HOW TO GET THE RIGHT MEAL TIME INSULIN DOSE WITH TYPE 1 DIABETES

Diabetic™
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THE INSULIN TO GLUCAGON RATIO

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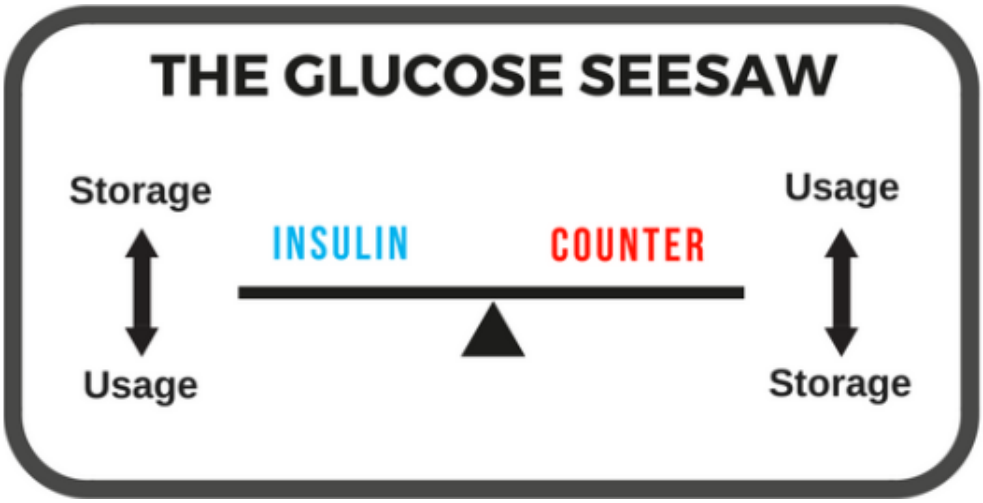
ABBREVIATIONS

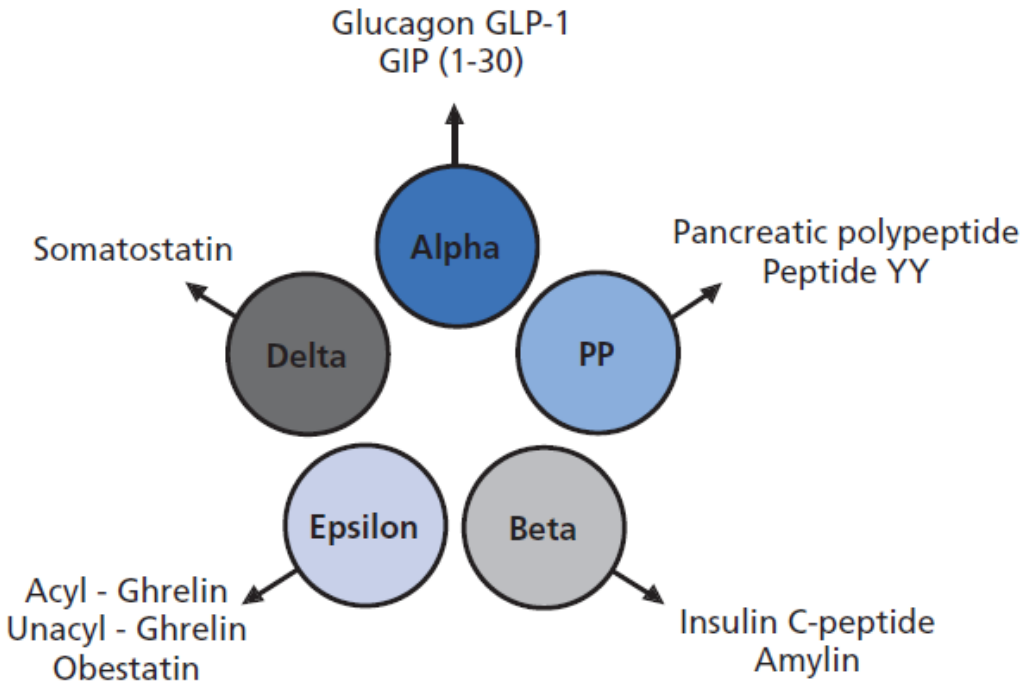
AA = Amino Acid
ADP = Adenosine Di Phosphate
ATP = Adenosine Tri Phosphate
AUC = Area Under the Curve
BCAA = Branches Chain Amino Acids
Ca = Calcium
CGM = Continuous Glucose Monitoring
FFA = Free Fatty Acid
FPU - Fat and Protein Units
GDH = Glutamate Dehydrogenase
GI = Glycaemic Index
GL = Glycaemic Load
GLP-1 = Glucagon-like peptide-1
GIP = Gastric Inhibitory Polypeptide
GPCR = G-Protein Coupled Receptor
I:G = Insulin to Glucagon ratio
ICR = Insulin to carbohydrate ratio
MDI = Multiple Daily Injections
MUFA = Monounsaturated Fatty Acids
KATP = ATP-regulated potassium channel
mTOR = mammalian target of rapamycin
SFA = Saturated Fatty Acid
TCA = Tri-Carboxyl-Acid cycle

THE INSULIN TO GLUCAGON RATIO (I:G)

After eating your blood glucose level is mainly determined by two hormones that are secreted by the pancreas, Insulin and Glucagon. An easy way to remember the basic principle is to think of a Seesaw. When your INSULIN is high and glucagon (glucagon is one of the COUNTER-regulatory hormones, along with Cortisol and adrenaline) low, you have a high I:G,and your body is in energy storage mode. When your I:G is low, your body is in energy usage mode.



In reality it is a little more complex, that's why we must consider all the hormones secreted by the pancreas cells.



Adapted from Hughes and Narendran (1)

At this stage you just need to recognise the different types of cells, and what hormones they secrete. We will move into why these are important, and under what circumstances they get secreted later.

Our main focus is discovering what happens when the I:G changes, and understanding the blood glucose consequences .

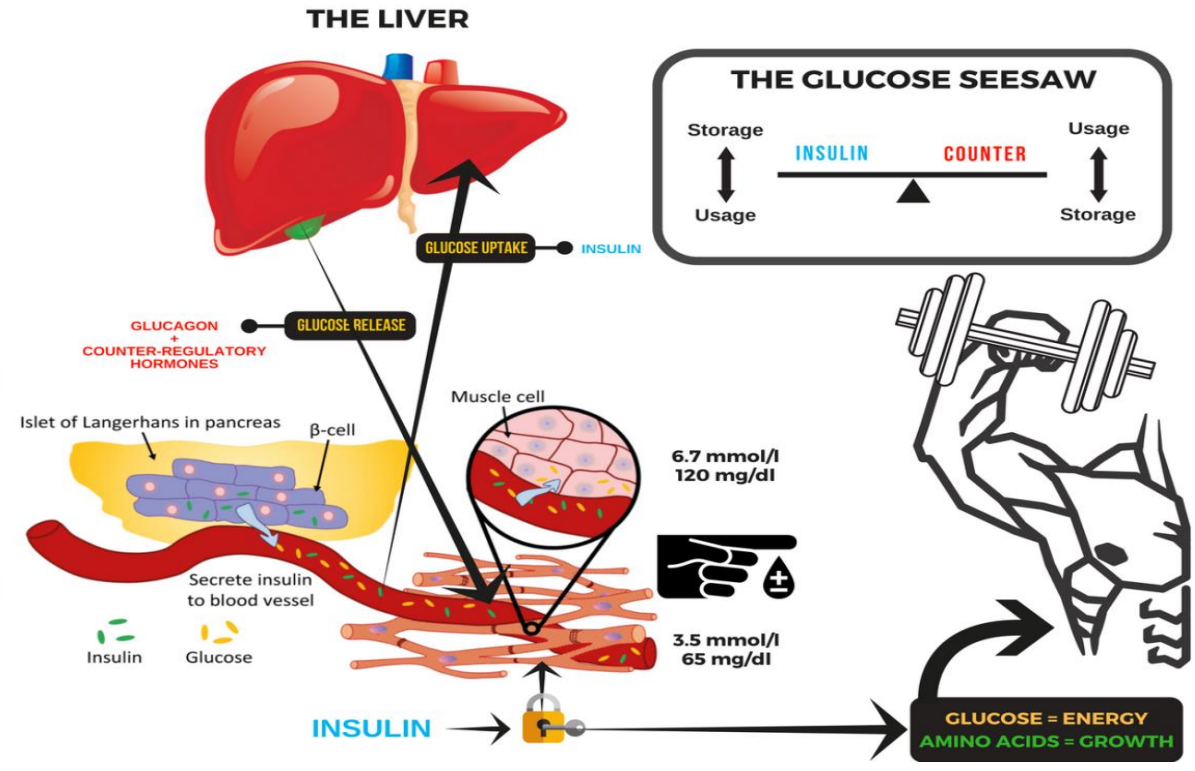
Let's get started with Insulin.

