Hormone circuits Lecture notes

Uri Alon (Spring 2021)
Lecture 3

The insulin-glucose circuit

Welcome to lecture 3 in our hormone circuit lecture notes. The purpose of this course is to study general principles of physiology, discover the regulatory circuits that are essential for health, and why these circuits fail in diseases. At the end of the course, I hope you will be able to ask questions about biological circuits and answer them with appropriate mathematical models.

In this lecture and the next, we will focus on the 'hydrogen atom' of hormone circuits: the glucose-insulin control circuit. When I say hydrogen atom, I mean the best-understood system which provides the conceptual tools to understand more complex cases, just as hydrogen was the testing ground for quantum mechanics. The glucose circuit highlights several important principles that apply to many other tissues. It is also important medically, because its failure is the basis for diabetes, a disease afflicting about 10% of the world's population (of which 90% is type-2 and 10% type-1 diabetes, see below).

Glucose concentration and dynamics is tightly controlled

The main variable in this system is the blood concentration of the sugar glucose. Glucose is an important energy and carbon source for the cells in our body. It is the major energy source for the brain and for red blood cells. **Glucose concentration in the blood is maintained within a tight range around 5mM**: different healthy people have a concentration of 5+/-1mM. This is different from fat mass or BMI that vary much more (factor of 2-4) between healthy people. This is not a setpoint that varies with parameters as in the leptin circuit of lectures 1 and 2. Hence, to explain the tight control of blood glucose, we need a new circuit and new principles.

Such rigorous control is important. It is called **homeostasis** in biology - the ability of the body to keep important variables within a tight range. If glucose drops below 3mM, the brain does not have enough energy and we can faint. Prolonged low glucose, called **hypoglycemia**, can be fatal. The body switches to alternative energy sources such as ketone bodies which can cause blood acidity which is potentially lethal. Similarly, if glucose is too high, above 7-10mM, it damages blood vessels and nerves, and over the years gives rise to the deadly symptoms of type-2 diabetes. The damaged blood vessels can give rise to heart attacks, to kidney diseases and, in the retina, to blindness. Damaged blood vessels can also lead to amputation of legs and other grim outcomes.

deep sigh of relief

In addition to the tight control over the steady-state level of glucose, **the entire glucose dynamics after a meal is tightly regulated.** These dynamics are measured, for example, in a clinical test for diabetes, called the glucose tolerance test (GTT). In GTT, you drink 75g of glucose, and measure blood glucose in the following two hours. Glucose rises to about twice its basal

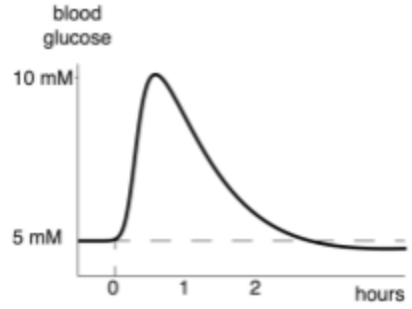


Figure 3.1

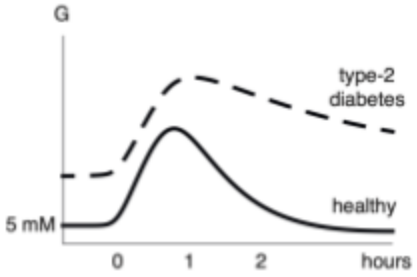


Figure 3.2

level of 5mM, and then falls back to baseline in about 2 hours (Fig 3.1). Different healthy people have similar glucose dynamics in the GTT. Aberrant dynamics are a sign of diabetes: glucose above 11mM at 2 hours is a clinical criterion for diabetes (Fig 3.2).

Clinical criteria for diabetes can also be based on a glucose blood test after at least 8h of fasting. Blood sugar level less than 5.6mM (100mg/dL) is normal, between 5.6mM and 6.9mM is **prediabetes**, and above 6.9mM (125 mg/dL) on two separate tests is diabetes.

Glucose concentration is controlled by insulin

How is this tight control of blood glucose concentration achieved? The answer is a feedback circuit involving the hormone **insulin**, a small protein that is found in the blood. Insulin allows glucose to enter cells in muscle, liver and fat, and glucose is thus removed from the blood. Glucose is unable to enter these cells without special glucose transporters (pumps) on the cell surface. The transporters are in storage vesicles inside the cell (Fig 3.3a). When insulin is in the

