PHYSIOLOGY

Sheet :15

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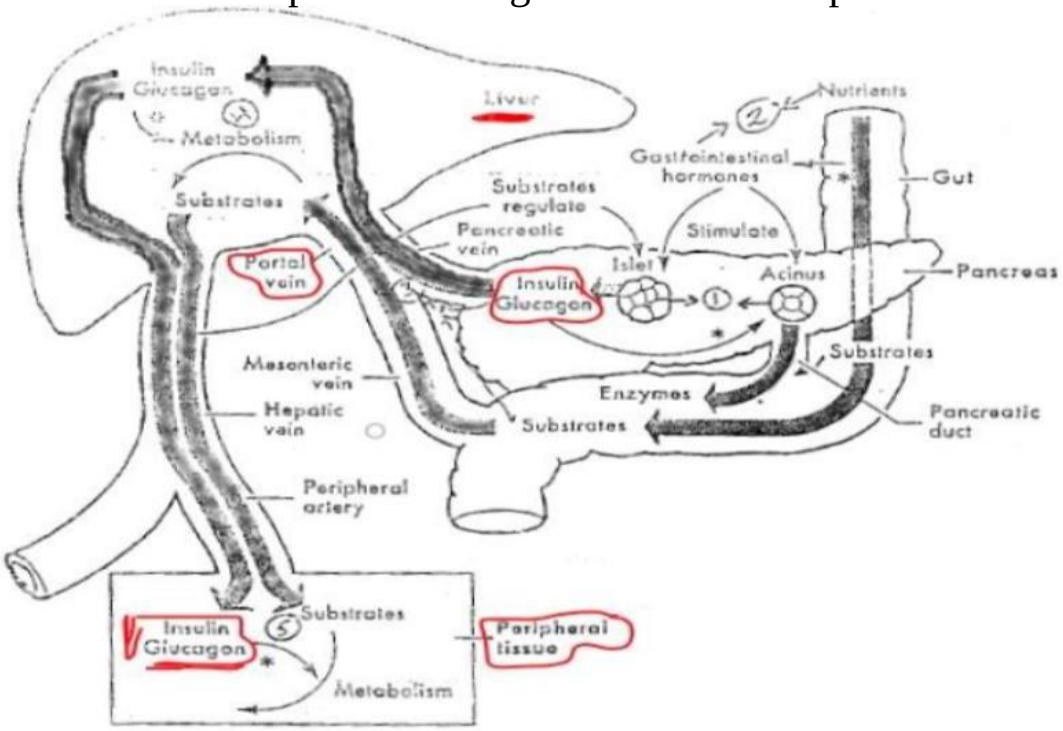
The Pancreas

Pancreatic enzymes are the most important enzymes in the digestive system as they are the only enzymes that has an affect on all food elements. The pancreas has **both exocrine and endocrine** functions. The exocrine function is represented by **enzymes**. While the endocrine function is represented **by hormones**.

The picture shows the pivotal strategic location of the pancreas:



The Endocrine Function Of The Pancreas:

The pancreas consists of two types of cells:

1. **The acini ➔ enzymes.**
2. **The islets of Langerhans➔ hormones.**

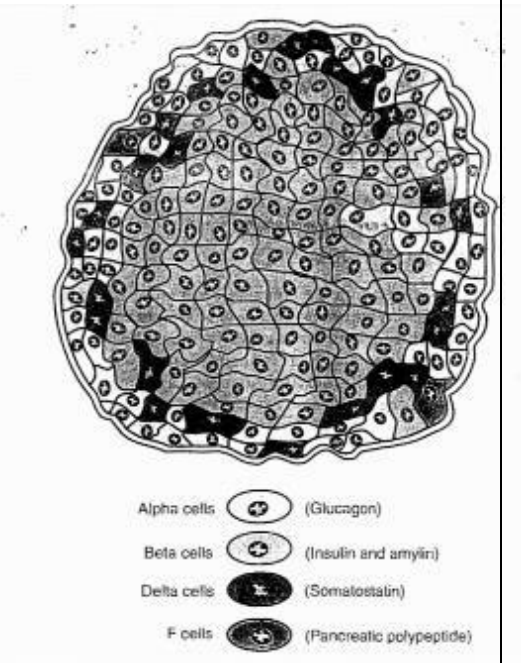
Islet cells & acini are stimulated by nutrients and GI hormones.

The most important hormones are insulin and glucagon. Both hormones are connected in an **antagonistic** type of connection.

Insulin and glucagon are transferred to the portal vein along with nutrients, then to the liver. Both hormones affect "metabolize" food elements "lipids, proteins, carbs" in the liver. Food substrates are transferred to peripheral tissues to feedback the secretion of insulin and glucagon.

Major Cell Types In Islets Of Langerhans:

Langerhans islets occupy 2% of the whole mass of the pancreas. If these 2% are absent or non-effective, then you will be dead.



Cell Types	Percentage	Hormones secreted
A alpha cells	20%	Glucagon+ proglucagone
B beta cells	75%	Insulin and amylin, c-peptide, proinsulin
D delta cells	3-5 %	Somatostatin
F cells (pp cells)	<2%	Pancreatic polypeptide
Epsilon cells	**<1%**	**Ghrelin**

**Our main concern is both alpha and beta cells.

Preclinical data indicate that amylin acts as a neuroendocrine hormone that is complementary to the action of insulin "synergism" in postprandial glucose homeostasis via several mechanisms.

