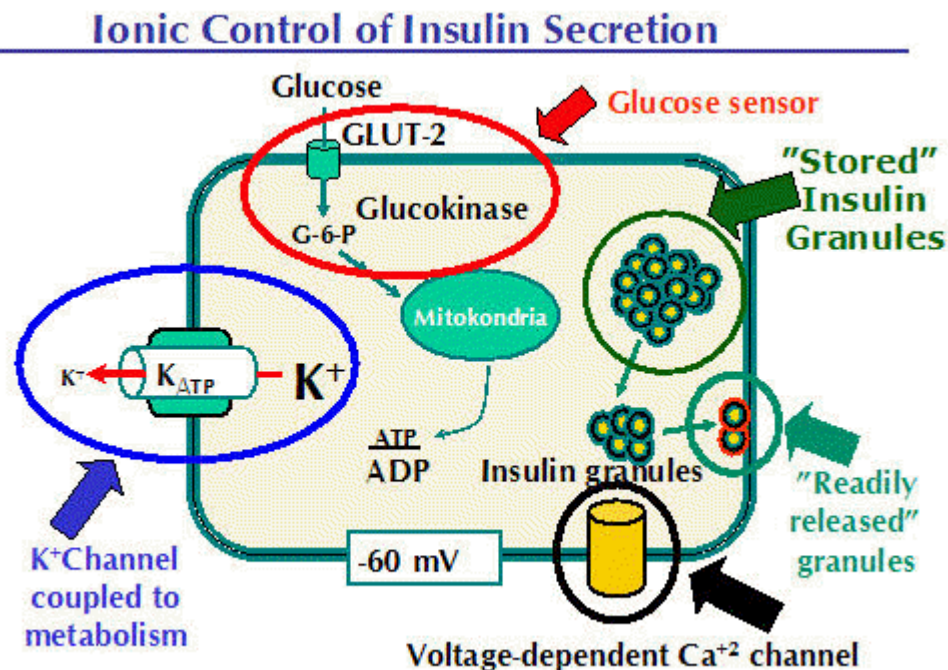


Secretion of Insulin and Glucagon

Coordination of metabolism in and between our various tissues is the cornerstone of life. The activities of many of the steps in metabolism are controlled by circulating hormones, the most prominent of these being the pancreatic hormones insulin and glucagon. Control of the rates of secretion of these two peptides is necessary to assure a stable inner milieu, allowing us to adjust our metabolism to meet the stresses of life. Meals, running after the bus, rest and sleep; all require adjustments in metabolic rates to allow us to function. Many of my readers perhaps associate insulin with sugar metabolism and diabetes. It is important to realize insulin, glucagon and many other hormones also control protein and lipid metabolism, feelings of hunger and satiation as well as sugar metabolism.

The pancreas contains clusters of cells known as the Islets of Langerhans. It is here that insulin and glucagon are produced and released. The islets contain three cell types: alpha cells that produce glucagon, beta cells that produce insulin, and delta cells where somatostatin is synthesized. Together, these cells and their hormone products are responsible for the minute-to-minute regulation of metabolism. Seemingly minor aberrations in function of these cells have large and often devastating effects on an individual's health. Production and secretion of these hormones is a full-time job. We often think of insulin release as a result of food intake while, in fact, about 50 % of the insulin secreted daily comes in periods between meals. Let us now look at how the body controls secretion of insulin.

The beta cell is extremely complex and not yet completely understood. A model of the beta cell showing the basic components for insulin secretion is presented below.



Ca⁺⁺ Initiates Insulin secretion.

The initiation of insulin secretion from the beta cell follows uptake of Ca⁺² ions over the cell's outer membrane. The Ca⁺² channel responsible for this is regulated by degree of polarization of the membrane. The cell's normal resting potential of about -60 mV does not activate the voltage-dependent Ca⁺⁺ channel nor insulin release. However, depolarization to -40 mV or less causes the Ca⁺² channel to open, increases the inward flow of Ca⁺⁺ and activates insulin secretion from "readily released" granules which are bound to the cell membrane. To date, most the theories concerning insulin secretion agree on this point, that is, postprandial insulin secretion from "readily released" insulin granules is initiated by depolarization of the plasma membrane and activation of the voltage-dependent Ca⁺² channel. So, the basic question is "what controls the beta cell's membrane potential?".

Control of membrane polarization; the ATP-linked potassium channel.

The original observation that depolarization of the beta cell membrane initiated by

Membrane Depolarization is Coupled to Insulin Secretion

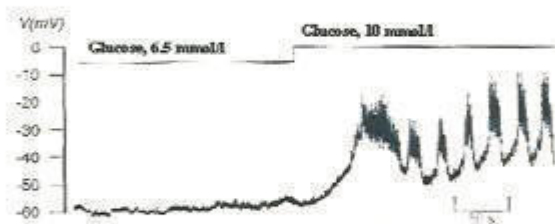


Fig. 1. The membrane potential (V) of a single beta cell within an intact pancreatic islet recorded in the presence of 6.5 and 10 mM glucose as indicated by the staircase.

Dean and Matthews, Nature 219, 209, 1968

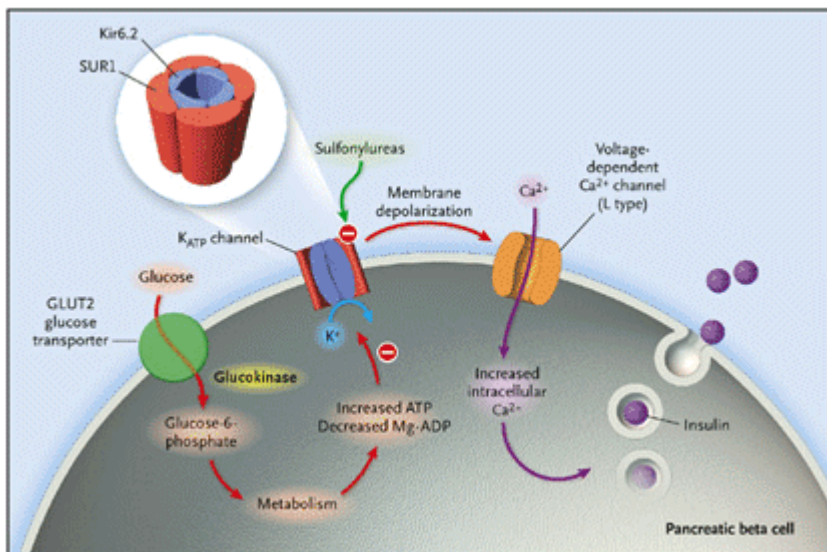
increased glucose levels was coupled to release of insulin was made by Dean and Matthews in 1968. These authors also observed that waves of depolarization and action potentials were initiated in intact pancreatic islet β -cells by glucose (Figure to the left). This was rather a new approach at that time.