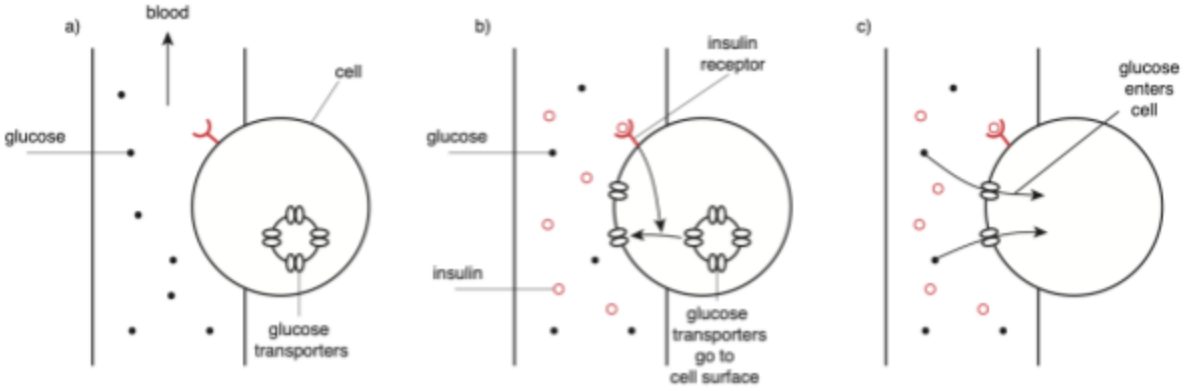


Figure 3.3

blood, it binds special sensors on the cell surface called insulin receptors (Fig 3.3b), which bind insulin like a lock and key. When bound, the receptors initiate signaling pathways inside the cell that move the glucose transporters to the cell surface (Fig 3.3b), where they pump glucose into the cell. As a result, insulin binding allows glucose to enter from the blood into the cell (Fig 3.3c).

Insulin is secreted by special cells in the pancreas called **beta-cells**. The pancreas is a thin gland about the size of a dollar bill located in our upper abdomen. In this gland are a million groups of cells called islets of Langerhans, each with about a thousand beta cells (Fig 3.4). The Islets also house other types of cells, like alpha cells that secrete glucagon, a hormone that acts to increase glucose production in the liver during fasting, which we will not discuss for now. In general, we ignore many details that are not crucial for the principles we wish to describe.

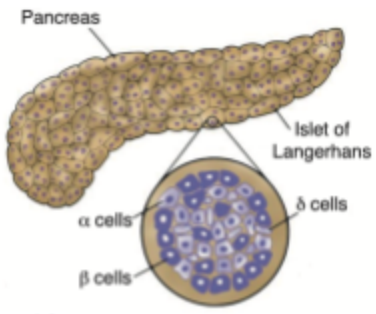


Figure 3.4

The beta cells sense glucose, and the more glucose around, the more insulin they secrete. Thus, a rise in glucose leads to insulin secreted to the blood. Insulin induces cells in the muscle and fat to take up glucose, and so blood glucose levels drop. This is a negative feedback loop: more glucose, more insulin, and thus less glucose (Fig 3.5). The input to the blood glucose comes from meals, and from the production of glucose by the liver from other nutrients. We denote these sources by *m* in Fig 3.5.

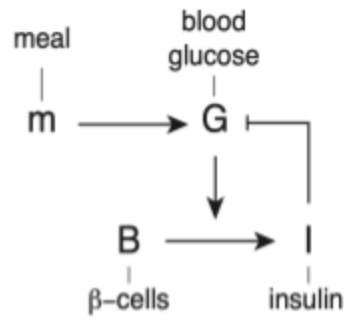


Figure 3.5

Diabetes is a malfunction in this system. In type-1 diabetes (T1D), the immune system attacks beta cells, and kills them off. As a result, there is no insulin and cells cannot obtain the glucose they need. To survive, T1D patients rely on insulin injections. Until the 1930s' type-1 diabetes was a death sentence to the children who got it (about 1% of the population gets T1D with a typical age of onset of 10-11y). With the discovery of insulin, those children could survive thanks to insulin injections. Still, keeping glucose under control is hard, and type-1 diabetes raises the risk for health complications.

In type-2 diabetes (T2D), beta cells do not secrete enough insulin to remove blood glucose effectively. Glucose rises and over the years causes damage to the body. A major cause of type-2 diabetes is insulin resistance, which we will describe in detail below.

We have now completed the verbal introduction to this system. It is a basic version of the more intricate verbal description generally taught to doctors and biologists. The verbal description is powerful in that it can explain intuitively the dynamics, such as the rise and fall after a GTT, and the basic phenomena in diabetes.

Song: Tangled up in glucose (Dylan)

Early one morning the sun was shining, I was sleeping in

Wondering if my beta cells were still making insulin

What with the rise of type-1 diabetes, and type-2 as well

all over the developed world, you know you never can tell

I was standing on the side of the road, rain falling down on my shoes

heading out for the clinic, god knows I paid my dues

getting through

Tangled up in glu-cose.

In this course we want to go beyond verbal descriptions and to write equations. Equations can help us focus on important parameters, and to generalize principles from one system to other systems. Most importantly, **equations help us to ask new questions**, such as what is the fundamental origin of diseases such as T1D and T2D. In this chapter we lay the foundations for the next two chapters in which we will make progress on these questions.

Mathematical models for the glucose-insulin circuit

In the glucose-insulin circuit, mathematical models developed since the 1970's benefitted clinical practice, because they helped to define important parameters like insulin resistance. They also give practical ways to estimate these parameters for each patient based on clinical measurements. An important model is the minimal model by Richard Bergman (1979), and we will use a version of this model as a basis for our exploration.

