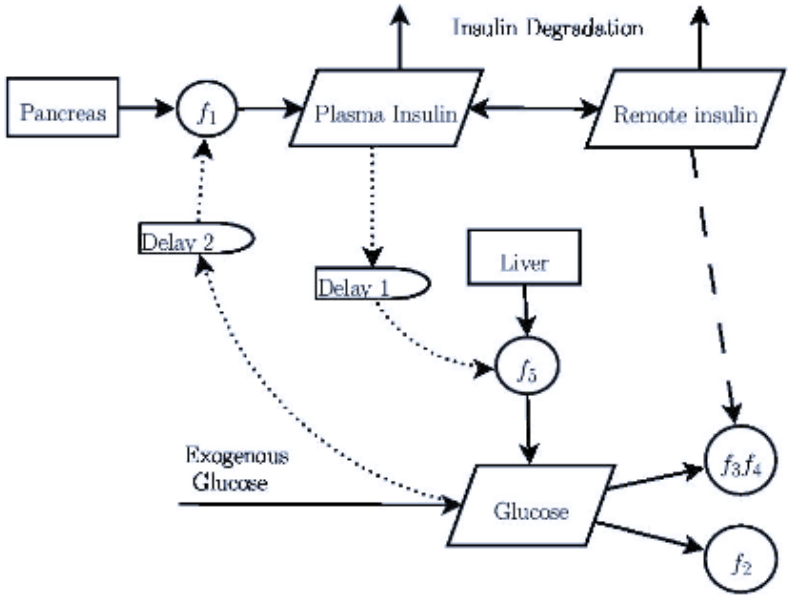
It is well known:

- that elevations of plasma glucose concentrations increase insulin secretion and that insulin enhances glucose uptake (utilization) and suppresses glucose production

- hyperglycemia per se increases glucose utilization and suppresses glucose production

Structure of the model

It is based on negative feedback loops, typically found in most biological systems



Homeostasis and feedback

- The homeostasis (the sleep homeostasis is an example) is the tendency of an organism (or cell) to regulate its internal environment and maintain equilibrium, usually by a system of control
- Almost all control systems are negative feedback mechanisms
- These mechanisms change the variable back to its original state, reducing the effect of the stimulus
- In a positive feedback, the output enhances the original stimulus

Some examples of feedback

In physics:

- thermostat; if the heating system is set at 70°F, the heat is turned on if the temperature drops below 70°F (positive feedback)

In medicine:

- insulin-glucose system; when glucose rises, insulin lowers glucose levels (negative feedback)

- glucagon-glucose system; when glucose decreases, glucagon raises glucose levels (positive feedback)

Diagram of the model

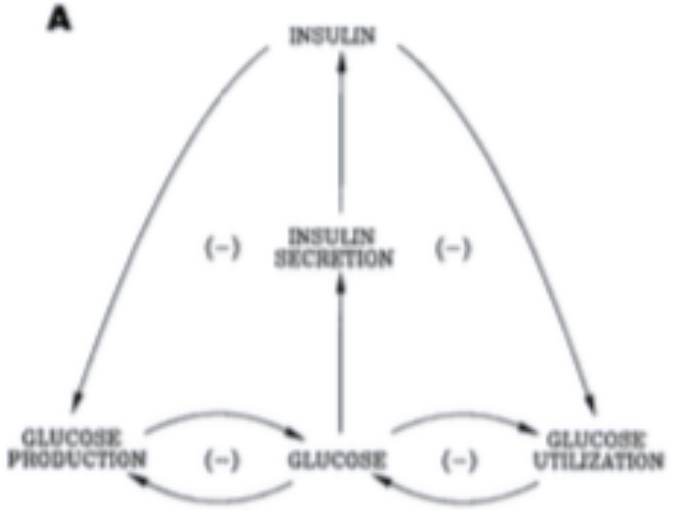
There are 4 negative feedback loops

Together these loops regulate the amounts of insulin and glucose in the body towards an equilibrium (not necessarily stable)

1- elevated glucose levels stimulate insulin secretion, and elevated insulin levels inhibit glucose production, which in turn lowers glucose levels (on the left)

Diagram of the model

2- elevated glucose levels stimulate insulin secretion, and insulin secretion stimulate glucose utilization, which in turn diminishes glucose levels (on the right)