INSULIN

Insulin is the main hormone secreted from the B-Cells of the pancreas. Insulin has an enormous number of direct and indirect effects on metabolism. We shall focus our discussion on the main ones of:

- Anabolism: using AA (amino Acids) for the synthesis of more complex molecules, mostly for growth and repair.
- Energy storage: Glucose as Glycogen and Free Fatty Acids (FFAs) as Fat.
- Energy production: the movement of Glucose into cells to be used as fuel.

Insulin moves glucose and AA from the blood into the cells of the body. Consider insulin as a key that unlocks the body's cell doors to allow glucose and AA to enter, a bit like a bouncer on a club door. See the below diagram for an overview. The next sections discuss what happens to the glucose and AA once they have been transported into the body's cells.

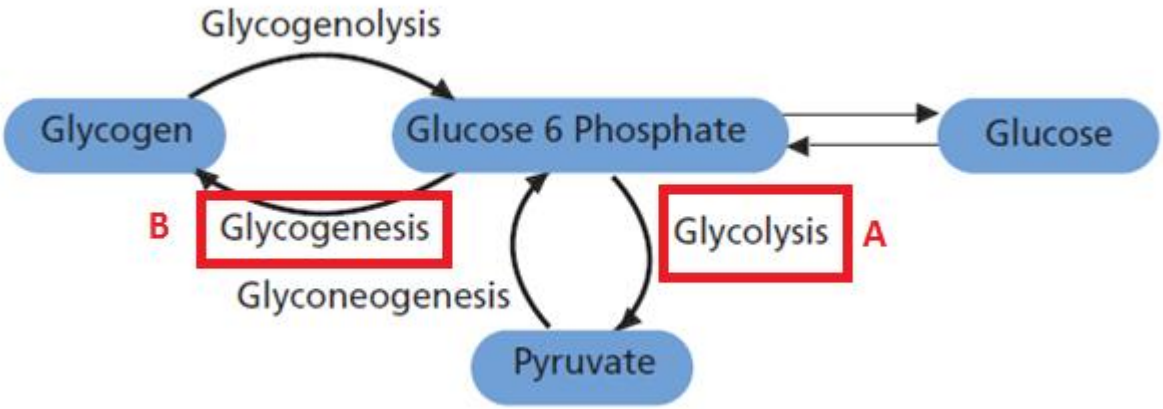


GLUCOSE

Once glucose is transported into the cells by insulin, it can take several paths depending on the energy state of the cells:

A. **If the cells have a low energy state**, glucose will be metabolised immediately to produce energy, by a process called glycolysis.

B. **If the cells have a medium to high energy state**, glucose will be stored glycogen, which is a collection of glucose molecules bonded together, by a process called glycogenisis. This happens in the liver cells first, and later in the muscle cells.



Adapted from Hughes &Narendran (1)

C. **If the cells have a very high or excess energy state**, glucose can be converted into fat in the liver cells, by a process called lipogenisis, the creation of new fat. You have to be continually overfeeding for this to happen. But as half of the population is overweight or obese, it's happening far more frequently than it should!

AMINO ACIDS

Once AA's are transported into cells by insulin, they can take several paths depending on the energy state of your cells.

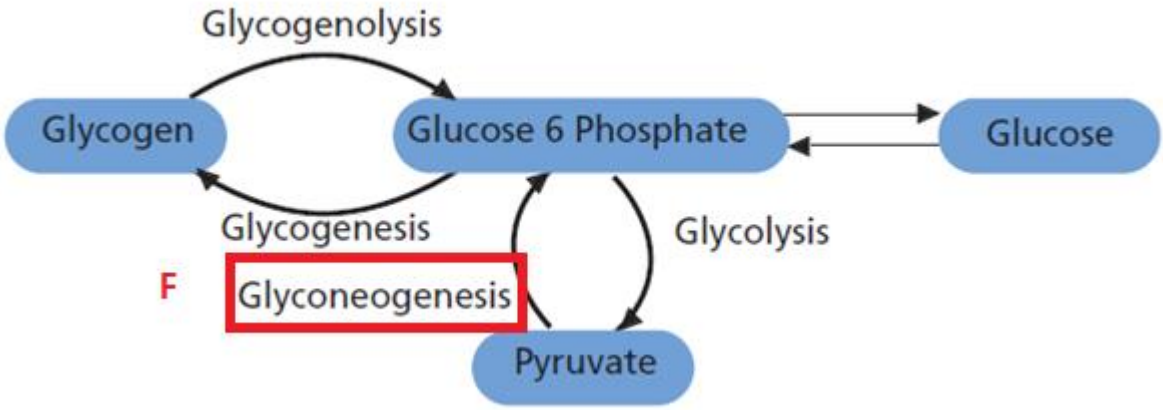
D. **If the cells have a low energy state**, AA can be converted into substrates for the production of energy from glycolysis. Think of substrates as an assembly line worker needed to produce car part. The worker is not the car part, but he is needed to ensure the process is done quickly and efficiently.

E. **If the cells have a medium to high energy state,** AA's will be used as building blocks for a massive array of metabolic processes that allow repair, regeneration and growth. Some of the more important ones are:

- **Anabolism**: muscle protein synthesis allows your muscles to adapt and remodel in response to the daily stresses.

- **Enzyme production** to ensure all the metabolic processes that are essential to sustain life run smoothly.

F. **If cells have a very high or excess energy state**, the AA not used as building blocks will be used for future energy production.
   - Excess AA's can be used as substrate to increase glycogen by a process call Glyconeogenisis.