In order to model the dynamics of the system, we use differential equations to describe rates of change of glucose and insulin concentrations in the blood. Blood glucose concentration, G(t), is supplied in two ways: the first is when we eat a meal and glucose enters the blood from the intestinal system. The second way occurs between meals, such as during fasting and sleep. Glucose is then produced by the liver, which stores glucose in times of plenty in a polymer called glycogen, and breaks it down when we fast. When it runs out of glycogen, the liver can also make glucose out of amino acids taken out of muscles, in a process called gluconeogenesis (new production of glucose).

Summing over meals and liver production of glucose, we have the glucose supply m(t). Glucose is removed by the action of insulin. Thus, the rate of change of glucose, dG/dt, is the sum of supply *m* minus removal

$$(1) \quad dG/dt = m - a\,G$$

Let's focus on removal term $-a\,G$. The rate parameter *a* is the probability per unit time to lose a glucose molecule from the blood. For example, suppose we start with glucose concentration of $G=G_0$=5mM, and then totally stop production, m=0. As a result, glucose is only removed,

$$(2) \quad dG/dt=-aG$$

The solution of this equation is an exponentially decaying concentration which drops over time from its initial level G_0 (Fig 3.6):

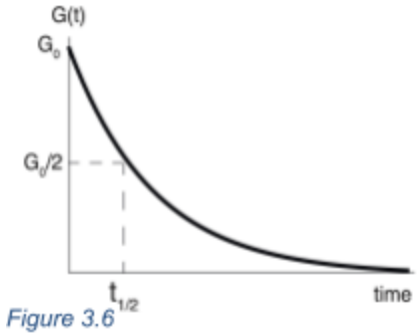


Figure 3.6

$$(3)\quad G(t) = G(0)\, exp(-a\, t)$$

The **half-life** of glucose is the time it takes to go halfway down from its initial level. This half-life, $t_{1/2}$, is when $G(t_{1/2}) = G_0/2$. Plugging this into equation (3), we find $exp(-a\, t_{1/2}) = 1/2$, and thus

$$(4)\quad t_{1/2} = ln(2)/a$$

This is a general result: **the half-life of a molecule is inversely related to its removal rate** (faster removal leads to shorter half-life). We saw this in lecture 2 on leptin and fat.

Since high levels of glucose are harmful, it makes sense to remove it quickly- to have a large removal rate *a*. However, this means that at night or fasting, the liver would need to make more glucose, because the steady-state is Gst=m/a, and to get a 5mM steady state, the higher removal a the larger production m needs to be. Thus a constant rapid glucose removal rate creates a wasteful cycle of high production and high removal. To avoid this wasteful cycle, the body uses insulin to increase the removal rate of glucose, but only when glucose is higher than 5mM.

Thus, glucose removal is due to insulin, so that $a = s\, I$. The parameter s is called **insulin sensitivity**- an important parameter. Insulin sensitivity is the effect of a unit of insulin on glucose removal rate. It can be measured by injecting insulin and noting the reduction in glucose, and in fact the models were calibrated using continuous infusions of glucose and/or insulin with measurement of insulin and glucose at high temporal resolution. Thus, our glucose equation is:

$$(5)\quad dG/dt = m - s\, I\, G$$

We can use our nullcline approach to draw the steady-state amount of glucose in a situation where insulin concentration is fixed, as in an intravenous clamp experiment. We simply set dG/dt=0 in Eq 5, to see that glucose level drops inversely with insulin $G_{st} = m/s\, I$, or equivalently $I = m/s\, G_{st}$ where m is steady-state production, such as liver production during fasting (Fig. 3.7).

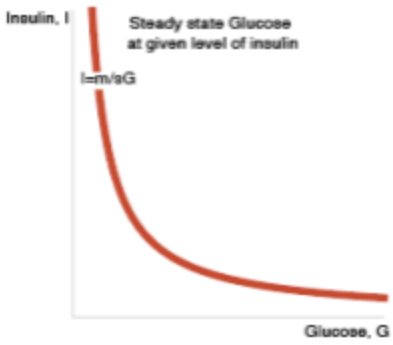


Figure 3.7

Now let's write the equation for the rate of change of insulin concentration in the blood, I(t). Insulin is produced by beta cells, and the production rate rises with glucose. Thus, each beta cell makes q f(G) units of insulin concentration per unit time, where q is the maximal production rate per unit biomass of beta cells, and f(G) is an increasing function of G, that goes between 0 and 1, that describes how glucose regulates the secretion rate. As in many biological circuits, f(G) is well described by a Hill function, an S-shaped rising curve given by

$$(6)\quad f(G) = \frac{G^n}{K^n + G^n}$$

which reaches halfway at a glucose concentration of $G = K$. This half-way concentration is about $K = 8mM$ in human islets. The steepness of the Hill function is higher the larger the Hill coefficient parameter n. For beta-cells, n=2-3 is a good approximation, Fig 3.8 (from Alcazar, 2019). Insulin secretion is further amplified by hormones released from the gut (GLP-1) that sense the incoming meal, and from brain inputs that can anticipate a meal. We won't deal with these additional inputs in this lecture. Another detail we won't go into is that insulin is secreted in two pulses, a brief spike followed by a prolonged insulin response to a meal.