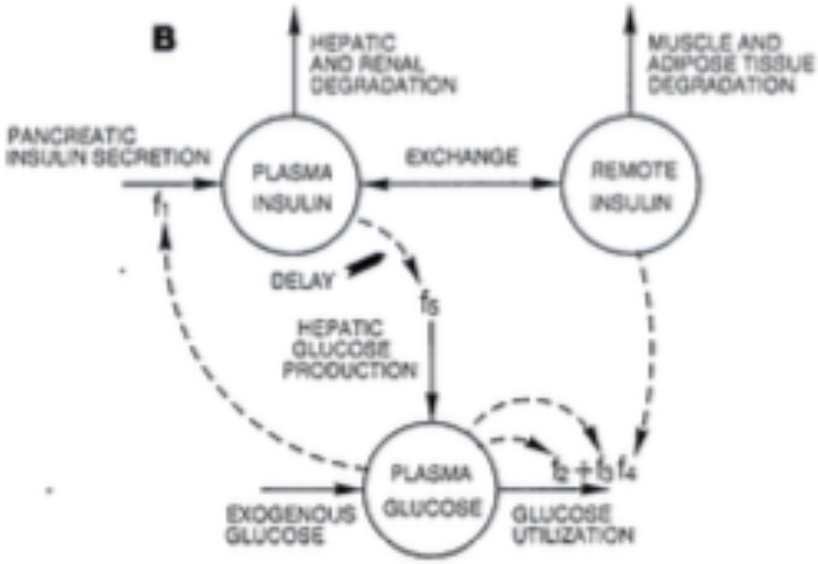
3- glucose inhibits its own production (on the left)

4- glucose stimulates its own utilization (on the right)

The main variables

3 main variables:

- the amount x of insulin in the plasma (mU)
- the amount y of remote insulin in the interstitial fluid (mU)
- the amount z of glucose in the plasma (mg)



The 3 main equations

The transport of insulin between plasma and intercellular space is assumed to be a passive diffusion process driven by the difference in insulin concentration between the 2 compartments, with transfer rate E

V_p volume of insulin in plasma space

V_i volume of insulin in interstitial fluid (intercellular space)

t_p time for plasma insulin degradation

t_i time for remote insulin degradation

G_{in} exogenous glucose infusion

$$\frac{dx}{dt} = f_1(z) - E\left(\frac{x}{V_p} - \frac{y}{V_i}\right) - \frac{x}{t_p},$$
$$\frac{dy}{dt} = E\left(\frac{x}{V_p} - \frac{y}{V_i}\right) - \frac{y}{t_i},$$
$$\frac{dz}{dt} = G_{in} + f_5(h_3) - f_2(z) - f_3(z)f_4(y),$$

The functions $f_1,\ldots,f_5$

The model includes 5 functions which represent the regulatory mechanisms of the system

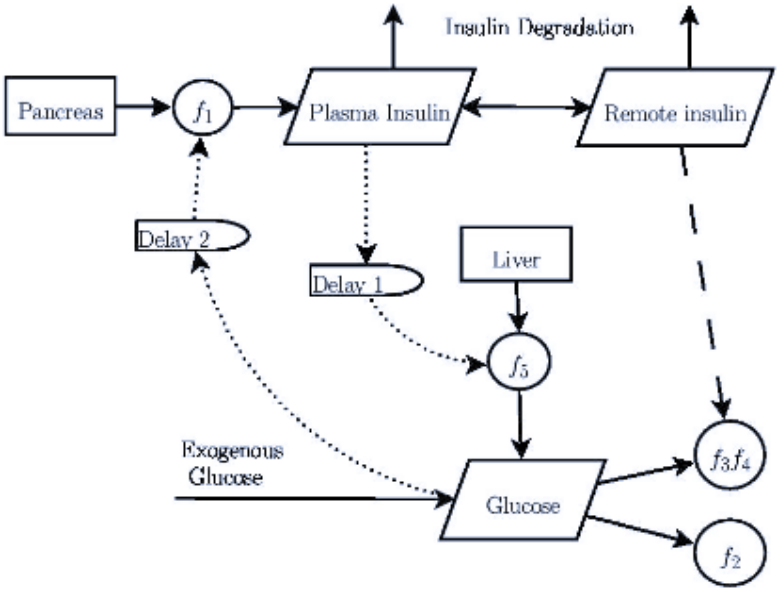
They are key features such that:

- f_1 is the effect of glucose on insulin secretion

- f_2 is the insulin independent glucose utilization (brain utilization of glucose)

- f_3 and f_4 are insulin-dependent glucose utilization

- f_5 represents the effect of insulin on glucose production (the regulation of liver glucose production is much more complex)



The functions $f_1,\ldots,f_5$

R_m is the maximum insulin infusion rate

V_g volume of glucose space

U_b maximum velocity of insulin-independent glucose utilization

U_m maximum velocity of insulin-dependent glucose utilization

V_i volume of the insulin in the interstitial space

U_0 the minimum velocity of insulin-dependent glucose utilization

R_g the maximum glucose infusion rate

V_p volume of insulin in plasma space

The parameters not described are auxiliary parameters and have no physiological meaning

$$f_1(z) = \frac{R_m}{1+\exp\left(\frac{-z}{300V_g}+6.6\right)}, \qquad f_2(z) = U_b\left(1-\exp\left(\frac{-z}{144V_g}\right)\right),$$

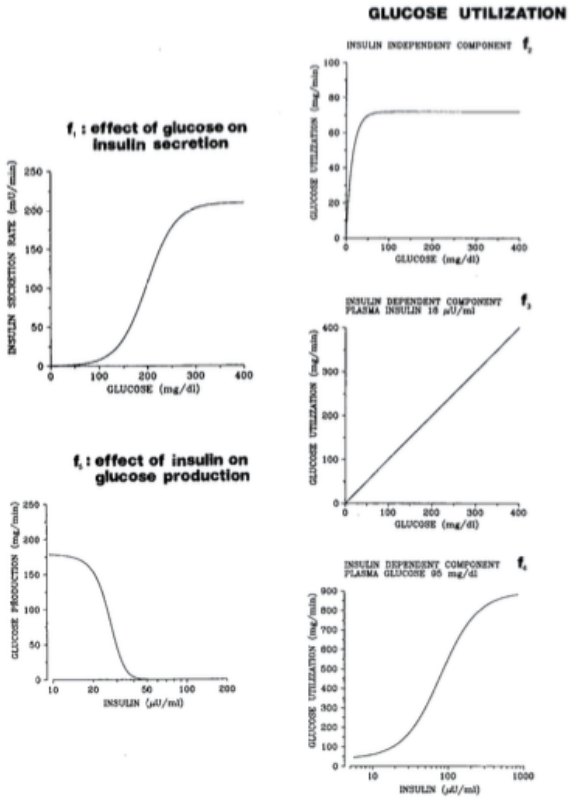
$$f_3(z) = \frac{0.01z}{V_g}, \qquad f_4(y) = \frac{U_m}{1+\exp(-1.772\log y\left(\frac{1}{V_i}+\frac{1}{(Et_i)}\right)+7.76)} + U_0,$$

$$f_5(h_3) = \frac{R_g}{1+\exp\left(\frac{0.29h_3}{V_p}-7.5\right)}.$$

The functions $f_1,\ldots,f_5$

These functions are commonly used in relation to glucose-insulin regulation

These functions are fitted to independent experimental results, published in literature



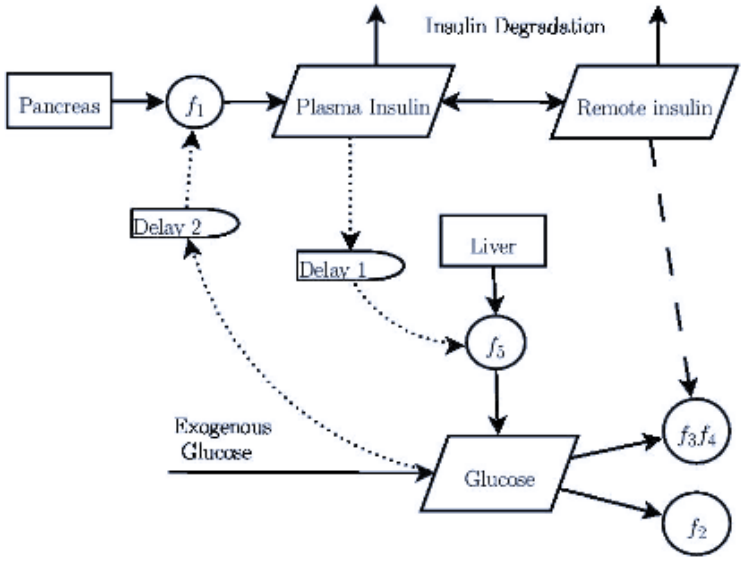
$$\frac{dx}{dt} = f_1(z) - E\left(\frac{x}{V_p} - \frac{y}{V_i}\right) - \frac{x}{t_p},$$