Adapted from Hughes &Narendran (1)

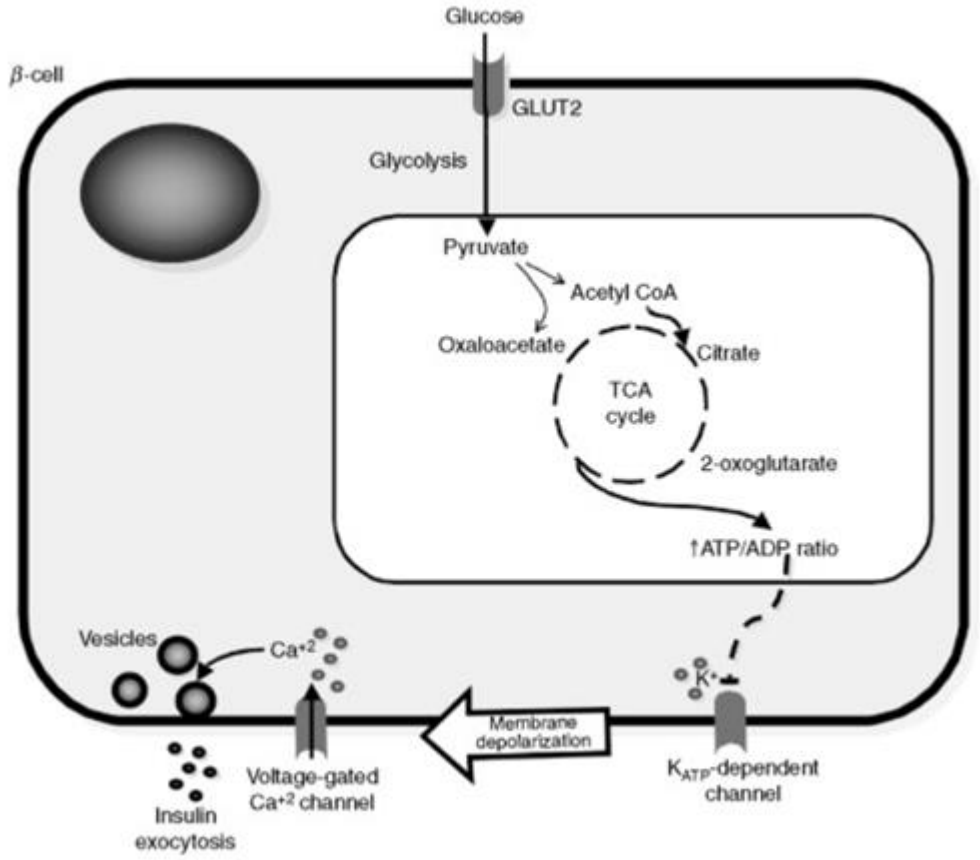
- Or AA will be converted in to new glucose that is delivered into the blood stream by a process called Gluconeogenisis. This basically means the creation of new glucose.

THE REGULATION OF INSULIN SECRETION

The regulation of Insulin secretion is very complex, and not yet fully understood. However, the key-regulators are well documented and are presented here.

GLUCOSE

The major positive regulator that stimulates insulin secretion is an elevation of glucose in the B-Cell, as shown below by the diagram below.



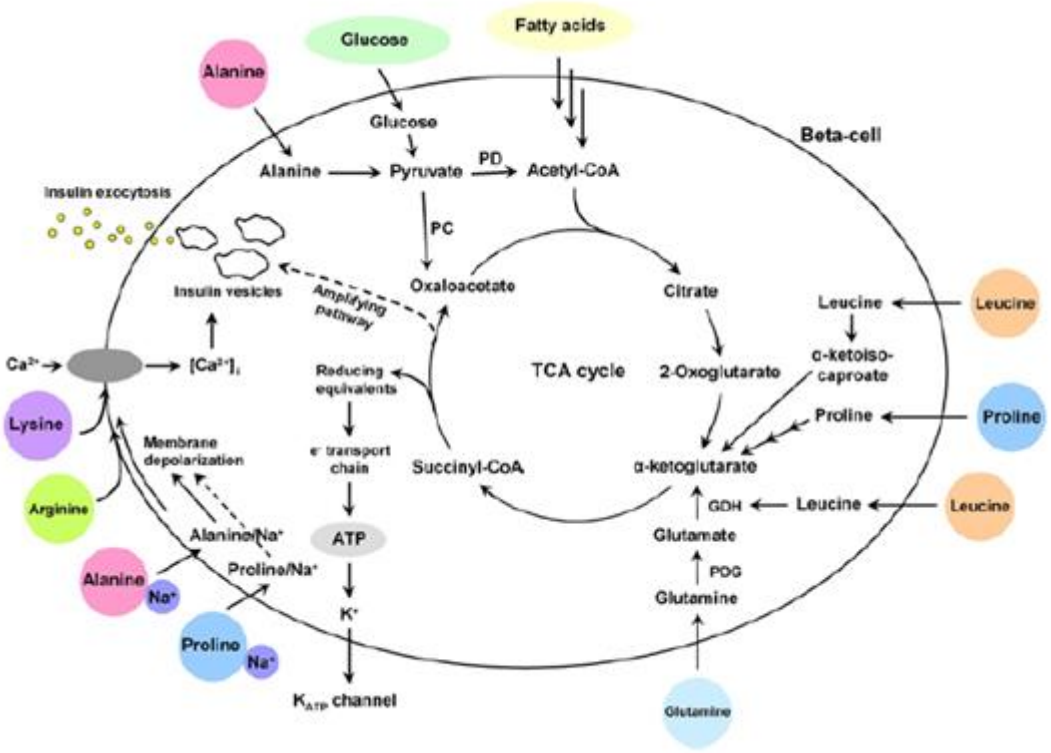
Adapted from Bell (67): The high energy state of the cell (high ATP/ADP ratio), from increased glucose availability and glycolysis, leads to depolarisation of the B-Cell membrane. The membrane depolarisation increases in-flux of Ca (Calcium), leading to insulinexocytosis from the form the vesicles into the blood stream.

Put simply, the B-Cell increases its energy state due to increased glycolysis, and stimulatesinsulin secretion in dose-dependent manner.

AMINO ACIDS

AA's can stimulate insulin secretion from the B-Cell by providing substrates to the Tri-Carboxyl-Acid cycle (TCA). The increase substrate availability speeds up energy production and increases energy state of the cell, a high ATP:ADP ratio. This elevation of energy state causes B-Cell membrane depolarization and insulin exocytosis. The speed and frequency of membrane depolarisation from elevated AA's in the B-Cell compared to glucose, is much slower and lower.

The below graphic shows where the different AA provides substrate for the TCA cycle to increase the ATP/ADP ratio. The graphic also shows the synergistic metabolic pathways that allow specific AA's to stimulate insulin secretion.



Copied from Bell (67)

ARGININE

Arginine is the most potent stimulator of insulin release in the presence of glucose in the B-Cell when given intravenously. It directly increases Ca stimulated insulin secretion by depolarising the membrane. However, when Arginine supplements are consumed orally, it is not possible to get a high enough blood level to stimulate insulin secretion without causing diarrhoea (60). Making it practically insignificant.

LEUCINE

Leucine when given intravenously is a very potent for increasing insulin secretion (59). This has been confirmed when ingested orally in combination with carbohydrate. Leucine was significantly correlating with the two hour postprandial insulin response (61).