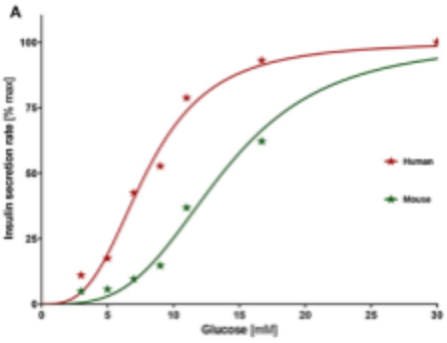


Figure 3.8

Note that insulin is secreted into the blood. The higher the blood volume, the more insulin is diluted. Thus, the secretion rate parameter q is the total number of molecules of insulin secreted per unit time per unit biomass, divided by the total blood volume, in order to get units of insulin concentration.

All that we need to do now is to multiply the production rate by the total beta cell mass B, to get a total insulin production of $q\ B\ f(G)$. Insulin is removed at rate γ , so that

$$(7) \quad dI/dt = q\ B\ f(G) - \gamma I$$

The removal parameter γ provides the insulin half-life in the circulation, of about ln(2)/γ =5 min. Insulin is removed primarily by degradation in the liver, where it flows to first; the remaining insulin flows in the circulation and is removed by the kidney which filters the blood.

We now have the minimal model equations, Eq 5 and 7. We can use the phase portrait to see where the setpoint is. We can add to our previous line for steady state glucose a line for steady state insulin at a fixed level of glucose, obtained from Eq 7 by using dI/dt=0. This line is shaped like the glucose Hill $Ist = qBf(G)/\gamma$ function (Fig 3.9). The two lines cross at the stepoint, in which the feedback loop sets a specific level of glucose and insulin.

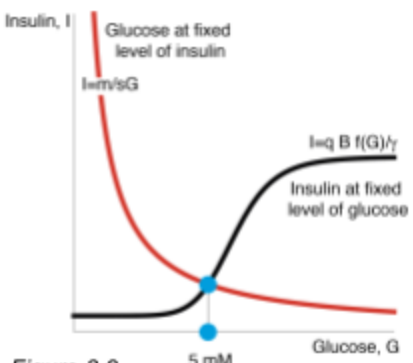


Figure 3.9

We now unveil the official definition of such lines- they are called **nullclines**, where d/dt of one variable=0. We have two equations, and thus two nullclines, one when dI/dt=0 and the other when dG/dt=0. Their intersection is a fixed point, because both I and G dont change, also called a steady-state solution, or setpoint.

Let's see how the equations do in the glucose tolerance test (Fig 3.10). We can solve the equations on the computer, and provide a pulse of input glucose m(t) to describe the glucose going into the body when we drink 75g of glucose solution. As a result, G(t) first rises, making insulin I(t) rise, increasing the

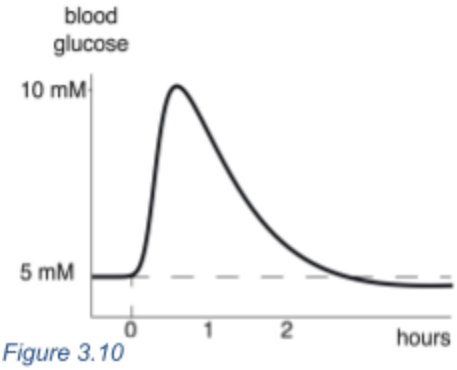


Figure 3.10

removal rate of G until it returns to baseline. This resembles the measured response of healthy people.

Pair and share. Math people form alliances with bio people.

Let's now ask about the tightness of glucose regulation. For example, is it plausible that G_{st} and the dynamics G(t) is so constant between people? The parameter to watch is insulin sensitivity, s. Insulin sensitivity varies between people: it is a physiological knob that allows the body to allocate glucose resources and determine which tissues get the glucose. For example, when we exercise, muscles need energy, and s rises. The effect of insulin is magnified by higher s, and muscles take up more glucose from the blood.

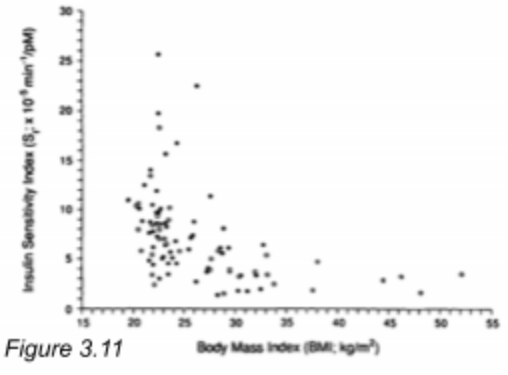


Figure 3.11

In contrast, in infection and inflammation, insulin sensitivity drops so that more glucose stays in the blood in order to help the immune system fight pathogens. Insulin sensitivity also drops during pregnancy, diverting glucose to the fetus. In obesity, *s* drops dramatically, sometimes by a factor of ten (see figure 3.11 from Kahn, 1993). This phenomenon is called **insulin resistance**, since each unit of insulin works less effectively than in non-resistant people. Insulin resistance in obesity is due to factors secreted by fat cells, and to chronic inflammation that often occurs in obesity. For example, in obesity, fat cells are overwhelmed and cannot take up excess fatty acids, which accumulates in muscles and in the liver causing signals that increase insulin resistance. Overwhelmed fat cells also secrete inflammatory signals which increase insulin resistance. Insulin resistance is usually coordinated between different tissues- muscle, fat and liver has similar resistance. Insulin resistance, as we will see, is an important factor in T2D.