Later work of P. Rorsman and others

demonstrated that the release of insulin following depolarization of the beta cell is coupled to entry of extracellular Ca⁺⁺. The "big question" was, therefore, "how is metabolism coupled to membrane potential"?

The K_{ATP} Channel.

The major link between metabolism and electrophysiology in many tissues including beta cells is the ATP-sensitive potassium channel (K_{ATP} channel). The membrane potential in most of our cells is determined by the cellular concentration of K^+ . The K_{ATP} channels control K^+ efflux and, therefore, cellular K^+ levels according to the cell's energy state. [As I will discuss a little later, other K^+ channels may also be involved in control of intracellular calcium levels.] The energy state of most cells is reflected by the cytoplasmic concentrations of ADP and ATP. These nucleotides strongly influence activity of K_{ATP} channels. They tightly couple energy metabolism (synthesis of ATP from ADP) and membrane potential (extracellular K^+ leaks into our cells and is pumped out again by these K_{ATP} channels). The balance between inward "leaking" of K^+ and outward K^+ "pumping" establishes the membrane potential of many cell types. The activity of these channels is instrumental in establishing the minute-to-minute polarization of cellular membranes. Again, the beta cell's polarization state is the main determinant of Ca^{+2} influx and insulin release.



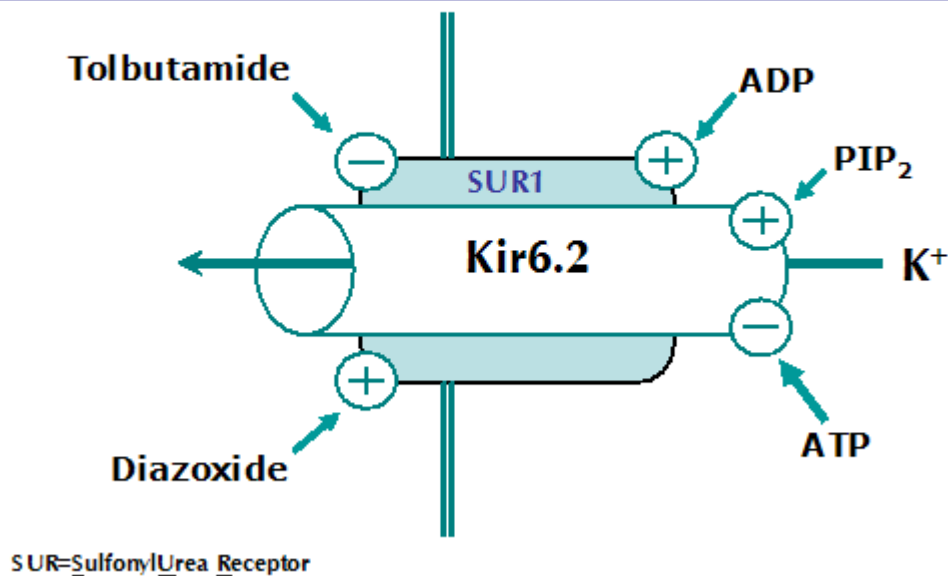
Let us look more closely at the K_{ATP} channel in beta cells. This is a complex formed by 4 Kir6.2 and 4 SUR1 peptides. The figure below has been taken from an article by Anna L. Gloyn et al, [\(N Engl J Med 2004; 350:1838-49\)](#). (Click on the title if you have library connections). The Kir6.2 elements form the K^+ -transporting

membrane pore while the SUR1, (sulfonylurea-binding peptides) are regulatory elements. When activated, the SUR1 peptides inhibit K^+ transport. The SUR name comes from the fact that this protein is the receptor for sulfonylurea drugs. These compounds have hypoglycemic actions, first reported by Janbon and coworkers in 1942. Tolbutamide, used as a hypoglycemic medication to treat diabetes type 2 since the 1950s, is one of these sulfonylurea compounds. The mechanism of these effects has only recently been identified.

The secret to understanding the link between metabolism (energy generation through formation of ATP from ADP) and K^+ flux is understanding the inhibitory and stimulatory actions of the nucleotides upon these peptide elements.

In the next figure I show the interactions which are generally accepted today. Note that "+" and "-" here refer to effects on K^+ transport out of the cell. A negative (inhibitory) effect indicates a reduction in K^+ flux leading to depolarization and increased insulin secretion. A "+" indicates increased K^+ flux out of the cell, polarization and decreased insulin secretion. K^+ flux can be almost completely inhibited by "-" or inhibitory agents! Remember, SUR1 activity inhibits Kir6.2 K^+ transport. Thus, tolbutamide increases the inhibitory actions of SUR1, inhibits K^+ flux and increases insulin release by the beta cell in a glucose-independent manner. This means that tolbutamide can stimulate insulin release even when glucose levels are reduced. This is a major danger with this drug and has led to development of

Control Elements for the K_{ATP} Channel in Pancreatic β -Cells, 2006



other agents which are coupled to blood glucose levels. ADP inhibits SUR1 activity and increases K^+ flux, thus slowing release of insulin. Agents which inhibit SUR1 (diazoxide) increase the membrane potential and reduce the rate of insulin secretion. ATP inhibits K^+ transport through its direct action on the Kir6.2 peptides. Simultaneously, ADP reduces the inhibitory effect of the SUR1 peptides on Kir6.2. The minute-to-minute balance between ATP and ADP is the most important regulator of the rate of K^+ transport through the cell's plasma membrane. Thus, the ATP/ADP ratio is the primary controller of the rate of Ca^{++} flux and insulin release. *NB: A high-protein meal increases insulin secretion through another mechanism. This is discussed further on.*

K_{ATP} is subject to phosphorylation by both protein kinase A and protein kinase C. It may therefore be subject to regulation by many hormones but these aspects are not clearly defined as yet. The effect of ATP upon Kir6.2 is strongly inhibited by phosphatidylinositol 4,5-bisphosphate (PIP₂), providing another hormone-activated control point in this complex system. Regulation of PIP₂ levels in the beta cell is poorly defined today. For an excellent review article over current knowledge see

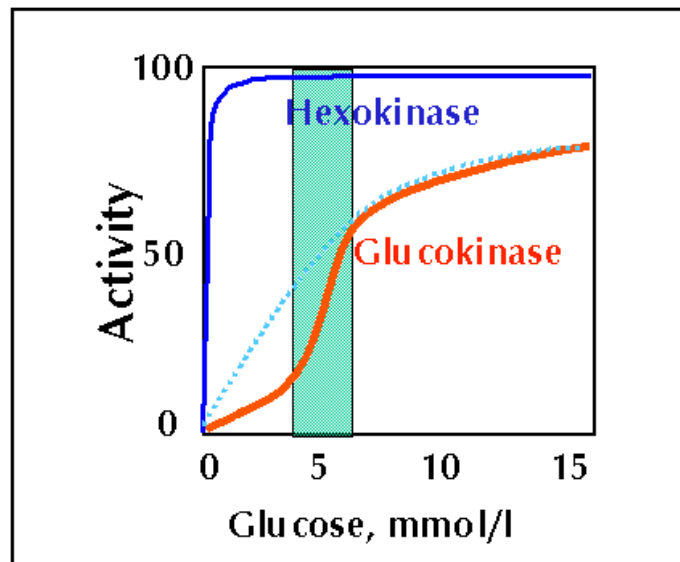
"Alchemy in the Soup: Transforming Metabolic Signals to Excitability, Colin G. Nichols, Sci STKE 2007, 410-414. [Click here if you have library connections.](#)

Coupling Blood Glucose Levels and Insulin Secretion.