Ghrelin: from the stomach , to increase food intake (appetite).

Insulin:

The upper molecule in the figure is proinsulin. Insulin is composed of two chains:

1.A chain

2.B chain(the active one)

A chain is composed of 21 amino acids while the B chain is composed of 30 amino acids.

Proinsulin is composed of A and B chains connected to C peptide.

In granules, there are both insulin and little proinsulin. There, the C peptide splits from insulin. A chain and B chain are connected via **disulfide bridges.** *There is an additional disulfide bridge found in A chain and its function is not known*.

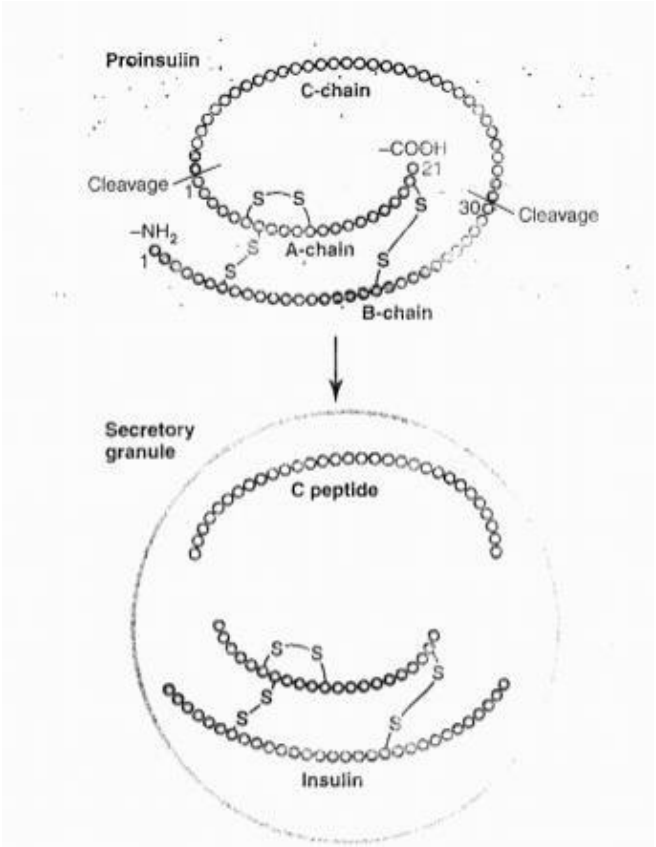


Figure 78-2 Schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and secreted in equimolar amounts, along with a small amount of proinsulin.

The amount of insulin secreted equals the amount of C peptide.

If we can't measure the amount of insulin and we are able to measure the amount of C peptide, then the amount of C peptide is the same amount of insulin.

Very Important Points:

- In vivo, proinsulin has a biologic potency that is only about 10% of that of insulin.
- It is of clinical significance that insulin and C peptide are co-secreted in equal amounts from secretory granules.

- 50-60% of insulin produced by the pancreas is extracted by the liver, without even reaching the systemic circulation.
- In contrast, the liver doesn't extract C peptide.

Actually, the insulin we measure in the systemic circulation is not the actual amount of insulin secreted by the pancreas.

Why? Read point 3.

- Because C peptide is secreted in **equimolar concentrations** with insulin and is NOT extracted by the liver. Beta cells' insulin secretion rate can be calculated.
- Another advantage of measuring C-peptide is that the standard insulin radioimmunoassay does not distinguish between endogenous and exogenous insulin "does not differentiate between insulin injection and insulin secreted", making it an ineffective measure of endogenous Beta cell function in an insulin-treated diabetic patient.

It is better to use the method of C peptide to measure insulin instead of measuring insulin itself because in this way:

1. We measure the actual amount of insulin secreted by the pancreas.

2. We measure the actual insulin secreted by the pancreas and not the injected insulin.

Regulation Of Plasma Glucose

Minute by minute for a long time, Glu is 100% regulated ; insulin regulates plasma glucose and is opposed by another hormone which is glucagon.

Insulin and glucagon provide short-term regulation of plasma glucose levels

Other hormones involved in the regulation of plasma glucose

Insulin and glucagon play a pivotal role in the fine regulation of plasma glucose levels—indeed, insulin is the only hormone capable of lowering plasma glucose, and glucagon is the most important hyperglycemic hormone. Nevertheless, a number of other agents also contribute to the maintenance of a stable blood glucose, as well as mobilizing glucose when necessary. These hormones include adrenal corticosteroids, growth hormone, the catecholamines, and the thyroid hormones.

The other hormones are for long term regulation while insulin and glucagon are for short term regulation.

Insulin ➔ only hypoglycemic hormone

Glucagon➔ most potent hyperglycemic hormone.