Despite the fact that people vary in *s* by as much as ten-old, most people have normal glucose levels and dynamics. For example, the majority of people with obesity, which all have low s, have normal 5mM glucose and GTT dynamics.

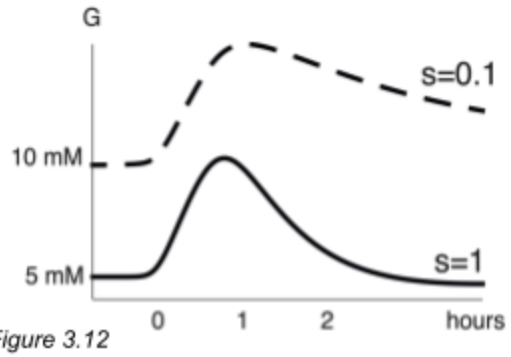


Figure 3.12

If we simulate the minimal model with a 10-fold lower s, we see that steady-state glucose concentration rises by a factor of about 2, and response time also greatly increases (Fig 3.12). Thus, the minimal model cannot explain how most people with obesity have normal glucose. In fact, no model based on the description of the system we studied so far can do so. We need to add another control loop to make glucose dynamics robust to variations in parameters such as s. We will do this in the next chapter.

We can see how insulin resistance increases glucose above 5mM in this model, using the phase portrait approach (Fig. 3.13). Suppose that s drops by a factor of 10: insulin is 10 times less effective at removing glucose. This does not affect the insulin line, but it does shift the glucose line to a higher level, because that line is inversely proportional to s: I=m/sG. As a result, the glucose set point shifts to higher levels, far above 5mM. **This creates a problem for the model, because most people with obesity have insulin resistance but normal glucose levels.**

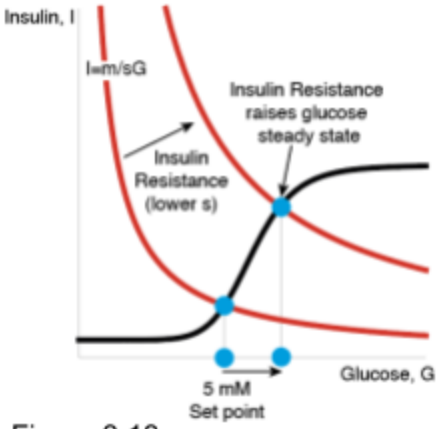


Figure 3.13

A second, more quantitative way to see how sensitive the minimal model is to variations in parameters, is to solve for the steady-state glucose:

Solved exercise 1: Show that the minimal model has steady-state glucose that depends on insulin sensitivity *s* and all other model parameters

Steady-state means no change with time, and thus we set the time derivatives to zero: $dG/dt = 0$ and $dI/dt = 0$. We find from Equation (5), that

$$(8) \quad s\, I_{st} G_{st} = m_{st}$$

where m_{st} is the fasting production of glucose from the liver. The subscripts "st" will denote steady-state throughout this course

Incidentally, this is the origin of the commonly used **HOMA-IR equation** used in research to estimate insulin sensitivity from steady-state glucose and insulin measurements:

$$s = m_{st} / I_{st}\, G_{st}$$

using the estimated parameter $m_{st} = 22.5$ whose units assume that glucose is measured in mM and insulin in $\mu U/ml$ [https://en.wikipedia.org/wiki/Homeostatic_model_assessment].

To find the steady-state solution of the insulin equation Eq. 7, let's approximate the regulation function f(G) as $(G/K)^2$, as suggested by Topp et al (2000). This approximation is derived from the Hill function of Eq. 6, with n=2 and is valid when $(G/K)^2 << 1$. This is not a terrible approximation, since (G/K)^2~(⅝)^2~0.3. As an aside, if Gst was larger than K, insulin secretion would saturate at 5mM glucose and beta cells would not be able to change their insulin secretion to match blood glucose. Thus, from the insulin Eq 7, solved at steady-state by setting with dI/dt=0, we find that $q\, B\, (G_{st}/K)^2 = \gamma I_{st}$. Plugging this into Eq 8, we obtain a steady state glucose level G_{st} that depends on the cube root of all parameters (the cube root comes from the $(G/K)^2$ regulation):

$$G_{st} = (\gamma K^2\, m_{st} / s\, q\, B)^{1/3}$$

Let's consider the case of insulin resistance due to an 8-fold drop in s, keeping all other parameters the same. This will result in a 2-fold rise in G_{st} (because 2 is the cube root of 8,

$8=2^3$). We see that G_{st} is not **robust** to changes in insulin resistance, which means it is sensitive to changes in this parameter, or to any of the other parameters in the model.