We have now seen that energy metabolism is coupled to K^+ transport in the beta cell and that this determines the rate of insulin secretion. But, what is the connection between blood glucose levels and ATP? How are blood glucose levels coupled to ATP synthesis and membrane potential?

The answer lies in the rather special metabolic design of the beta cell. Let us take this point wise:

- The beta cell is quite dependent upon glucose as its substrate for energy metabolism. Neither fatty acids or amino acids can serve as substrates to support high ATP levels.
- Unlike most other tissues (with the exception of the liver), beta cells are dependent upon glucokinase (GK) for initiating glucose metabolism. The K_m for human pancreatic glucokinase is 5.5 mmol/l while the various hexokinase



enzymes have K_m values of around 0.01 mmol/l. Glucokinase activity increases and decreases parallel to changes in blood glucose levels within the physiological range (shown in green). Note that glucokinase exhibits sigmoid

kinetics (the dotted blue line represents a normal activity curve). Glucokinase activity is, therefore, most sensitive to changes in blood glucose concentration within the physiological range (approximately 4-6 mmol/l).

Consequently, both uptake of glucose by the beta cell and initiation of glycolysis closely follow blood glucose levels. We have a system that responds to increases in blood glucose with a rapid uptake and metabolism of glucose, but which is rather sluggish at the glucose levels found between meals. The "glucose sensor pair" GLUT2-GK is also found in the liver and hypothalamus and seems to be the universal glucose sensor. Recent findings in the glucagon-releasing alpha cell suggest that there are subclasses of glucose sensors. In the alpha cell, GLUT1 is coupled to glucokinase. This results in a glucose sensor that is quite sensitive for the changes in the lower range of physiological blood glucose levels (< 4 mmol/l), while that found in the liver and pancreas is most responsive to blood glucose alterations over 4 mmol/l.

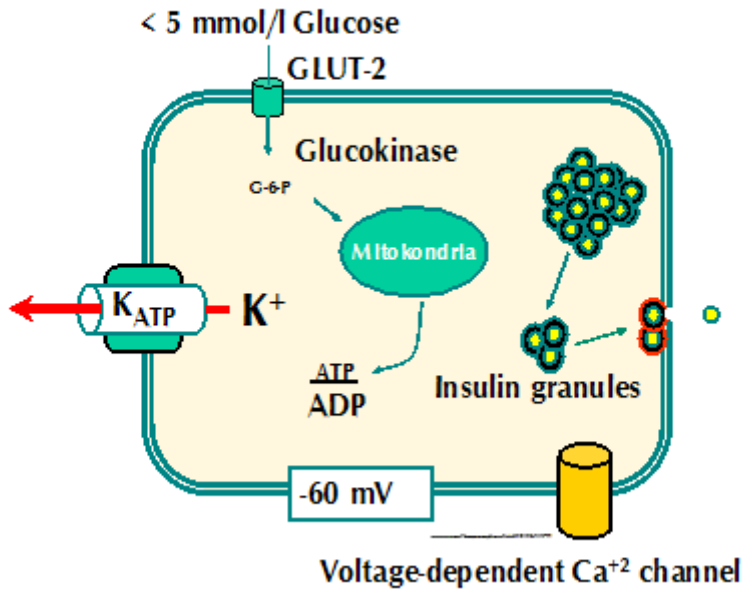
- All cells must have a transport system to take up glucose from the blood stream. Beta cells have glucose transport protein 2 (GLUT2) to do this job. While GLUT2 can be quite active, it has a low affinity for glucose, the K_m lying around 15-20 mmol/l. ([Click here for details about glucose transport proteins](#)).
- The combination of a phosphorylating enzyme with a high K_m with a transport system requiring high levels of glucose (GLUT2) results in a system for uptake and metabolizing glucose with a "total K_m " around 5 mmol/l.

The physiological result of this "beta cell specialization" is a system that has a "normal activity" at our "steady state" blood glucose levels. The GLUT2/GK system rapidly accelerates when glucose levels rise after a meal. A minor fall in blood glucose from about 4.5-5 mmol/l postprandial quickly leads to a fall in glucose uptake and phosphorylation in the beta cell. These changes in the rate of carbohydrate metabolism give immediate changes in the rate of ATP synthesis and the ATP/ADP ratio within the beta cell. Since the K_{ATP} channel is very sensitive to adenine nucleotide levels, alterations in the rate of glucose metabolism give brisk alterations in K^+ flux, membrane potential, Ca^{++} transport and insulin release.

A Little Repeat, with Figures.

The ATP/ADP ratio is relatively low in beta cells exposed to fasting blood glucose levels. The accelerated glucose uptake found at circulating glucose levels over 5

Ionic Control of Insulin Secretion

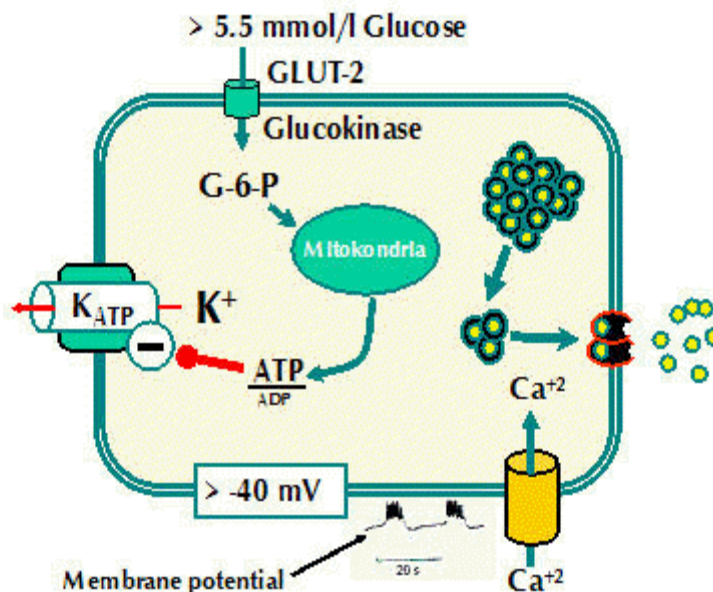


mmoles/l augments ATP synthesis. In other words, ATP synthesis is dependent upon the rates of glucose uptake and aerobic glycolysis. We have seen that these events are coupled to blood glucose concentration through GLUT2 and glucokinase. Variations in ATP levels occur parallel to changes in blood glucose concentration. Neither lipid nor amino acid oxidation lead to high an increased ATP/ADP ratio in

beta cells.