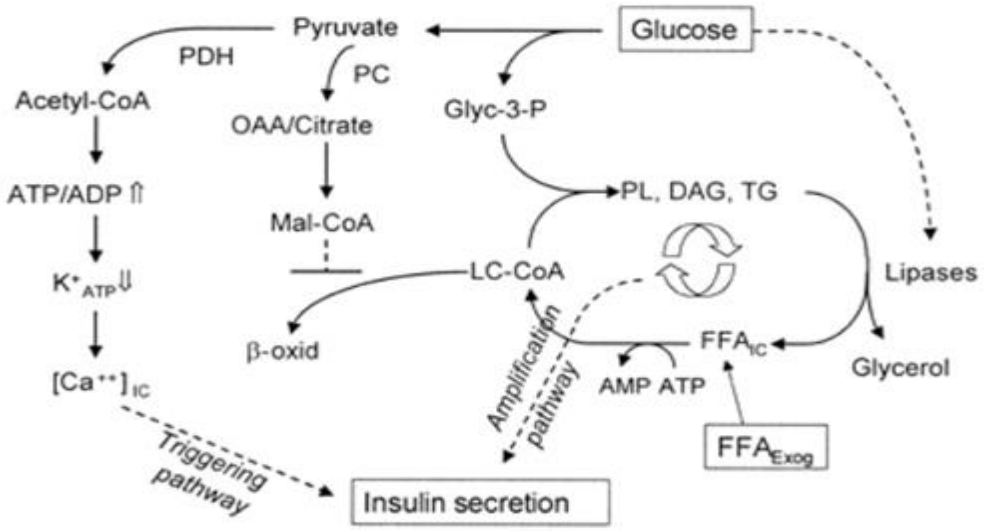
B-Cell studies have shown that Leucine activates glutamate dehydrogenase (GDH) in the B-Cell, therefore acting as both a substrate and positive regulator. GDH is a key enzyme controlling AA metabolism in the B-cells. GDH activation increases glutaminolysis and causes a subsequent increase in the TCA cycle activity, inhibition of the ATP-regulated potassium (KATP) channel activity, and thus enhanced insulin secretion (60).

Another mechanism by which Leucine may stimulate insulin secretion is through the activation of mammalian target of rapamycin (mTOR). Activation of mTOR significantly increases gene transcription and protein synthesis in pancreatic B-cells, which in turn increases insulin secretion (63).

Dairy products, particularly whey protein, are well-known to increase insulin secretion despite their low glycaemic impact. The increase secretion has been attributed to the high Leucine content. The rapidly available Leucine in the blood from quickly digested Whey elicits a stronger insulin response compared to casein. This is because although casein has high Leucine content, the proteins are coagulated, therefore blood Leucine concentration does not rise as rapidly (61).

FREE FATTY ACIDS

FFA's do not stimulate insulin release directly, however their presence is essential for glucose stimulated insulin secretion. A high FFA level amplifies the glucose stimulated insulin response (64). The diagram below shows an abundance of FFA changes the metabolic flux to promote glycolysis, which drives membrane depolarisation, and subsequent insulin secretion.



Copied from Bell (67)

Fat ingestion also increase GLP-1 (Glucagon-Like-Peptide 1), which directly stimulates insulin release (64). Acute FFA stimulates insulin secretion, however chronic exposure to high FFA levels leads to B-Cell death (64).

INCRETIN HORMONES: GLP-1 & GIP

GLP-1 and Gastric Inhibitory Polypeptide (GIP) are the two incretin hormones that are secreted by enteroendocrine cells in the intestine. GLP-1 is synthesised in the L-cells of the intestines and the A-Cells of the pancreas. GLP-1 has the most potent positive regulation on insulin secretion of the incretin hormones. GIP is synthesised in the K Cells and is weaker stimulating insulin secretion when compared to GLP-1. GIP is more potent at stimulating Glucagon secretion from the A-Cells, which we will discuss later. The picture below that shows the incretin hormones dynamic relationship, among many other signalling pathways of the B-Cell. The solid line represents positive regulation, the dashed line represents negative regulation.

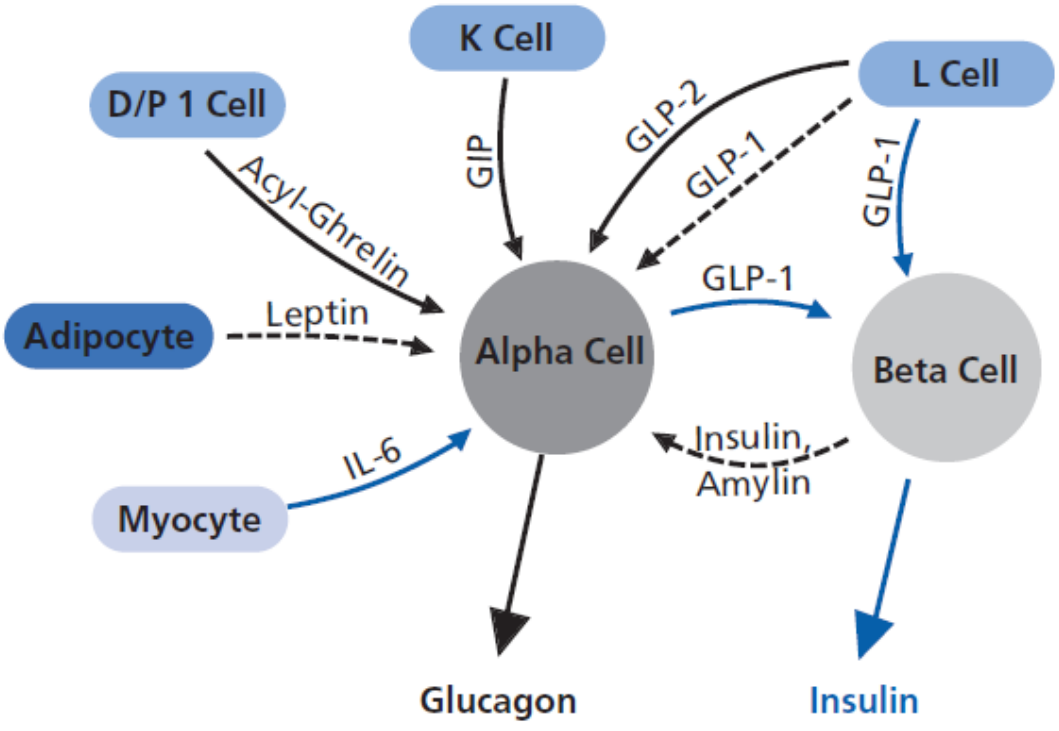
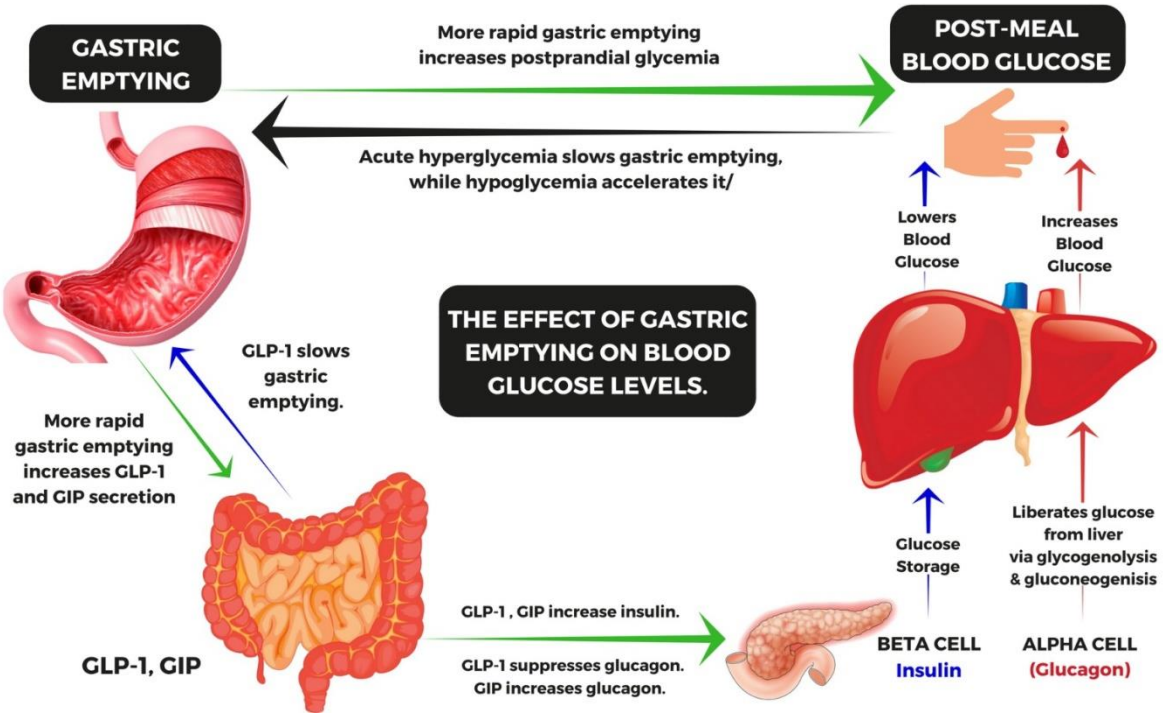


Figure Copied from Hughes &Narendran (1)

The diagram below shows that GLP-1 and GIP play a major role in the speed of stomach emptying. It also highlights their regulatory effect on the B-Cells and A-Cells of the pancreas.