Also, we see from Eq 9 that glucose steady state is not robust to any of the other model parameters, including q, the maximal insulin production rate per beta cell. This parameter can also change as beta cell metabolism depends on many factors such as time of day and age. A subtle point is that q also depends on **total blood volume**, as mentioned above, which dilutes the number of insulin molecules to give rise to insulin concentration. Blood volume, which is about 5L in adults, increases by 50% in pregnancy. It changes during childhood growth, and in other physiological conditions. So being robust to q is also biologically important in order to achieve 5mM strict control.

Solved exercise 2: Show that half-life of glucose in the blood is also not robust to insulin sensitivity in the minimal model

Likewise, the half-life of glucose in the blood is not robust. To see this, let's recall the removal term of glucose, namely s I G. The removal parameter- the factor multiplying G that has units of 1/time - is $a = s\,I$. The half-life, as discussed in the beginning of the chapter, is therefore $t_{1/2} = ln(2)/a = ln(2)/s\,I$. Let's consider the case that the system is at steady state, and now a small amount of glucose is added to the blood, that hardly affects insulin concentration. Since at steady state $I = I_{st}$, the half-life is $ln(2)/s\ I_{st}$. We can compute I_{st} from Eq. 8 and 9: $I_{st} = (m_{st}{}^2\, q\, B/s^2\, \gamma K^2)^{1/3}$ and thus the half life is $t_{1/2} = ln(2)/s$ Ist= $ln(2)/(s\, m_{st}{}^2\, q\, B/\gamma K^2)^{1/3}$. Therefore, glucose half-life depends inversely on the cube root of insulin sensitivity, $s^{-1/3}$. Half-life doubles if s shrink by a factor of 8. With insulin resistance, therefore, the minimal model predicts that glucose is removed more slowly, all things being equal.

Thus, the prose description of the insulin-glucose circuit seems to work qualitatively well. But when we write the equations, we can see that we need additional mechanisms to explain the robustness of glucose concentration and its dynamics with respect to physiological parameters. We need to explain why most people with obesity, pregnancy or athletic lifestyles have very different insulin resistance but normal 5mM glucose and normal dynamics in the glucose tolerance test.

In the next lecture we will see how answering the question of robustness of glucose dynamics opens up general principles for feedback control in tissues. This new feedback will have unavoidable fragilities that explain why beta cells fail in T2D, as we will see in the next lecture, and why the body attacks its own beta cells in T1D, as well see later on in the course.

See you next week:)

deep sigh of relief

References:

Osmosis video on Diabetes Mellitus https://www.youtube.com/watch?v=-B-RVybvffU

Topp B, Promislow K, deVries G, Miura RM, Finegood DT. A model of beta-cell mass, insulin, and glucose kinetics: pathways to diabetes. J Theor Biol. 2000 Oct 21;206(4):605-19.

Alcazar O, Buchwald P, Concentration-Dependency and Time Profile of Insulin Secretion: Dynamic Perifusion Studies with Human and Murine Islets. Front. Endocrinol. (2019)

Handbook of Diabetes, 4th Edition, Excerpt #4: Normal Physiology of Insulin Secretion and Action (superb summary of physiology):

http://www.diabetesincontrol.com/handbook-of-diabetes-4th-edition-excerpt-4-normal-physiology-of-insulin-secretion-and-action/

https://www.frontiersin.org/articles/10.3389/fendo.2019.00680/full

Slides on T2D pathogenesis:

https://www.memorangapp.com/flashcards/155900/Molecular+Basis+of+Type+2+Diabetes+5%2F4-5%2F5/

History of minimal model:

Bergemann (2020) https://www.frontiersin.org/articles/10.3389/fendo.2020.583016/full

HOMA estimates based on minimal model:

Insulin resistance: HOMA-IR=I G/c where c=22.5 mM mIU/ml

Beta-cell function: HOMA-B=20 I/(G-3.5)

Appendix (for the mathematically curious):

Exactly solvable approximation for response time in the minimal model

$$dG/dt = m - s\,I\,G$$

$$dI/dt = qB\,f(G) - \gamma\,I$$

Suppose a big long meal, m(t)=m_1. Glucose rises and maximizes f(G) to f(G)=1 for enough time that I reaches its high steady state

$$I_1 = q\,B/\gamma$$

Glucose when the meal ends is at its high level

$$G_1 = \frac{m_1}{s} I_1 .$$

Now meal ends and $m(t)$ drops to its basal level m_0 (liver glucose production is repressed by insulin.

$$G(t) = G_o + (G_1 - G_o)exp(-\,s\,I_1\,t) = G_o + (G_1 - G_o)\,exp(-\,[s\,q\,B\,/\gamma]\,t)$$

Response time is $t_{1/2}$=ln(2) γ /s q B – depends on all parameters. Area under the G(t) curve in the decline phase is about G_1 $t_{1/2}$~m_1 $(\gamma/sq\,B)^2$; goes up very high with s and q. In the BIG model, in contrast,

$$dB/dt = B\,\mu(G)$$

G_{st}=G_o, and hence I_{st}=m_0/s G_o, and B_{st}= γ m_o/(s q G_o f(G_o))

Response time is $t_{1/2}$=ln(2) γ /sq B=ln(2) G_o f(G_o)/m_o independent on s,q, γ

G_1=m_1/s I_1 = m_1 γ / s q B =m_1 G_o f(G_o)/m_o, area under curve independent on s and q.