TABLE 18-4 SUMMARY OF GLUCOSE-COUNTERREGULATORY CONTROLS*

	Glucagon	Epinephrine	Cortisol	Growth hormone
Glycogenolysis	X	X		
Gluconeogenesis	X	X	X	X
Lipolysis	–	X	X	X
Inhibition of glucose uptake	–	–	X	X

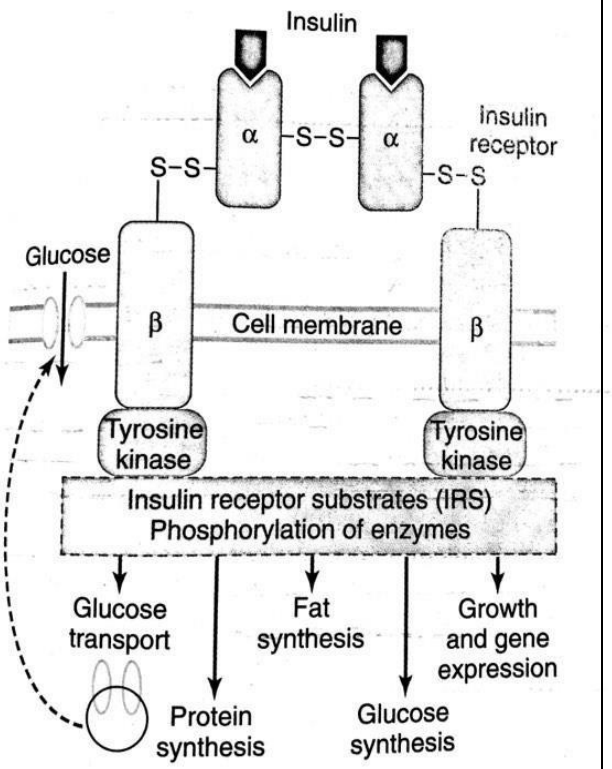
X means that the hormone stimulates the process.

Cortisol has a permissive action on glucagon facilitating it's function. So, cortisol has a permissive action on gluconeogenesis with glucagon. **Cortisol doesn't stimulate glycogenolysis.**

Insulin As A Second Messenger

Some hormones produce cAMP as a second messenger. Other amino acid or steroid derived hormones produce mRNA. There are exceptions; insulin is one of them.

As you can see from the figure that the insulin receptor is different **"2 alpha 2 beta".**
Alpha and beta, alpha and alpha subunits are connected to each other via disulfide bridges.



Alpha subunits are located on the surface of cell membranes. While beta subunits can penetrate cell membranes.

Insulin binds to alpha subunit. After binding, beta subunits are activated, that leads to the activation of **tyrosine kinase as a second messenger.**

If tyrosine kinase is not activated, insulin loses its function.

Summary Of Insulin Functions

1. **Transactivation of glucose transporters.** The presence of various glucose transporters "GLUT1,2,3,…" is due to the presence of different types of tissues.

2. **Stimulates protein synthesis** as growth hormone cannot function without insulin.

3. Stimulates fat synthesis.
4. Promotes growth and gene expression.

Insulin also produces the other two second messengers**: inositol triphosphate and Diacylglycerol.** Most probably, due to the action of these two second messengers results in amino acids entry.

Insulin also affects potassium entry, phosphate, and magnesium.

Patients with diabetes mellitus should monitor their potassium levels.