GLP-1 and GIP release follows a biphasic pattern, early release within 5 to 15 minutes, and a prolonged release follows within 30 to 60 minutes. The early phase release is likely due to neural signals from food anticipation, because the nutrients cannot have reached the K and L Cells by that time. The latter phase is when glucose, FFAs and AAs reach the L and K Cells.

The incretin hormones cause insulin secretion by binding to their specific receptors, GIPR and GLP-1R, on the B-cell. This activates a host of metabolic processes resulting in closing the KATP channels, elevation of the intracellular Ca concentration, increasing mitochondrial ATP synthesis, all of which ultimately enhance exocytosis of insulin.

This GLP-1 positive regulation of insulin secretion is dose-dependent, and often accounts for half of the total insulin secretion. GLP-1 is most strongly secreted in response to ingestion of glucose. least by the ingestion of FFA's, while AAs are an intermediate stimulus (65). **This point is crucial to remember.**

SUMMARY

There are multiple regulators of insulin secretion from the B-Cells, if the B-Cells are functioning normally. The key ones stimulating insulin secretion by positive regulation are:

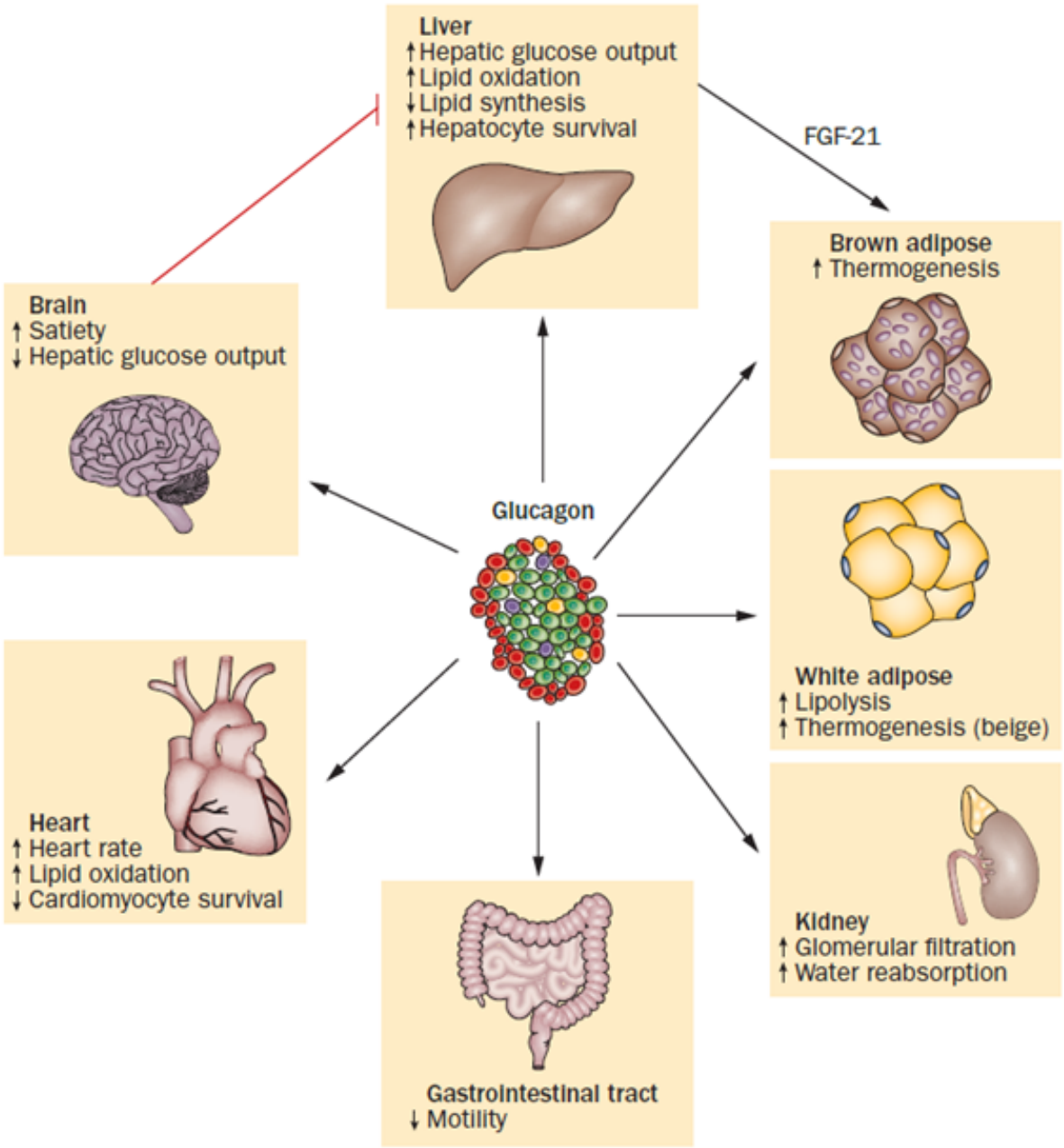
- Glucose
- AA, especially Leucine
- GLP-1

When the B-Cells have been destroyed, as happens with Type 1 Diabetes, all these signals are lost. Therefore the job of a person with Type 1 Diabetes is to match insulin delivery to what the B-Cells would have secreted in response to the meal composition, so that:

- Glucose can be transported from the blood into the cells for usage via glycolysis, and storage as glycogen.
- AA can be transported into cells for protein synthesis, enzyme re-generation, and to provide substrate for glucose metabolism.

GLUCAGON

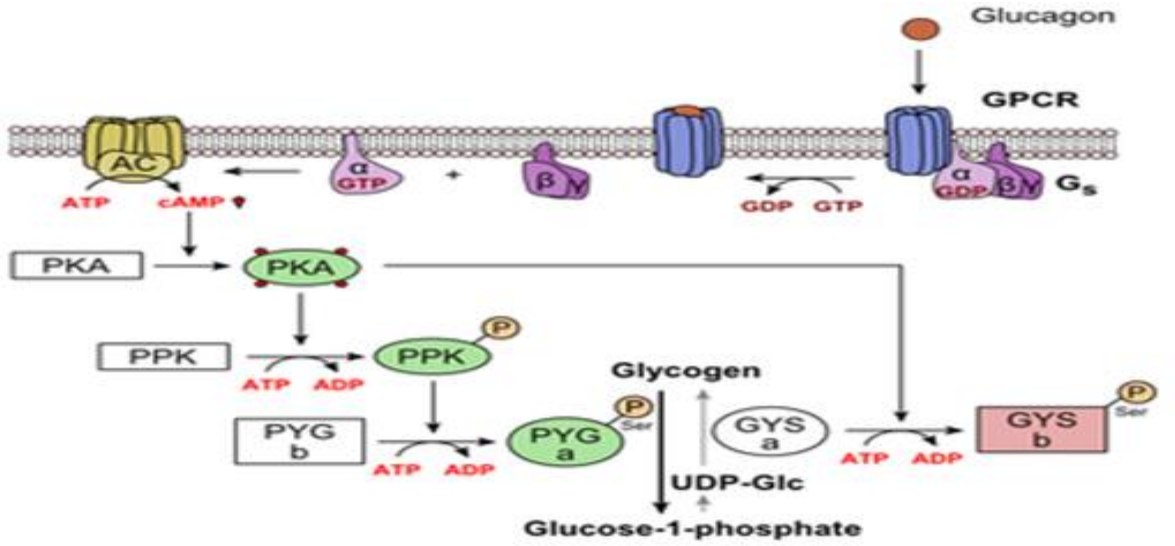
Glucagon is the main hormone secreted from the A-Cells of the pancreas. It has many functions in catabolism, the breaking down of more complex molecules, which include glucose liberation, glucose creation, and energy production. The diagram below shows the sites glucagon exerts an effect, and the number of different metabolic processes it initiates.