ATP acts as a second messenger in these cells, informing the K_{ATP} channel of variations in blood glucose levels. Stated simply: more glucose, more ATP, increased INHIBITION of K⁺ transport, depolarization of the beta cell and then, release of insulin.

Ionic Control of Insulin Secretion



Remember, this is a simplification, there are many other factors that appear to play in on insulin release. However, blood glucose levels are apparently the major determinant of the rate of insulin secretion

and regulation of K^+ transport does indeed seem to be the key to the system.

An Important Update on K_{ATP} Channel Regulation.

For up-to-date information about the coupling of metabolism and the ATP-regulated K^+ channel see: Colin G. Nichols, [K_{ATP} channels as molecular sensors of cellular metabolism](#), Nature, (2006) 440 470-476. [You can click here if you have library connections.](#) The roles of the various adenine nucleotides, sulfonylurea compounds and phosphatidylinositol biphosphate (PIP₂ or, more correctly, phosphatidylinositol-4,5-bisphosphate) in regulation of membrane potentials and insulin secretion are discussed and clinical aspects are presented.

Mutations of K_{ATP} Can Cause Neonatal Diabetes.

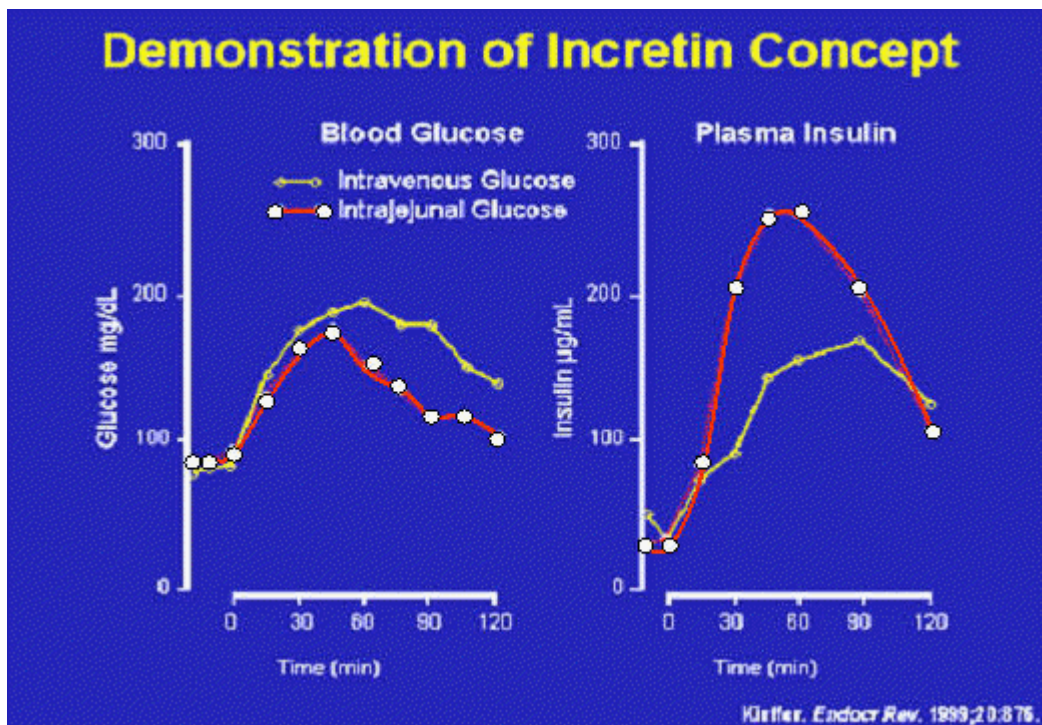
A recent article in a Norwegian newspaper reported that "the last prick" for Silius was soon a fact". Silius, a boy about four years old, had a rather seldom form of diabetes and was dependent upon insulin injections for control of his metabolism. However, a recent study indicated that some such patients (with neonatal diabetes) have a fail in the coupling of the K_{ATP} channel to metabolism. The channel does not respond to ATP. These patients produce insulin but not in response to increased blood glucose. They do respond to sulfonylurea compounds. That is, the K_{ATP} is not inhibited by increases in the ATP/ADP ratio while the SUR1 moiety can still block K^+ flux. In these patients tolbutamide tablets just might be able to replace insulin in these patients. This is now being tested.



As you can see, the Norwegian boy, Silius, really looked forward to escaping "the insulin needle"!

Incretins; Intestinal Agents which Increase Insulin Secretion in a Glucose-coupled Manner.

One of the first review articles which indicated that the intestines were involved in control of insulin secretion was published by Kieffer in *Endocrinology Reviews* in 1999. A figure from that publication can be seen at the below. Identical amounts of glucose are administered intravenously or directly into the intestine. In the latter case, blood glucose levels returned to normal more quickly than when the challenge was given intravenously. Furthermore, plasma insulin increased more rapidly and to

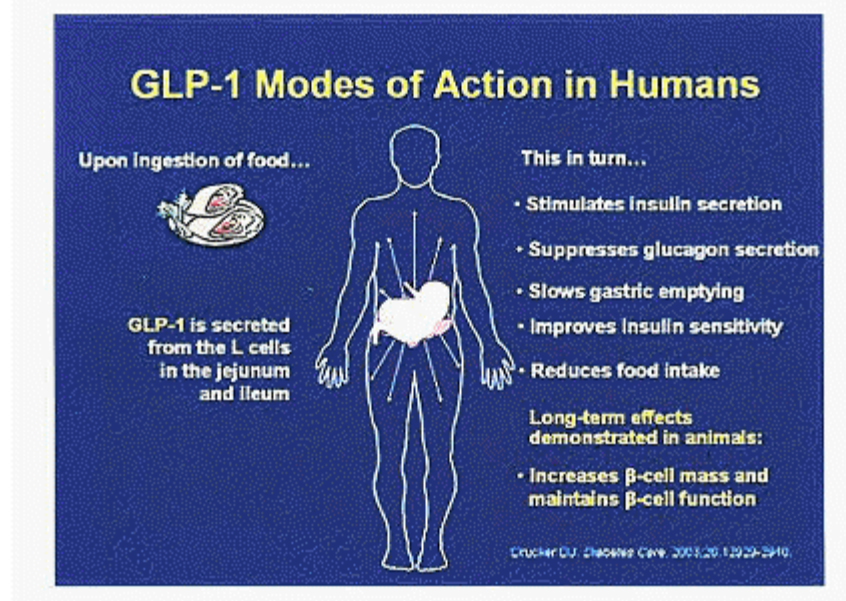


much higher levels following intestinal administration of glucose.