$$\frac{dy}{dt} = E\left(\frac{x}{V_p} - \frac{y}{V_i}\right) - \frac{y}{t_i},$$

$$\frac{dz}{dt} = G_{in} + f_5(h_3) - f_2(z) - f_3(z)f_4(y),$$

Time delay

An interesting feature of the system is the inclusion of a time delay representing the delayed effect of insulin on inhibiting glucose production

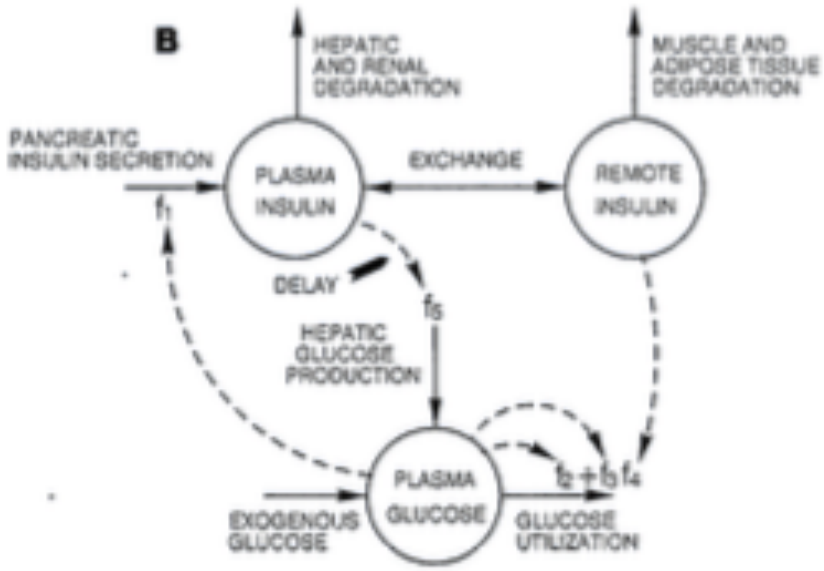


Time delay

In the original paper, there are at least 2 delays:

- a time delay of 30-45 min for the suppressive effect of insulin on glucose production

- a sluggish effect of insulin on glucose utilization, because insulin also acts from a compartment remote from plasma (substantially as insulin in the interstitial fluid between cells)



Time delay

As known, the effect of insulin on glucose production is not immediate but involves a substantial time delay

The time delay is represented by a 3 linear system introducing a chain of 3 intermediate (or auxiliary) variables (h_1, h_2, h_3) linking plasma insulin to the hepatic glucose production (delay of 3^{rd} order)

Time delay

t_d is the total time delay
Taking the expression for the derivative of h_1 without the coefficient,