Copied from Hughes &Narendran (1)

For the purpose of our discussion, the main focus is glucose liberation, which is achieved

through the G-Protein Coupled Receptor (GPCR). GPCR is a single G protein-coupled receptor expressed in the liver as well as multiple tissues, such as the brain, heart, kidney, gastrointestinal tract and adipose tissues. Once Glucagon hits the GPCR, you can see in the below diagram the cascade of metabolic processes, leading to increasing glucose availability from glycogen.

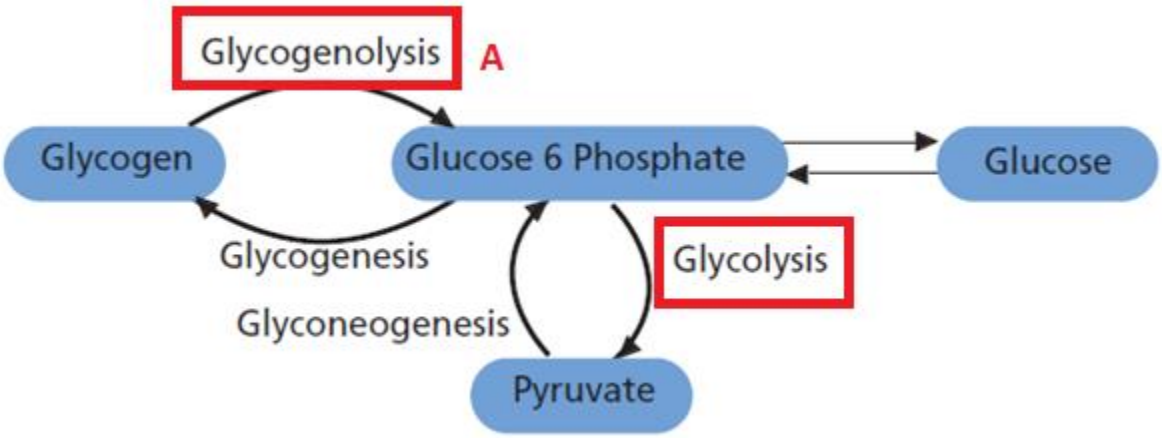


Copied from https://en.wikipedia.org/wiki/Glucagon

The metabolic process glucagon initiates depends on the energy state of the cells it binds to:

1) **If the cells have a low energy state or the I:G is low,** Glucagon will ramp up energy production and glucose availability for usage by;

    a) Glucagon will liberate glucose from glycogen, by a process called **glycogenolysis**, simply the breakdown of glycogen to free glucose. The glucose will be metabolised to produce energy via glycolysis

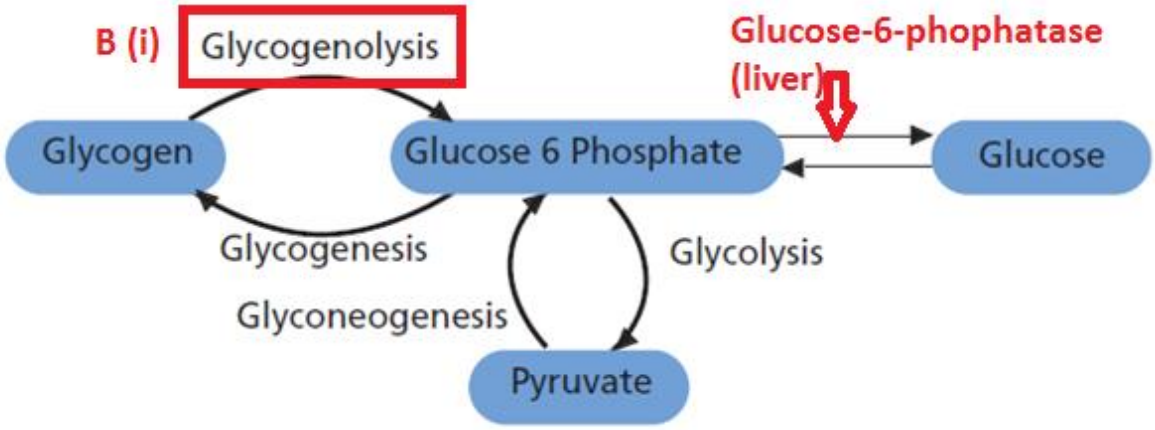


Adapted from Hughes &Narendran (1)

    b) Glucagon will ensure the blood glucose level is maintained by acting primarily in the liver:

        i) Liberating glucose from liver glycogen, by a process called **liver glycogenolysis,** so it can be pushed into the blood to supply the body's cells with glucose.

Glucose-6-phophate from liver glycogenolysis can be metabolised to glucose by the enzyme Glucose-6-phosphatase. The glucose can then freely move from the liver cells into the blood. This cannot happen in the muscle cells, because they lack the Glucose-6-phosphatase enzyme.



Adapted from Hughes &Narendran (1)

ii) A low I:G is needed for the liver to release glucose (8). This is important for people with Type 1 Diabetes for two reasons:

(1) When insulin delivery is too high, this stops glucagon liberating glucose from the liver when needed. This results hypogylcaemia.

(2) When insulin delivery is too low, or non-existent, the influence of Glucagon in the liver is exaggerated. This results in increasing glucose levels.

iii) Glucagon will start a cascade of events that creates new glucose from AA, this process is called **Gluconeogenisis,** basically the creation of new glucose.