To make a long story short, it was soon realized that the L-cells of the intestine produce and secrete a peptide derived from a form of pro-glucagon, now known as glucagon-like protein-1 or GLP-1. This has several effects in the pancreas and is mainly involved in increasing insulin secretion and inhibiting glucagon release. The next figure, taken from Medscape illustrates this.

A GLP-1-like peptide is found in a lizard which eats only a few times each year, controlling insulin secretion to pass the eating habits of that strange animal. [Click here for more information](#). The working mechanism of GLP-1 in the beta cell was suggested to be activation of adenylyl cyclase and protein kinase A. This could lead to phosphorylation of a voltage-dependent K^+ channel. Thus two K^+ channels, K_{ATP} and K_v may be involved in adjusting K^+ levels in the beta cell.

Intestinal Hormones (Incretins) Control Pancreatic Hormone Release



The incretin area has advanced quite rapidly and several preparations are now in use clinically. I refer my readers to Medscape.com, which has an extensive "resource center" dedicated to this subject. [Click here to connect.](#) Use of Medscape requires cost-free registration.

Several Potassium Channels Determine Membrane Potential and Steer Insulin Secretion.

The Voltage-Dependent K^+ Channel (K_v channel).

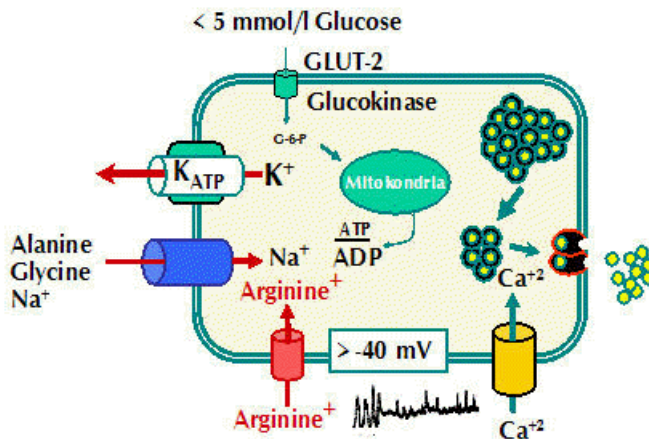
Insulin release from beta cells is controlled by the intracellular K^+ concentration. As described above, flux of K^+ from these cells is believed to be controlled by the K_{ATP} channel. However, there are several other potassium-carrying pores in beta cells and the intracellular concentration of K^+ reflects the balance between these.

The most interesting today is perhaps the K_v channel. This pore system is voltage-dependent. It opens following depolarization of the cell membrane, in a manner similar to the voltage-dependent Ca^{++} channel (VDCC channel).

While depolarization of the cell membrane follows inhibition of the potassium-releasing channel, repolarization is the result of activation of a channel which ships potassium out of the cell! The potassium (K^+) level in the beta cell (and, therefore, the membrane potential) is dependent upon the balance between these two port systems. The rate of insulin secretion is, therefore, also dependent upon the balance between these two K^+ transport mechanisms.

That is, their entry into the beta cell leads to ionic changes that depolarize the beta cell, trigger Ca^{++} uptake and stimulate exocytose of insulin-containing granules. However, the K_{ATP} channel is not involved in this process.

Glycine, Alanine and Arginine are Insulin Secretagogues



How can these amino acids (alanine, glycine and arginine) cause depolarization of the beta cell without involving K^+ transport?

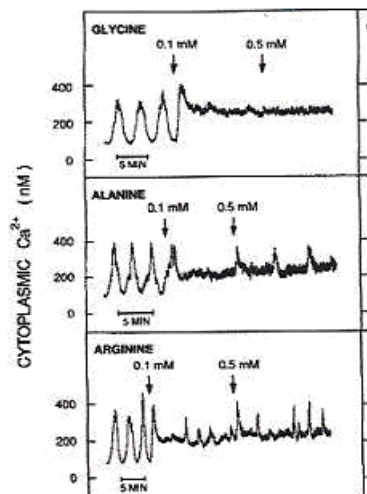
Alanine and glycine share a symport that also transports Na^+ into the beta cell. The amino acid-induced influx of Na^+ is sufficient to depolarize the cell, activating the Ca^{++} channel with ensuing Ca^{++} uptake and insulin release.

A dedicated arginine transport protein is also present in the beta cell plasma membrane. Arginine is a cation at physiological pH and can directly depolarize

the beta cell. Arginine is, in fact, the strongest insulin secretagogue, measured on a mole for mole basis. It is often used to initiate insulin secretion in clinical testing of beta cell capacity.

The effects of these three amino acids on Ca^{++} influx can be seen in the next figure. The Ca^{++} waves were initiated by incubation with 10 mM glucose. The three named amino acids caused further and sustained Ca^{++} influx.

Glycine, Alanine and Arginine increase Cytoplasmic Ca^{++}

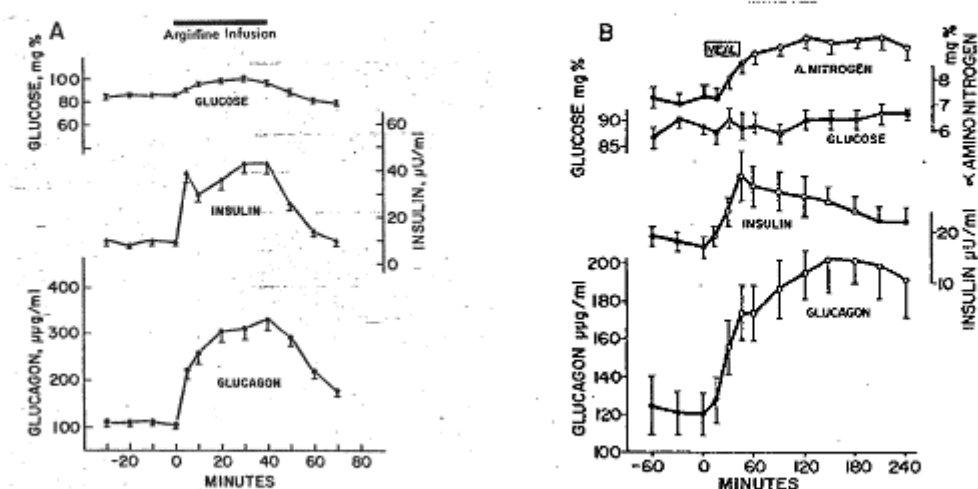


Ahmed, C. Raupengast and Hellman, J. Endocrinology 160, 191, 1999

Protein Meals Stimulate Both Insulin and Glucagon Secretion.