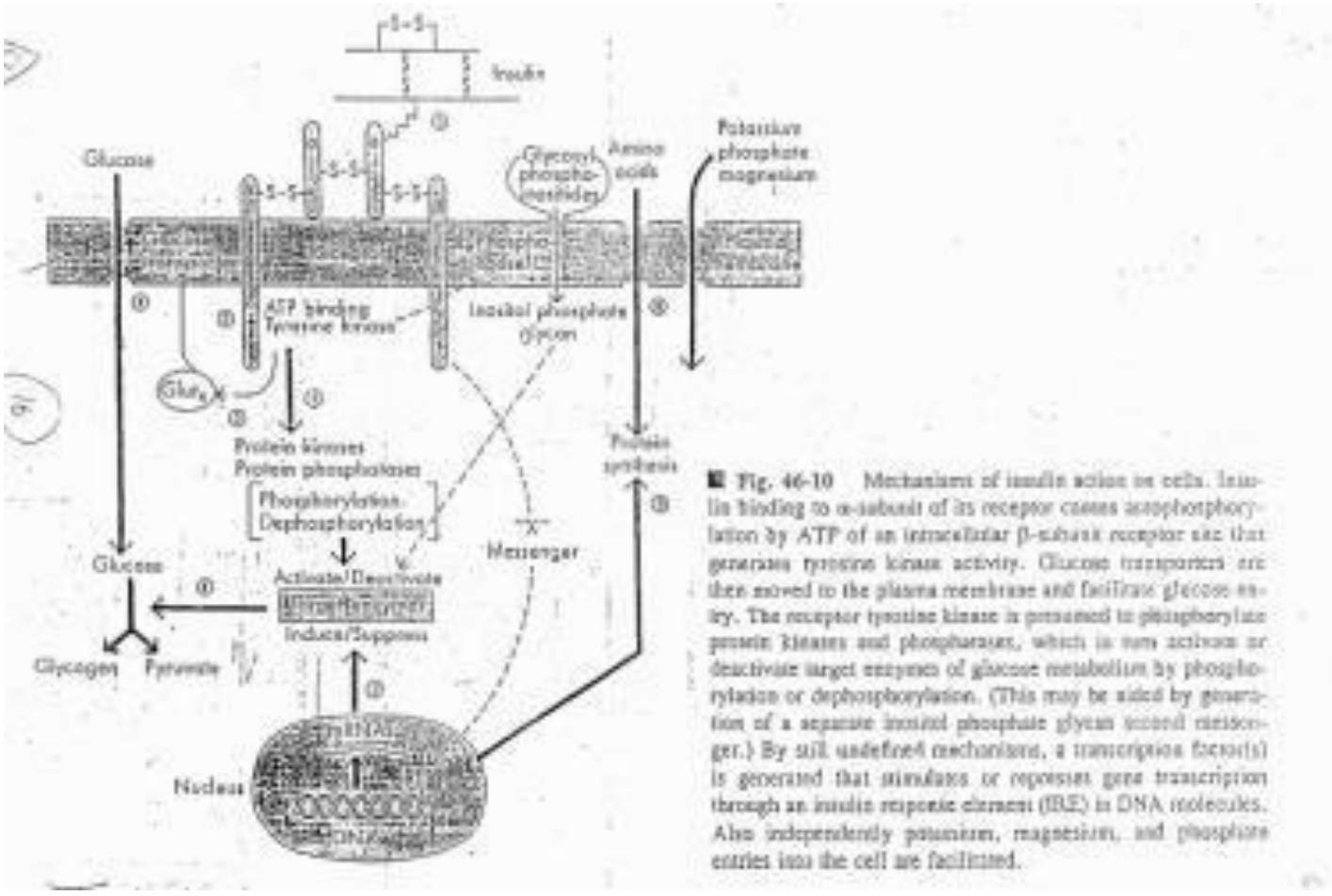
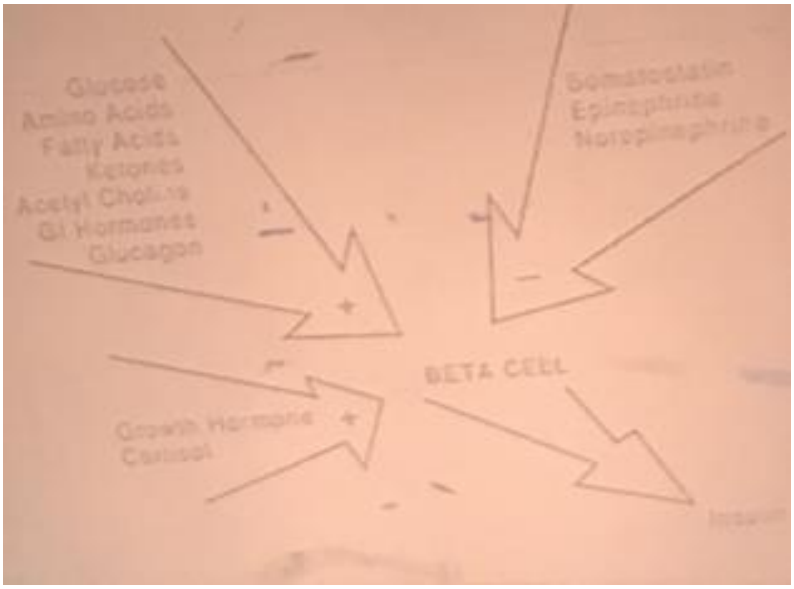


Fig. 46-10 Mechanism of insulin action on cells. Insulin binding to α-subunit of its receptor causes autophosphorylation by ATP of an intracellular β-subunit receptor site that generates tyrosine kinase activity. Glucose transporters are then moved to the plasma membrane and facilitate glucose entry. The receptor tyrosine kinase is presumed to phosphorylate protein kinases and phosphatases, which in turn activate or deactivate target enzymes of glucose metabolism by phosphorylation or dephosphorylation. (This may be aided by generation of a separate inositol phosphate glycan second messenger.) By still undefined mechanisms, a transcription factor(s) is generated that stimulates or represses gene transcription through an insulin response element (IRE) in DNA molecules. Also independently potassium, magnesium, and phosphate entries into the cell are facilitated.

Stimulators And Inhibitors For Insulin Secretion:

The most important stimulator is glucose.

People who are exposed to continuous stress “mainly acetylcholine”, they are more likely to have diabetes mellitus.(low potassium level).



Obesity itself stimulates insulin secretion.

Table 78-1 Factors and Conditions That Increase or Decrease Insulin Secretion

Increase Insulin Secretion	Decrease Insulin Secretion
Increased blood glucose	Decreased blood glucose
Increased blood free fatty acids	Fasting
Increased blood amino acids	Somatostatin
Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)	α-Adrenergic activity
Glucagon, growth hormone, cortisol	Leptin
Parasympathetic stimulation; acetylcholine	**Exercise**
β-Adrenergic stimulation	
Insulin resistance; obesity	
Sulfonylurea drugs (glyburide, tolbutamide)	

Calcium is present ➔ secretion of insulin.

No calcium ➔ no secretion of insulin.