(1) A massively important point here is that the rate of Gluconeogenisis very stable on a day to day basis, regardless of diet type. A comprehensive research review shows that Gluconeogenisis is a demand driven process. In the normal person who is not fasting, the demand stays extremely stable, so production remains unchanged (8). So simply providing more AA will not increase new glucose production. The authors concluded:

> **" the rate of Gluconeogenisis remains remarkably stable in widely varying metabolic conditions. The mechanism by which Gluconeogenisis remains relatively constant, even in the setting of excess substrates, is not known. One interesting speculation is that gluconeogenic substrates substitute for each other depending on availability. Thus, the overall rate is either unaffected or only modestly changed."(8)**

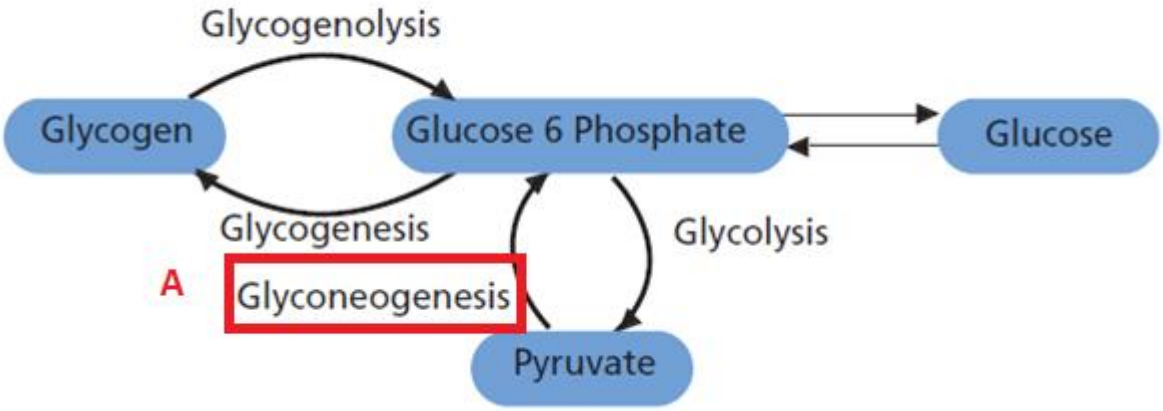
(2) This is a very important point to remember when we move into talking about Type 1 Diabetes and insulin needs later, **so take note.**

iv) Glucagon will start a cascade of events in the cells to liberate FFA from fat stores to produce energy. This reduces the usage of glucose and helps maintain the blood glucose level (13).

2) **If the cells have a medium to very high energy state**, generally the I:G will be high. Therefore the body will be in anabolism and energy storage mode. However, when a high protein low carbohydrate meal is consumed, both insulin and glucagon are elevated. Why?

a) Glucagon will ensure the blood glucose level is maintained whilst insulin moves AA and glucose into the body's cells for anabolism. Glucagon stimulates liver glycogenolysis, to maintain the blood glucose level.

- We have already discussed that Gluconeogenisis is a demand driven process, and is not stimulated by excess substrate supply such as AA (8). This was shown neatly in a study where 50g of protein (beef) was consumed to see the fate of the AA. The amount of AA converted into glucose was 11-13g, but only 2g ended up in the blood supply. Therefore 9-11g were stored in the liver as glycogen, by process called glyconeogenisis (12).Glucogenic AA can be metabolised into TCA cycle substrates, and then into pyruvate. Pyruvate can then be metabolised into glycogen, as can be seen from the diagram below.



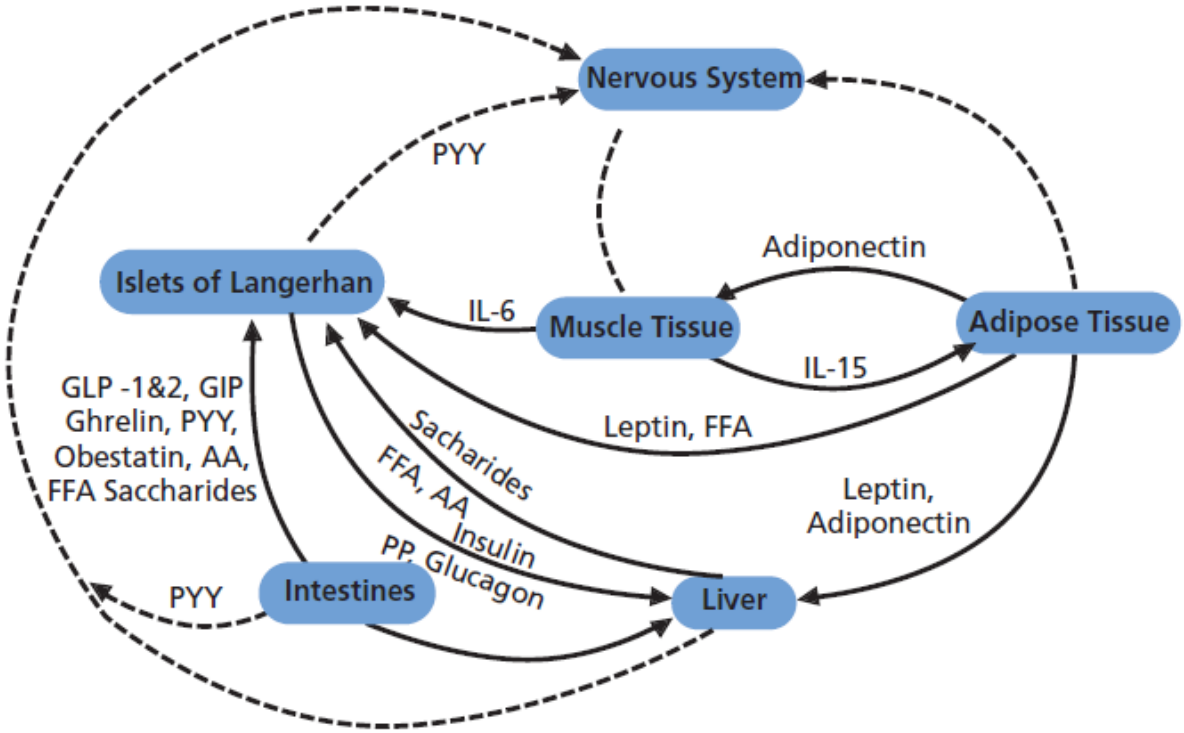
Adapted from Hughes &Narendran (1)

The above discussion shows the importance of Glucagon in maintaining the glucose level, and how the I:Gis the major determinant. You can imagine how easy it is to disrupt the I:G by delivering insulin in the wrong amounts.

Therefore understanding the regulation of glucagon secretion is a very important part of the puzzle. Let's take a deeper look.

THE REGULATION OF GLUCAGON SECRETION

The regulation of glucagon secretion from the A-Cells is very complex, and is less well understood than insulin regulation. To put the complexity into perspective, cast your eyes on the diagram below.



Adapted from Hughes &Narendran (1)

This diagram shows the complex network of hormonal, neural, endocrine, muscle and adipose tissue signals communicating pancreatic islets of Langerhans cells. It is way beyond the scope of this article to cover all of these in detail. I refer you to three excellent reviews for exploration (1,13,15). The articles by Hughes and Narendran (1) is aimed specifically at type 1 diabetes. The highlights are:

- The central nervous system stimulates Glucagon release:
    - Low blood glucose is detected in the hypothalamus leading to central nervous system activation. The end results is adrenaline release which positively regulates A-Cell secretion of Glucagon.