Secretion of insulin and glucagon are most often opposed; ingestion of a balanced meal leads to increased insulin secretion and a very marked fall in glucagon secretion. The opposite occurs in the post-adsorptive period or when exercising. However, a striking exception to this "rule" is intake of a protein-rich meal (a steak, a salad and a glass of a good red wine). In the following figure you can see that levels of both insulin and glucagon rise after an arginine infusion or a protein-rich meal. What is the logic behind this?

Insulin and Glucagon Secretion is Stimulated by Arginine or a Protein Meal



Muller et al., *New Engl. J. Med* 285, 1450-1454 (1971)

Amino acids obtained from degradation of muscle proteins are the body's largest reserve of precursors for gluconeogenesis. During periods without food glucagon secretion increases and insulin levels fall. One of the major metabolic effects of this is stimulation of hepatic gluconeogenesis.

Following a protein meal we absorb large quantities of amino acids. There is no storage form for these. After requirements for amino acids for protein synthesis are covered, the remaining amino acids are either converted to glucose or lost to the urine. Conversion of amino acids to glucose requires activation of gluconeogenesis. The increased levels of glucagon that follow a protein meal do just this, leading to

synthesis of glucose from the ingested amino acids. However, this does not lead to marked changes in blood glucose. You can see from panel B in this figure that blood glucose levels are relatively stable after a protein meal. This is due to the balance between insulin and glucagon secretion. Glucagon stimulates conversion of amino acids to glucose in the liver, insulin stimulates uptake of this glucose in muscle tissue and storage as glycogen. We can see in panel A that arginine infusion has a strong and similar effect.

Do Circulating Fatty Acids Influence Insulin Secretion?

Fatty acids and their breakdown products, ketone bodies, are important substrates for energy production in most of the body's tissues. Important exceptions are the CNS and blood cells. Insulin is a major factor in regulation of fatty acid metabolism. This hormone down-regulates lipolysis and release of fatty acids from adipose tissue. Thus, the increased levels of insulin that following a meal strongly inhibit lipolysis and fatty acid release. This action is reversed postprandially. Insulin levels are down-regulated between meals, allowing lipolysis and fatty acid release to increase parallel to the sinking plasma carbohydrate levels. This stabilizes supply a substrate for energy metabolism in working tissues.

Insulin is also involved in hepatic synthesis of lipids from carbohydrates and storage of triglycerides in adipose tissue.

One would expect, therefore, that fatty acids were one of the factors involved in control of insulin release from beta cells. Indeed, this has been discussed in the literature over many years. The problem is that earlier work has shown "no effect", increased insulin release, and decreased insulin secretion following exposure of pancreas to fatty acids and ketone bodies. However, there now seems to be agreement that fatty acids and ketone bodies do activate K_{ATP} through effects on SUR1 and that these can suppress the direct effects of ATP on Kir6.2. In other words, fatty acids (or their CoA derivatives) increase K^+ flux out of the beta cell, increasing polarization and reducing insulin release. A balance may exist between the insulin-releasing actions of glucose and amino acids on one hand, and inhibition by fatty acids on the other. The details and further references can be called up here: "Alchemy in the Soup: Transforming Metabolic Signals to Excitability, Colin G. Nichols, Sci STKE 2007, 410-414". [Click here if you have library connections.](#)

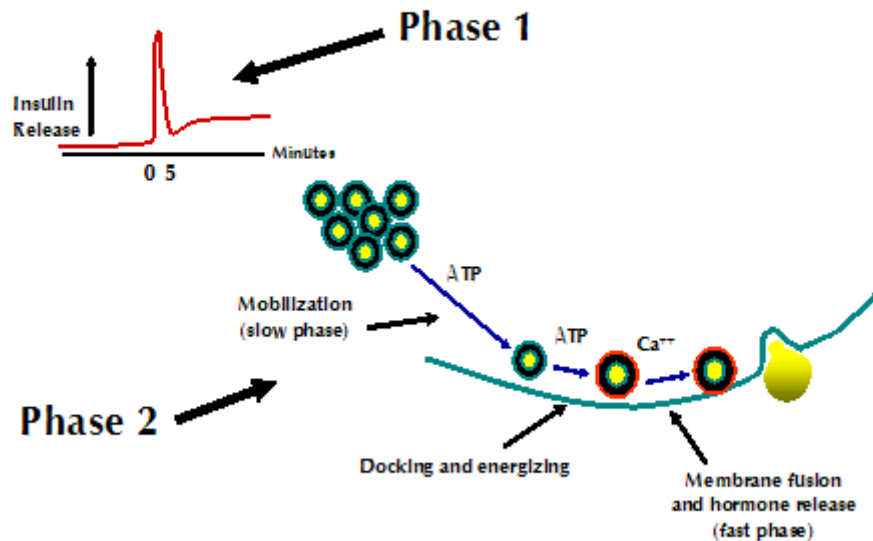
Insulin Secretion is Biphasic.

Ingestion of sugar is followed by a biphasic insulin release. A very rapid rise in insulin secretion is seen within minutes after administration of a glucose load. A rapid fall in secretion follows, then pursued by a long-lasting but slower release of the hormone. The first top results from exocytosis of granules from the "readily released" pool and comprises 5-10% of the insulin stored in the beta cells. The sustained slow release is comprised of granules from the "reserve pool". Maximum insulin levels are reached approximately 60 minutes after a mixed meal. Closer examination of this phenomenon has greatly increased knowledge about insulin secretion. Let us examine a few of the details in these processes.

1: A fast phase requiring ATP and Ca^{++} in which granules in the "readily released pool" are already "docked" and "energized". This is the rapid first phase of insulin release and is depicted in the next figure. This phase of insulin secretion accounts for only about 5% on the total released after a meal.