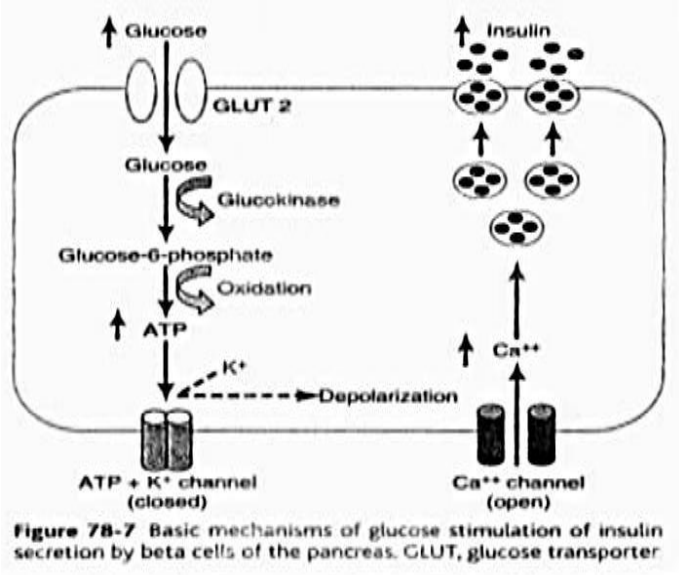


Figure 78-7 Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter

X-axis: plasma glucose level

Y-axis: insulin secretion

When plasma glucose levels equal to 50 or below ➔ *almost* no insulin secretion.

When plasma glucose levels equal = 300 or above ➔ maximal level of insulin secretion.

When plasma glucose levels are above 500 → almost no increase in the levels of insulin secretion.

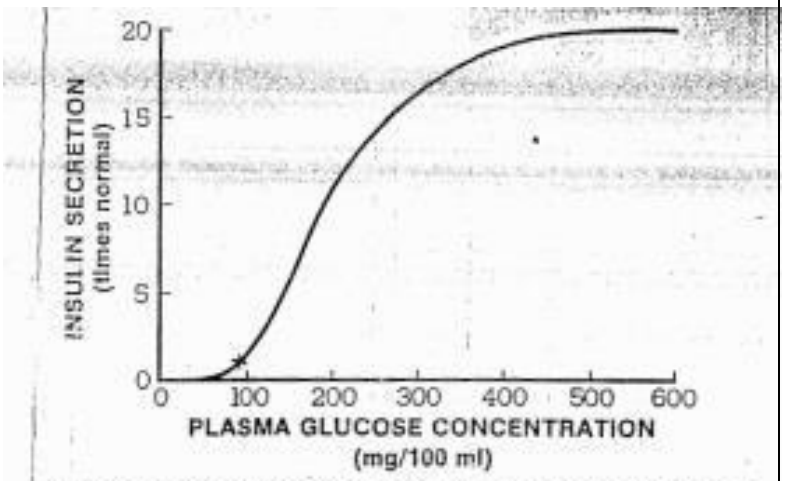


Figure 78–8. Approximate increase in insulin secretion at different plasma glucose levels.

As we discussed earlier about **downregulation**, What do we mean by downregulation?

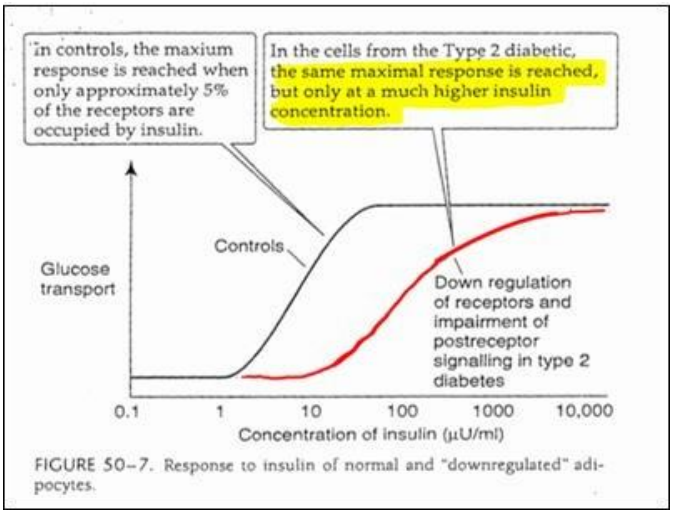


FIGURE 50–7. Response to insulin of normal and "downregulated" adipocytes.

It happens When the hormone's receptors decrease in number, or their affinity to the substrate (certain hormone) is decreased.

For example: if the normal person needs 300 particles of this hormone to receive a response, the down-regulated person will need 500.

So, we need a higher concentration of the hormone to be secreted in order to have the same effect of a normal person.

Increased Blood Glucose Stimulates Insulin Secretion:

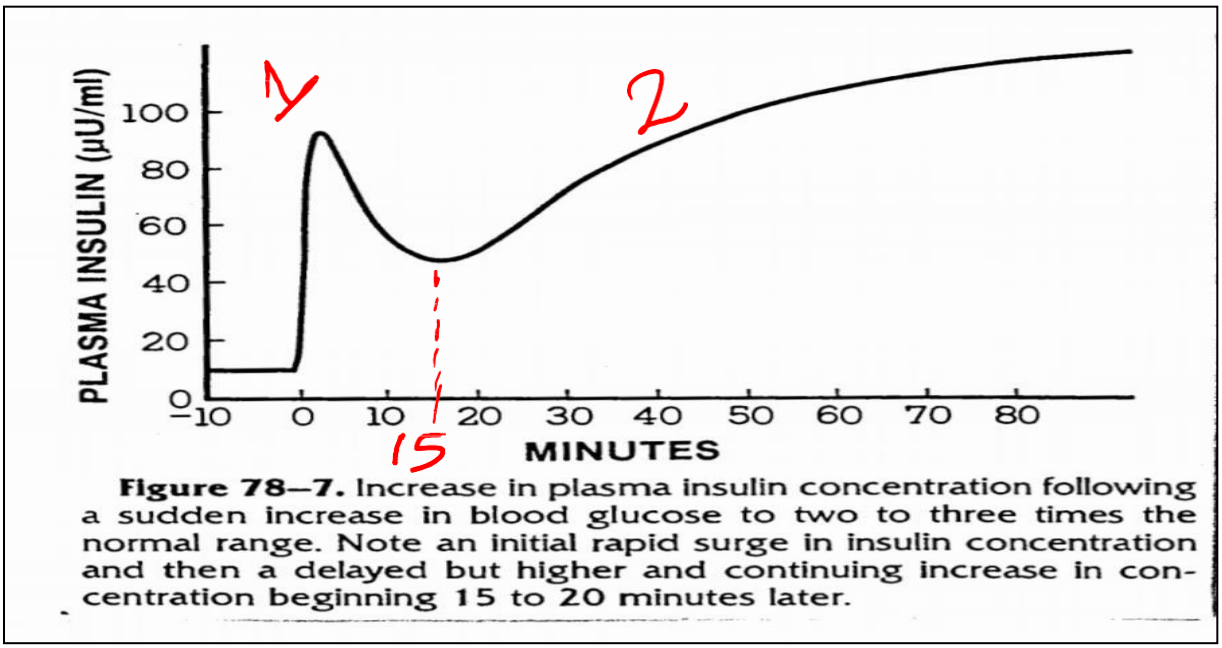


Figure 78–7. Increase in plasma insulin concentration following a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.

* At a normal blood glucose fasting level (of 80 to 90 mg/100 ml), the rate of insulin secretion is *minimal*—a level that has only slight physiological activity. If the blood glucose concentration suddenly increases to a level of two to three times normal and is kept at this high

level thereafter, insulin secretion increases markedly in two stages, as shown by the changes in plasma insulin concentration in Figure 78-7.

1. The concentration of insulin in plasma increases almost 10-fold within 3 to 5 minutes after the acute elevation of blood glucose. This increase results In an immediate dumping of preformed insulin from beta cells of islets of Langerhans. However, the initial high rate of secretion is not maintained; instead, the insulin concentration decreases about halfway back toward normal in another 5 to 10 minutes.

3. starting at 15 minutes, insulin secretion rises and reaches a new plateau in 2 to 3 hours, this time usually at a rate of secretion even greater than that in the initial phase. This secretion results from:

the additional release of the preformed insulin and from the activation of the enzyme system that synthesizes and releases new insulin from cells.

To sum up, all the previous lectures: till now, we knew that insulin functions on:

1.Carbohydrate metabolism:

Insulin facilitates the entry of glucose to cells by activating transporters.

2. lipid metabolism(later)

3. protein metabolism

As we said before, there is no protein synthesis without insulin; because insulin has an important role in the the entry of amino acids.!

How? By activating the two second messengers inositol triphosphate & diacylglycerol

4.ion transport

Phosphate, potassium and magnesium 'insulin controls the entry of these ions'.

5. growth and development.

Table 7.6
Biological effects of insulin

A. On carbohydrate metabolism
1. Reduces rate of release of glucose from liver
   a. by inhibiting glycogenolysis.
   b. by stimulating glycogen synthesis.
   c. by stimulating glucose uptake.
   d. by stimulating glycolysis.
   e. by indirectly inhibiting gluconeogenesis via inhibition of fatty acid mobilization from adipose tissue.
2. Increases rate of uptake of glucose into all insulin-sensitive tissues, notably muscle and adipose tissue
   a. directly, by stimulating glucose transport across the plasma membrane.
   b. indirectly, by reducing plasma-free fatty acid levels.

B. On lipid metabolism
1. Reduces rate of release of free fatty acids from adipose tissue.
2. Stimulates de novo fatty acid synthesis and also conversion of fatty acids to triglycerides in liver.

C. On protein metabolism
1. Stimulates transport of free amino acids across the plasma membrane in liver and muscle.
2. Stimulates protein biosynthesis and reduces release of amino acid from muscle.

D. On ion transport

E. On growth and development

Effect of insulin on glucose uptake in tissues in which it has been investigated:

Almost all the cells in our body need insulin which facilitates glucose uptake, by the activation of transporters "as we said before. transporters are numbered according to the type of the cells".

As shown in the following table:
there are many tissues that need insulin to take in glucose.
ex (skeletal muscle, adipose tissue, aorta…etc)

Table 19–3. Effect of insulin on glucose uptake in tissues in which it has been investigated.

Tissues in which insulin facilitates glucose uptake
Skeletal muscle
Cardiac muscle
Smooth muscle
Adipose tissue
Leukocytes
Crystalline lens of the eye
Pituitary
Fibroblasts
Mammary gland
Aorta
A cells of pancreatic islets
Tissues in which insulin does not facilitate glucose uptake
Brain (except probably part of hypothalamus)
Kidney tubules
Intestinal mucosa
Red blood cells

But there are **Exceptions: (vital tissues/organs) Brain, kidney tubules, intestinal mucosa, RBCs.**

Vital organs ❼ you cannot survive without them

These vital organs/tissues **do not** need insulin, spontaneously they take glucose "their cells are permeable to glucose and can use glucose without the intermediation of insulin ". On the other hand, the other tissues **cannot use glucose without insulin.**