Biological appendix (for true enthusiasts):

Source: https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-45015-5_8

In order to appreciate the multiple pathophysiologic disturbances responsible for the development of impaired glucose metabolism in individuals with type 2 diabetes mellitus (T2DM), a review of the whole body, organ, and cellular mechanisms involved in the maintenance of normal glucose homeostasis in the postabsorptive state (10–12-h overnight fast) and following ingestion of a typical mixed meal is warranted (DeFronzo 1998, 1997, 2009; DeFronzo and Ferrannini 2010). During the sleeping and throughout the postabsorptive state, the great majority of total body glucose disposal takes place in insulin independent tissues, primarily the brain and other neural tissues which account for ~50% of all glucose utilization. Brain glucose utilization is insulin independent and saturates at a plasma glucose concentration of ~40 mg/dl (DeFronzo and Ferrannini 2010; Grill 1990). Since the normal fasting plasma glucose (FPG) concentration is ~70–80 mg/dl, this provides a large window of protection against cerebral neuroglycopenia. During the postabsorptive state, ~25% of glucose disposal takes in the splanchnic area (liver plus gastrointestinal tissues) and is insulin independent. Insulin-dependent tissues, primarily muscle and to a lesser extent adipose tissue, account for the remaining ~25% of glucose utilization. Basal glucose utilization averages ~2.0 mg/kg per min and is precisely matched by the rate of endogenous glucose production. Approximately 85% of endogenous glucose production is contributed by the liver and the remaining ~15% by the kidney. The ratio of insulin to glucagon in the portal circulation is the primary regulator of hepatic glucose production (Cherrington 1999), while in the kidney insulin is the primary regulator of renal glucose production (Meyer et al. 1998a). Glucagon has been reported to have no effect on renal glucose production (Stumvoll et al. 1998). Glycogenolysis and gluconeogenesis contribute approximately equally to the basal rate of hepatic glucose production, while gluconeogenesis is responsible for all renal glucose production (Cherrington 1999; Gerich et al. 2001).

Following ingestion of glucose or a mixed meal, the plasma glucose concentration rises resulting in the stimulation of insulin secretion by the pancreatic beta cells (DeFronzo and Ferrannini 2010; Ferrannini and DeFronzo 2015). The combination of hyperinsulinemia and hyperglycemia (i) stimulates glucose uptake by splanchnic (liver and gut) and peripheral (muscle and adipose) tissues and (ii) suppresses endogenous (hepatic and renal) glucose production (DeFronzo 1998, 1997, 2009; DeFronzo and Ferrannini 2010, 1987; Ferrannini and DeFronzo 2015; DeFronzo et al. 1985, 1981; Ferrannini et al. 1985; Mandarino et al. 2001). Muscle accounts for the majority (~80–85%) of glucose uptake by peripheral tissues, with a small amount (~5%) being disposed of by adipocytes. Although fat accounts for only a small amount of glucose disposal, it contributes to the maintenance of total body glucose homeostasis by regulating the release of free fatty acids (FFA) from stored triglycerides and through the production of adipocytokines that influence insulin sensitivity in muscle and liver (Bays et al. 2004; Groop et al. 1989; Bergman 2000). Lipolysis is highly sensitive to insulin, and the rise in plasma insulin concentration following glucose/meal ingestion results in a decline in plasma FFA concentration (Groop et al. 1989). FFA inhibits glucose uptake in muscle and stimulates hepatic glucose production (Belfort et al. 2005; Bajaj et al. 2005; Groop et al. 1991). As the plasma FFA concentration declines following glucose/meal ingestion, muscle glucose uptake is increased and hepatic glucose

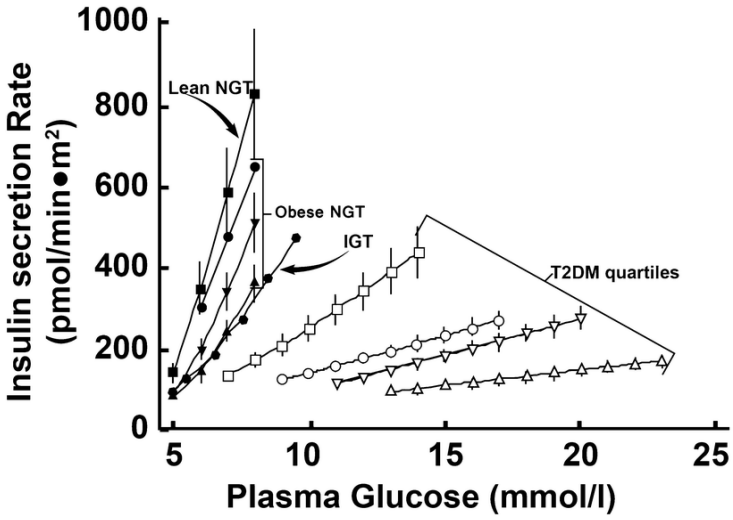
production is inhibited. Thus, the reduction in plasma FFA concentration in response to the increases in plasma insulin and glucose concentrations plays an important role in the maintenance of normal glucose homeostasis (Bays et al. 2004; Groop et al. 1989; Bergman 2000; Belfort et al. 2005).