2: A slow second phase requiring ATP. Here, granules are moved from the "reserve pool" to the "readily released" pool of insulin

Insulin Secretion is Biphasic



Modified from F. Kozman, *Diabetologia* 40, 487-495, 1997

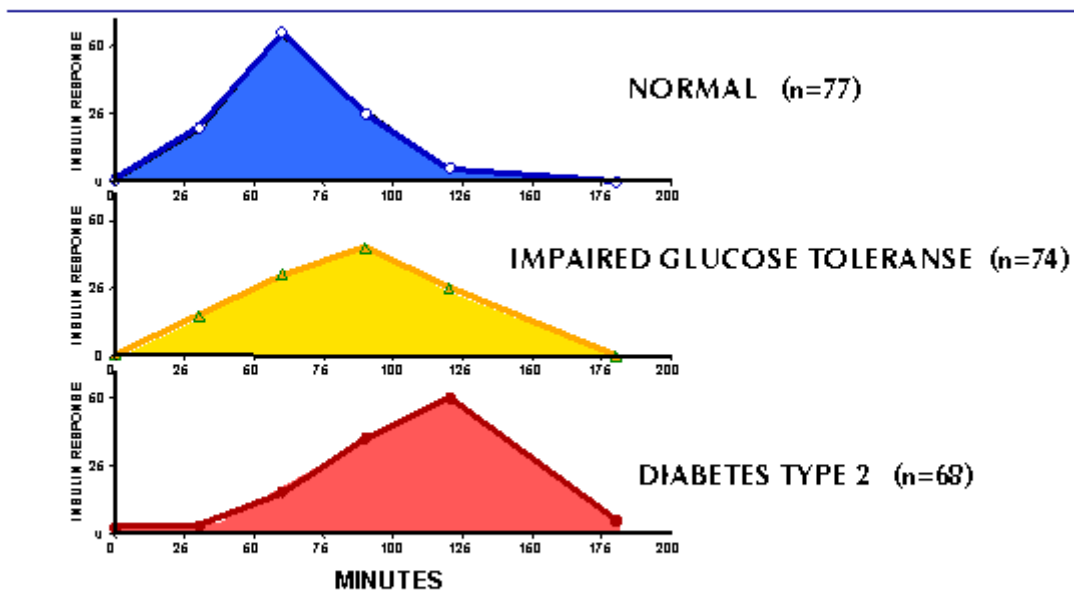
granules. Docking and energizing of the granules are part of this slow second phase. This slow phase is the major contributor to insulin release.

Please note that this discussion is merely an introduction to control of insulin release. For more and very up-to-date information please go to [Insulin Granule Dynamics in Pancreatic Beta Cells, P. Rorsman and E. Renström, *Diabetologia* 46, 1029 2003.](#) Just click on the title.

The Rate of Insulin Secretion in Impaired Glucose Tolerance (IGT) and Diabetes Type 2.

An understanding of these processes has clinical importance. It is well known that patients with diabetes type 2 and those with impaired glucose tolerance (pre-diabetes) exhibit a delayed response to a glucose load. While these patients produce apparently sufficient quantities of insulin in response to a challenge, secretion is not

Peak Insulin Response after Oral Glucose



R.W. BERGSTRÖM, J. CLIN. ENDOCRINOL. METAB. 71: 1447-1453, 1990

properly timed. The initial rapid rise in blood glucose does not illicit the usual "insulin spike"; the rapid first phase is reduced or lacking. Because of the lack of correlation between carbohydrate uptake from meals and timing of insulin secretion, these patients experience hyperglycemic periods after meals.

Medication and dietary treatment of patients can in many cases provide adequate adjustment of the amount of insulin released from beta cells in diabetic and IGT patients. However, loss of the rapid first phase of insulin release remains a major problem. To date, treatment does not restore correct timing. This can lead to glucose "tops" after meals in excess of acceptable levels. These periods of increased blood glucose levels are thought to lead to the development of diabetic complications.

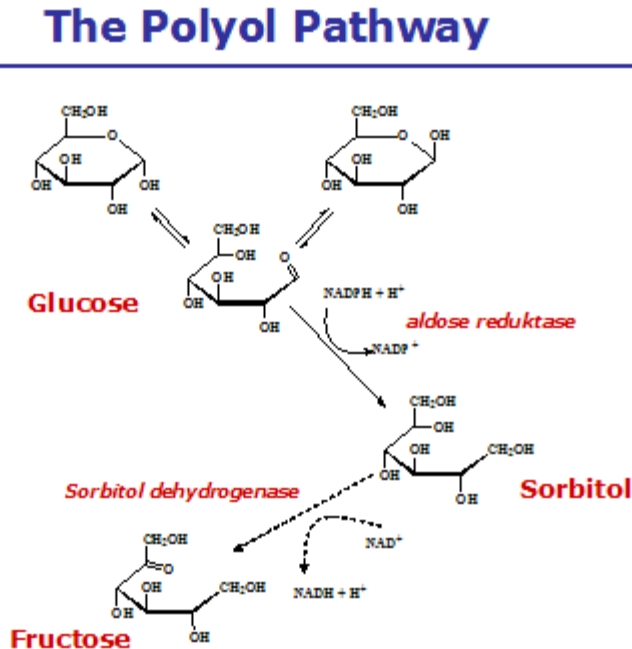
Once again, What is Wrong with Glucose "Overshoots"?

Three pathological processes seem to follow hyperglycemia.

1. Conversion of glucose to sorbitol with ensuing osmotic disturbance.

This occurs through the "polyol pathway", a normal reaction sequence in testes but

not other tissues. In the first step, Glucose is converted to sorbitol by aldose reductase. The sorbitol formed is then oxidized to fructose.



A problem arises when sorbitol production occurs in tissues other than testes. At high glucose levels, aldose reductase activity

occurs in other organs which often lack sorbitol dehydrogenase. This leads to an accumulation of sorbitol in these tissues, notably in the lens of the eye, leading to cataract formation due to osmotic damage.

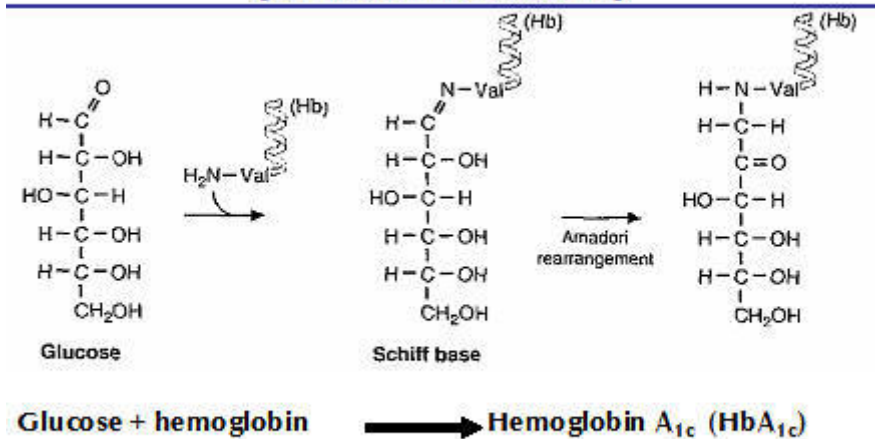
2. Spontaneous non-enzymatic glycation of proteins (Maillard Reaction).