HEMEOSTASIS:

The normal glucose range is 80-90 mg/dL." ideal range "if it was a little bit higher or lower its normal.
When blood glucose level exceeds 160-180 mg/dL the *proximal kidney tubules become overwhelmed and begin to excrete glucose in the urine. "this point is called the RENAL THRESHOLD of glucose"

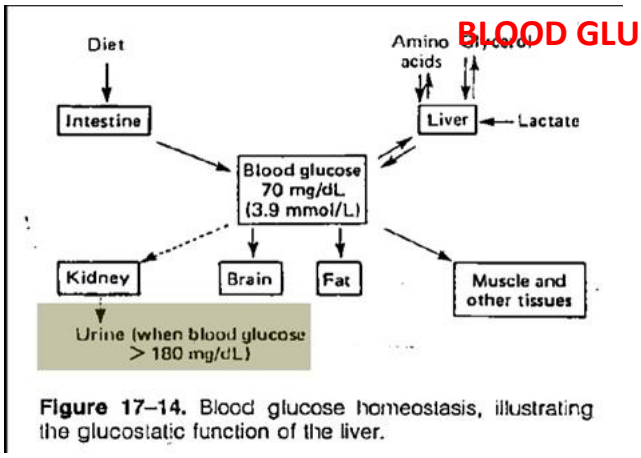


Figure 17–14. Blood glucose homeostasis, illustrating the glucostatic function of the liver.

So we reach the renal threshold when the glucose level is a little bit below 180. /the brain doesn't need insulin so the glucose is transferred into fat mainly, also its transferred to muscles, other tissues, and liver.

Disordered blood glucose homeostasis in insulin deficiency :

The figure shows what happens to tissues/organs in our body when the blood glucose reaches 300mg/dl as well as insulin deficiency:(follow the numbers!!!!)

1. when blood glucose reaches 300mg/dL this case is called "HYPERGLYCEMIA"

The maximal level of insulin occurs when glucose levels is about 300mg/dL, then it increases very slightly till the glucose reaches 500, after reaching 500mg/dL there is **NO increase in insulin levels.**

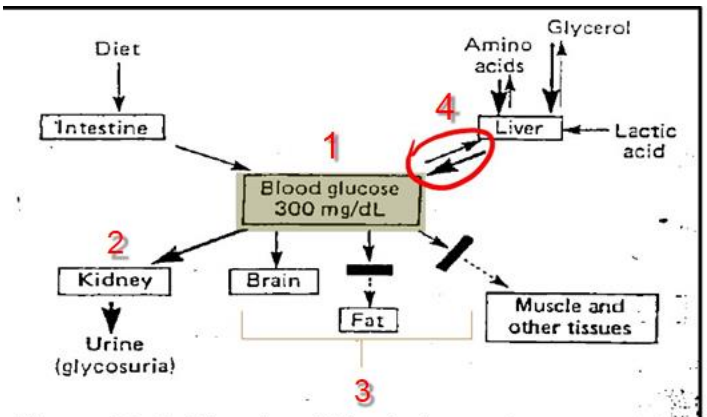


Figure 19–7. Disordered blood glucose homeostasis in insulin deficiency. Compare with Fig 17–14. The heavy arrows indicate reactions that are accentuated. The rectangles across arrows indicate reactions that are blocked.

2. So, 300 means above 180 which means that we passed the threshold point so the glucose will be secreted in the urine so there is glucose in the urine (glycosuria).
3. As we said earlier that the brain doesn't need insulin and the glucose will be transferred into fat and so on, BUT when the glucose reaches 300mg/dL the transferring of glucose into fat will be affected ❼ BLOCKED, and also muscles and the other tissues will be affected.

4. What about the liver? the glucose which is coming from the liver is more than that going into the liver (red circle up)

Diabetes:

Diabetes is a disease in which your blood glucose or blood sugar levels are too high.

How to know that this patient has DIABETES? (symptoms)

1. Urination test → to check if he has diabetes insipidus (ADH deficiency).
2. Increased food consumption.
3. Always thirsty, dry skin why? Because of excessive urination
4. Weight loss (in diabetes mellitus type 1)

And because diabetic patients have a deficiency in insulin LIPOLYSIS occurs:

****insulin deficiency activates enzymes" that work on lipids" in the liver we call them "enzyme hormone-sensitive lipases". When these enzymes are activated, Hydrolysis of lipids occurs"LIPOLYSIS"**

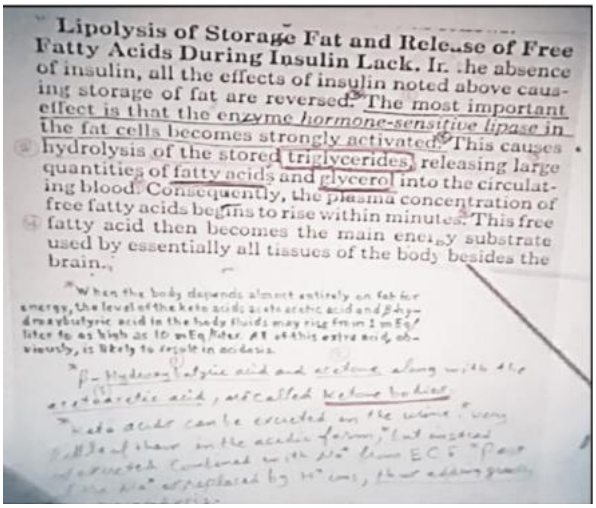
again:1. enzymes that break down lipids are activated

2. lipolysis occurs (hydrolysis of triglycerides)

3.when hydrolysis of lipids occurs free fatty acids are produced, few of these fatty acids are used for energy (when the glucose is not readily available) and the remaining fatty acids are used to produce ketone bodies which cause acidosis 'hydroxybutyric acid, acetoacetate and acetone '

So, acidosis occurs because of the disorder in lipid metabolism.