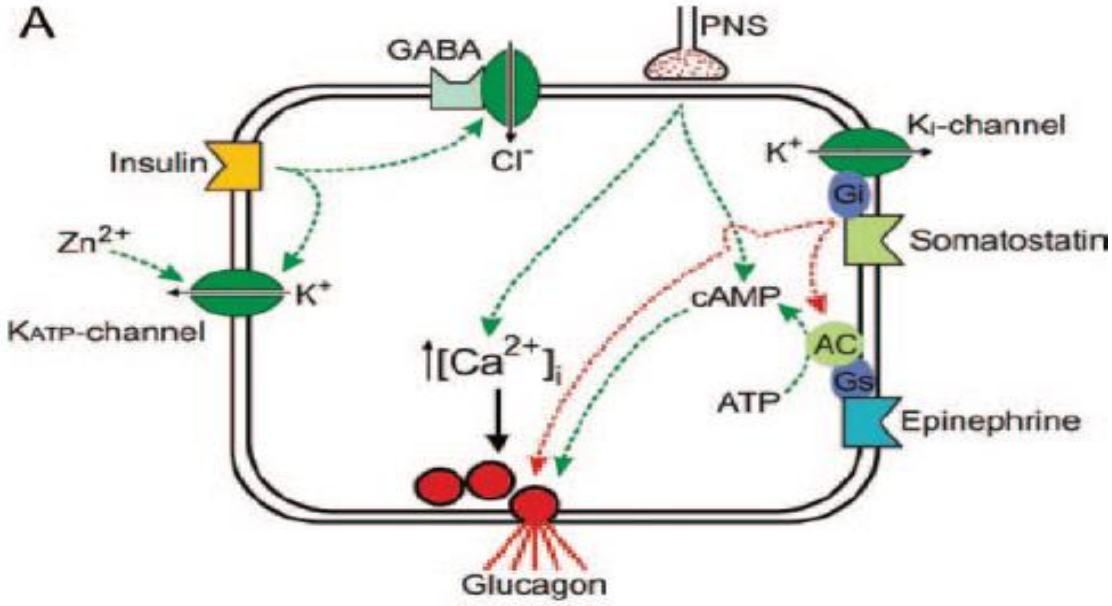
    - Parasympathetic stimulation of the vagus nerve leads to acetylcholine release that stimulates both B-Cells and A-Cells, but B-Cell stimulation is predominate. However, in Type 1 Diabetes where the B-Cell insulin secretion does not happen, A-Cells glucagon secretion predominates from parasympathetic stimulation.

- Leptin increase negatively regulates A-Cell secretion of Glucagon. Essentially the more satiated you are the lower Glucagon release.

- Arginine is a potent stimulator of Glucagon secretion.

- IL-6 from exercise increases Glucagon secretion

The diagram below shows how different signals regulate Glucagon secretion. The main stimulation is achieved by changing the cellular energy level, and elevating substrate

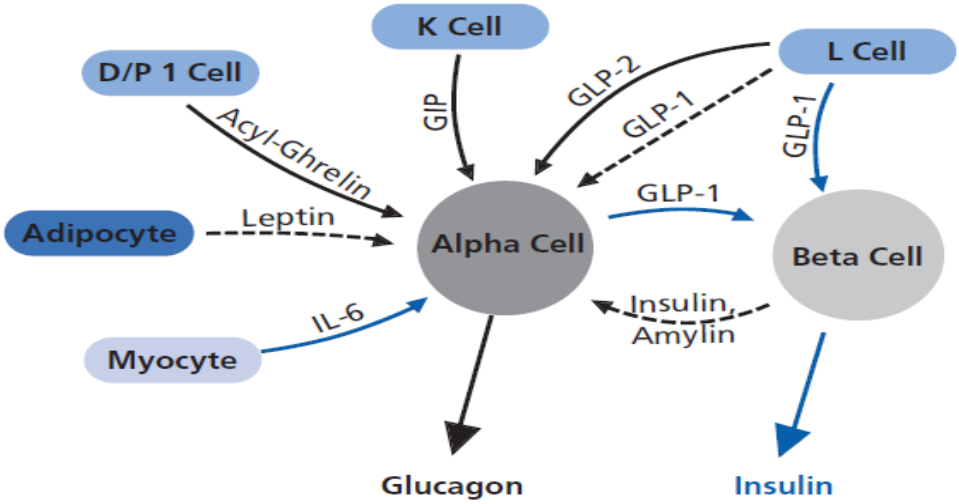


availability.

Copied from Gromada et al (13)

For this discussion we will take a deep dive into what is currently known about the key regulators that are influenced by digestion of carbohydrate, fat and protein.

The below diagram shows there are large number of hormonal regulators on A-Cell secretion of Glucagon. The dashed lines indicate negative regulation, and the solid lines indicated a positive regulation.



Adapted from Hughes &Narendran (1)

Let's breakdown how these different hormones regulate A-Cell Glucagon secretion:

- Intestinal K Cell secretion of GIP:
    - Positive regulation of glucagon. In healthy people GIP has a dose-dependent relationship with glucagon secretion (3)

- Intestinal L Cell secretion GLP-1 & GLP-2:
    - GLP-1:negative regulation of Glucagon
    - GLP-2: positive regulation of Glucagon

- B-Cell secretion of Insulin:
    - Very strong negative regulation of Glucagon. The most potent of all the negative regulators.

- D-Cell Somatostain Secretion
    - Negative regulation of Glucagon

SUMMARY

There are multiple regulators of glucagon secretion from the A-Cells. The key ones stimulating secretion by positive regulation are:

- GIP
- CNS via adrenaline

The key ones inhibiting secretion by negative regulation are:

- Insulin
- GLP-1

When the B-Cells have been destroyed, as happens with Type 1 Diabetes, the negative regulation signals are lost. Therefore, the job of a person with Type 1 Diabetes is to match insulin delivery to what the B-Cells would have secreted in response to the meal composition, so that:

- Glucagon can be suppressed from rising too high after eating high protein and fat meals. If this does not happen Glucagon will increase liver output of glucose too much, causing hyperglycaemia.

- Glucagon is not suppressed too much by delivering a very large bolus of insulin. If this happens glucagon will not be released to prevent hypoglycaemia.

INSULIN AND GLUCAGON SUMMARY

Let's simplify this, Insulin is the **big brother and master** in this hormonal relationship. Insulin trumps the action of other hormones when it comes to regulating Glucagon secretion. A high I:G will prevent glycogenolysis and gluconeogenisis, whilst simultaneously increasing glycolysis, glycogenisis and anabolism (4).

This works beautifully when the B-Cells of the pancreas are in full working order, and the adjustments are automatic. However, when you have Type 1 Diabetes, insulin secretion is not automatic, you must learn to be the master controller!

When B-Cells are working normally, if the glucose level starts to drop and is heading toward 3.5mmol/l (65mg/dl), there are multiple signals that stop insulin secretion. Simultaneously there are multiple signals that increase Glucagon secretion, which stimulates liver glycogenolysis and glucose release. Result, hypo prevented. But when too much insulin has been administered for a meal, the I:G is way too high and there is no off switch for insulin action. The result is a hypo, and potentially a nasty one if the insulin dose was way too high.

This was borne out is the landmark trial, the DCCT, In this trial the intensification of insulin treatment in the experimental group massively improved their HbA1c and future health (18). This trial is the reason why the holy grail is getting a HbA1c <6.5% (<48mmol/mol). However ,the experimental group administered more insulin every day, increased their weight, and unsurprisingly had more hypos and severe hypos, 200-300% more.

Why?

The intensification of insulin dampened the response of Glucagon to pending hypoglycaemia.

Further evidence of this comes from studies conducted on adults and children with T1DM using a dual hormone pump. The dual pump infuses both insulin and glucagon. Glucagon infusion is triggered and insulin stopped when the CGM detects a dangerous downward trend in glucose. The dual infusion pump has recorded positive early results in reversing the frequency and severity of hypoglycaemia (19, 20).

So it's a big responsibility for the person with type 1 diabetes to use this trump card at the right time, and in the right amounts!

We have now built a foundational knowledge of the functions of insulin and Glucagon, and understand their key regulators. Let's move onto seeing how this hormonal relationship works after eating different types of meals. This will provide the model that people with Type 1 diabetes need to follow when delivering insulin for their meals.

To gain a full understanding we must ask very specific questions. What does the

pancreas do to maintain blood glucose level, and what is different for the person with Type 1 Diabetes;

- When carbohydrate only is consumed?
- When protein only is consumed?
- When fat only is consumed?
- When carbs and protein and consumed?
- When carbs and fat and consumed?
- When fat and protein are consumed?
- When carbohydrate, fat and protein are consumed?

The next sections answer these questions in great depth.

Diabetic™

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