Glucagon secretion by the alpha cell also plays a central role in the regulation of fasting and postprandial glycemic (Cherrington 1999; Baron et al. 1987). During fasting conditions, approximately half of total hepatic glucose output is dependent upon glucagon, and inhibition of basal glucagon secretion with somatostatin reduces hepatic glucose output and plasma glucose concentration. After a meal glucagon secretion is inhibited by insulin, and the decline in plasma glucagon plays a pivotal role in the suppression of hepatic glucose production and maintenance of normal postprandial glucose tolerance. If, following a meal, glucose enters from both the liver and gastrointestinal tract, postprandial hyperglycemia will ensue. Within the pancreas, approximately 70% of the beta cells are in direct communication with nonbeta cells, including alpha cells, through gap junctions containing connexin proteins (Bosco et al. 2010; Orci et al. 1975; Benninger and Piston 2014). In addition, beta cells can influence alpha cell secretion via intraislet blood flow (Jain and Lammert 2009). Thus, the local paracrine effect of insulin, as well as the rise in circulating plasma insulin concentration, conspires to inhibit glucagon secretion.

Following oral glucose administration, the amount of insulin which is secreted is 2.5–3 fold greater than if glucose were given intravenously to mimic the plasma glucose concentration observed following glucose ingestion. This is referred to as the incretin effect and is related to the release of glucagon-like peptide-1 (GLP-1) from the L cells in the distal small bowel/large intestine and glucose-dependent insulinotropic polypeptide (previously called gastric inhibitory polypeptide) (GIP) from the K cells in the early part of the small intestine (Drucker 2006, 2013; Holst 2007; Nauck and Meier 2016). Collectively, GLP-1 plus GIP account for 60–70% of the insulin that is secreted during a meal. All nutrients (glucose, protein, fat) stimulate GLP-1 and GIP secretion, but glucose is the most potent. GLP-1, but not GIP, also inhibits glucagon secretion, and the decline in plasma glucagon concentration contributes to suppression of hepatic glucose production following meal ingestion. Within minutes after ingestion of a meal, circulating levels of GLP-1 and GIP increase. This occurs long before nutrients can reach the K cells in the duodenum and the L cells in the more distal intestine. This rapid release of GLP-1 and GIP is mediated via neural impulses that are carried to the hypothalamus and back to the intestinal cells via the vagus nerve (Nauch and Meier 2016). GLP-1 and GIP bind to their respective receptors on the β cell, leading to activation of adenyl cyclase and an increase in insulin secretion (Drucker 2006, 2013; Holst 2007; Nauck and Meier 2016). Importantly, the stimulation of insulin secretion by GLP1 and GIP is glucose-dependent; that is, insulin release is augmented in the presence of hyperglycemia and wanes as the blood glucose concentration returns to normoglycemic levels. Similarly, the inhibitory effect of GLP-1 on glucagon secretion wanes as the plasma glucose concentration returns to its baseline level, allowing hepatic glucose production to increase, thereby preventing hypoglycemia.

The route of glucose entry into the body also plays an important role in glucose homeostasis (Cherrington 1999; DeFronzo et al. 1978a; Ferrannini et al. 1980). IV glucose exerts a modest

effect to increase splanchnic glucose uptake, and the increase in SGU is directly proportional to the increase in plasma glucose concentration (DeFronzo et al. 1985). Similarly, intravenous insulin exerts only a small stimulatory effect on splanchnic (liver plus gut) glucose uptake. In contrast, when glucose is ingested, splanchnic glucose uptake increases markedly in direct proportion to the negative hepatic artery-portal vein glucose concentration gradient (Cherrington 1999). As this gradient widens, a neural reflex is activated in which vagal activity is enhanced and sympathetic nerves innervating the liver are inhibited. These neural changes stimulate hepatic glycogen synthase, inhibit glycogen phosphorylase, and augment liver glucose uptake and glycogen formation. Consequently, following oral glucose administration, splanchnic tissues remove ~30–40% of the ingested glucose. This is in marked contrast to IV glucose/insulin administration, where muscle accounts for the majority (~85%) of glucose disposal.



Plot of insulin secretion rate against the concomitant plasma glucose concentration in subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (T2D) by quartile of fasting hyperglycemia. The mean slope of the fitting functions measures β-cell glucose sensitivity. (Source: Ferrannini et al., J Clin Endocrinol Metab 90:493–500, 2005)