Glycation of proteins is a normal process which follows reaction of the carbonyl group in glucose with amino groups in proteins. The Maillard reaction, which we all enjoy as the browning of meats and development of good smells from the kitchen, is based on this non-enzymatic reactions between carbohydrates and the proteins in meat. The carbonyl group in glucose makes it a reactive compound. Glycation proceeds at a rate which is proportional to the concentration of glucose in the blood.

Hemoglobin A1c (HbA_{1c}).

As I mentioned above, the degree of glycation of the body's proteins is related to blood glucose levels. Hemoglobin has a half-life of about 100 days. The degree of glycation of hemoglobin gives, therefore, a picture of average blood glucose levels

Non-enzymatic Glycation of Proteins (Amadori Reaction)



Marks, Marks, and Smith, s. 88

for the previous three month period. Glycated hemoglobin is known as HbA_{1c}. Normally, HbA_{1c} accounts for approximately 5-6 % of the total hemoglobin. Diabetic patients often have HbA_{1c} in excess of 8-10%. It has been usually assumed that glycation of hemoglobin followed reaction with glucose, as shown in the next figure. Current studies have, as

noted above, indicated that other reactive species, especially methylglyoxal, may be involved in this process. Note that the degree of glycation of hemoglobin is an indication of the extent of glycation of many of the body's proteins and possible ensuing cellular damage.

Successful Treatment of Diabetes Lowers HbA_{1c} levels.

Effect of Improved Glycemic Control on Complications of Diabetes

Study	N	Follow-up, years	Risk reduction per 1% fall in HbA _{1c}			
			Retinopathy	Renal	Neural	CV
1	739	6.5	33%	25%	32%	40%
2	55	6	33%	50%	↑NCV*	25%
3	4209	9	19%	26%	18%	18%

* Neural conduction velocity

Kelwyn from Medscape CME, "Diabetes Management in the 21st Century: Multiple Therapeutic Options for Achieving Glycemic Control", (03.2001)

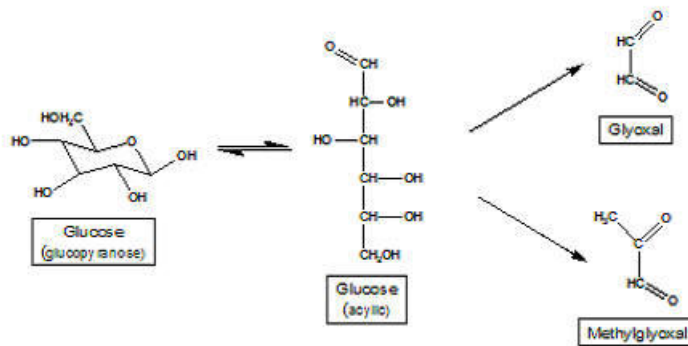
Treatment of diabetes type 2 is often monitored by follow alterations of HbA_{1c} levels. Marked improvements are seen with small changes in this parameter. In the following table we can see that a 1% fall in HbA_{1c} resulted in improvement in retinopathy and kidney, nerve and cardiac function in the studies quoted here. Today's clinical goal for treatment of diabetes is to reduce HbA_{1c} levels < 6.5 % (November 2007).

3. Formation of reactive α -oxoaldehydes from glucose; glyoxal and methylglyoxal.

Several studies published during the past few years have shown that reactive aldehydes are normally formed in the body from glucose. These are found at rather low levels at normal blood sugar levels, but increase with age and in type 2 diabetes. Reaction with glucose or these breakdown products leads to increased glycation and formation of so-called "advanced glycation end-products" or AGE. These are stable proteins formed from those found normally in the body. Unfortunately, these often lose their physiological functions when glycated. It seems that damage to the retina (retinopathy) and lens of the eye (cataracts), nerves

(neuropathy) and the kidneys (nephropathy) at least partially due to glycation of cellular proteins.

Conversion of Glucose to α -oxoaldehydes



Two of the reactive α -oxoaldehydes formed from glucose are glyoxal and methylglyoxal. These are synthesized from normal intermediates in glycolysis, dihydroxyacetone phosphate and glyceraldehyde-3-

phosphate. These substances are present at about 0.3% of the blood glucose concentration. Long-lasting increases in glucose levels leads to accumulation of methyl glyoxal in various tissues with ensuing glycation and damage to cellular proteins. Check the following references for more information: Ramasamy et al, Cell (2006) 124, 258-260; Thornally et.al., Biochem. J. 344(1999) 109-166; Ahmed et. al., Invest Ophthalmol Vis Sci (2003); 44: 5287-5292.

Glucagon Secretion.

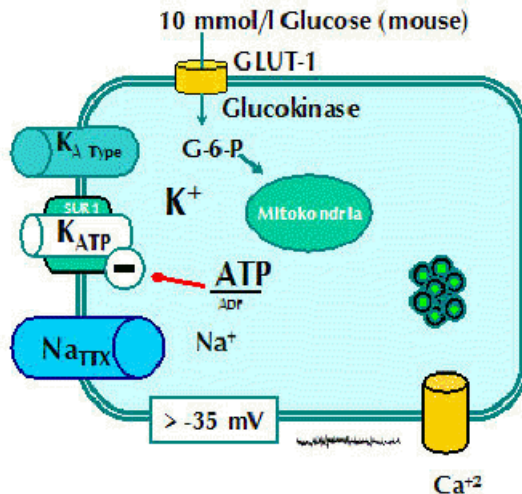
Control of glucagon secretion is not as well understood as that of insulin. Secretion of glucagon is clearly linked to the alpha cell's metabolism. Lack of substrate, anoxia and metabolic poisons lead to release of glucagon from these cells. In short, they release their hormone in response to "metabolic stress". As is the case of the beta cell's release of insulin, it has become clear that regulation of the membrane potential is decisive for control of glucagon secretion.

to be initiated by an influx of Na^+ and Ca^{++} and to be terminated by voltage-dependent K^+ channels. Release of glucagon from the "readily released pool" is a function of Ca^{++} entry.

Increased glucose levels lead to quiescence in the alpha cell. The K_A channel, the

Na_{TTX} channel and the Ca^{++} channel become inactive at higher glucose concentrations. Secretion of glucagon falls to basal levels.

Ionic Control of Glucagon Secretion



Cöpell et al. *J. Physiol.* 328, 509-520 (2000)

Although mouse alpha cells do metabolize glucose, the link between control of the ion channels and metabolism has not yet been identified.

As you can understand now, secretion of insulin and glucagon are extremely complicated processes. Many elements play a role in determining the

sensitivity of alpha and beta cells to plasma signal substances. The review articles mentioned above give insight into current knowledge. You will have to follow the literature to keep up with advances in this clinically important field.