$$x(t - t_d) = h_1(t - t_d) + h_1'(t - t_d)t_d.$$

This is equivalent to the Taylor expansion of $h_1(t)$ at time t - t_d

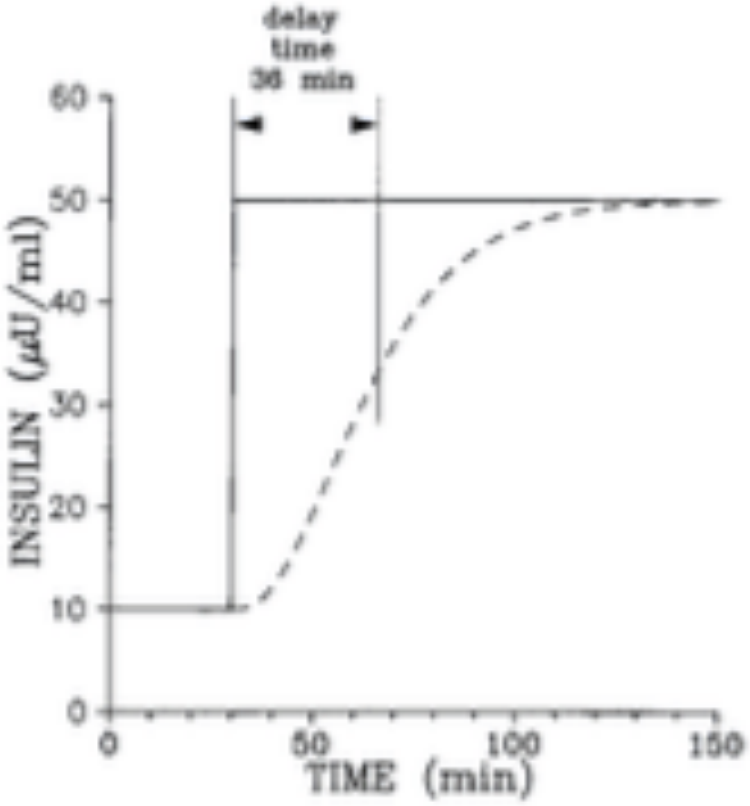
Therefore, the auxiliary variable $h_1(t) \approx x(t - t_d)$.

When this is extended to the 3rd order case, including h_2 and h_3, there is not a Taylor expansion but a 3-system where each auxiliary variable is an approximation of the previous

$$\frac{dh_1}{dt} = \frac{3(x - h_1)}{t_d}, \qquad \frac{dh_2}{dt} = \frac{3(h_1 - h_2)}{t_d}, \qquad \frac{dh_3}{dt} = \frac{3(h_2 - h_3)}{t_d}.$$

Time delay

- This picture illustrated the insulin increase with $t_d = 36$ min (from experimental data)
- Delay time of order n is defined as n times the transfer rate constant between n compartments used to model the delay
- Probably, the effect of insulin on glucose is both direct and indirect, and insulin in part acts from the remote insulin compartment; so the Authors suppose n = 3



Time delaying physiological factors

Two noticeable time delays exist in this system:

- one is due to the electric action inside of beta-cells upon glucose stimulation to release insulin;

- the other represents the delayed effect of insulin on hepatic glucose production (mainly, time it takes for the insulin to travel through the cells, and time to activate receptors to accept glucose into the cell)

Weaknesses

- The biological process responsible for the time delay are not completely understood, in the original article
- It should be noted that a second time delay for the slow effect of insulin on glucose utilization is mentioned by Sturis but not explicitly modeled
- While it is not directly modeled by the ODEs system, it is an effect of the movement of insulin between the plasma and remote compartment as the action on glucose is only seen in the plasma

Conclusions

The model of Sturis and colleagues provide a plausible mechanism for the genesis of the oscillations

The occurrence of ultradian oscillations is found to be dependent on the existence of a delay between the insulin concentration and the subsequent effect on glucose production

Their analysis suggests that the ultradian oscillations in insulin secretion and glucose levels could originate from the interactions between glucose and insulin

There are no proofs to postulate the existence of an intra-pancreatic pacemaker to account for their existence

Some references

- Grodsky GM. A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling. J Clin Invest. 1972 Aug;51(8):2047-59

- Sturis J, Polonsky KS, Mosekilde E, Van Cauter E. Computer model for mechanisms underlying ultradian oscillations of insulin and glucose. Am J Physiol. 1991 May;260(5 Pt 1):E801-9

A possible exercise

To find an alternative way to express the time delay of the action of insulin on glucose

List of biomathematical models

- Hodgkin-Huxley's model (conductance-based model)
- Macculloch-Pitts model (neuron as computational unit)
- Trion model (model of the neocortex)
- Borbely's model (2-process model)
- McCarley's model (ultradian alternation of REM-nonREM by using reciprocal interaction; "Lotka-Volterra"-based model)
- Grodsky's model (2-compartment model with a threshold hypothesis)
- Sturis' model (3-compartment model with a time delay)