'in general, we need a small number of hormones in our body' So a very slight amount of insulin is needed to activate EHSL. Otherwise, a huge amount of insulin will not activate EHSL.



Lipolysis of Storage Fat and Release of Free Fatty Acids During Insulin Lack. In the absence of insulin, all the effects of insulin noted above causing storage of fat are reversed. The most important effect is that the enzyme *hormone-sensitive lipase* in the fat cells becomes strongly activated. This causes hydrolysis of the stored triglycerides, releasing large quantities of fatty acids and glycerol into the circulating blood. Consequently, the plasma concentration of free fatty acids begins to rise within minutes. This free fatty acid then becomes the main energy substrate used by essentially all tissues of the body besides the brain.

What about proteins?

As we said before No growth without insulin so "no protein synthesis with insulin deficiency or the absence of insulin"

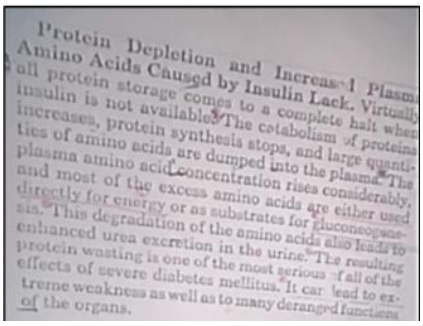
In severe diabetes there is no protein synthesis what happens is catabolism of proteins (breaking down of proteins into amino acids), few of amino acids are used for energy, the remaining amino acids produce glucose which will cause HYPERGLYCEMIA

****Gluconeogenesis is The process in which glucose is produced from a noncarbohydrate source.**

To sum up, hyperglycemia occurs because of:

1.a problem in carbohydrate metabolism→decrease glucose uptake by the cell→glycosuria

2.the produced glucose from protein catabolism.



Protein Depletion and Increased Plasma Amino Acids Caused by Insulin Lack. Virtually all protein storage comes to a complete halt when insulin is not available. The catabolism of proteins increases, protein synthesis stops, and large quantities of amino acids are dumped into the plasma. The plasma amino acid concentration rises considerably, and most of the excess amino acids are either used directly for energy or as substrates for gluconeogenesis. This degradation of the amino acids also leads to enhanced urea excretion in the urine. The resulting protein wasting is one of the most serious effects of severe diabetes mellitus. It can lead to extreme weakness as well as to many deranged functions of the organs.

***Glycosuria causes osmotic diuresis (high osmotic pressure in the urinary tubules which will cause retention of water in the urine so a lot of water will be excreted when there is osmotic diuresis electrolytes will be excreted with water"electrolyte depletion," because water is not reabsorbed so it drags with it electrolytes. Sodium is one of these electrolytes, so once the sodium is excreted it will be replaced by hydrogen. Therefore, acidosis will occur.)**

Glycosuria→osmotic diuresis → □ osmotic pressure →water retention in the urine→ electrolyte depletion → replacement of sodium with hydrogen → acidosis +dehydration →coma → death.

to sum up, Acidosis occurs because of:

1. Replacement of sodium by hydrogen.

2. Production of ketone bodies from lipolysis.

So dehydration and acidosis leads to coma and death.

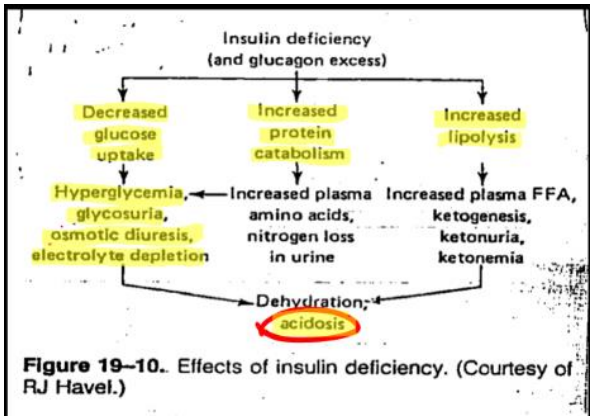


Figure 19–10. Effects of insulin deficiency. (Courtesy of RJ Havel.)

***Doctor always advises Diabetic patient who takes insulin injection to keep some sugar candies with them, why? To prevent <u>HYPOGLYCEMIA</u> <u>which leads to coma</u>.**

So, coma will occur either because of HYPERGLYCEMIA(acidosis) OR HYPOGLYCEMIA(when glucose level below 40).

****To sum up, coma will occur because of:**

1. Hyperglycemia(acidosis)

2. Hypoglycemia (when glucose level below 40mg/dL)

3. Hyperosmolar

4. Lactic acidosis "acidosis because of lactic acid accumulation "
5. Brain edema "occurs in about 1% of children with ketoacidosis ", it is a serious complication with a mortality rate of about 25%.

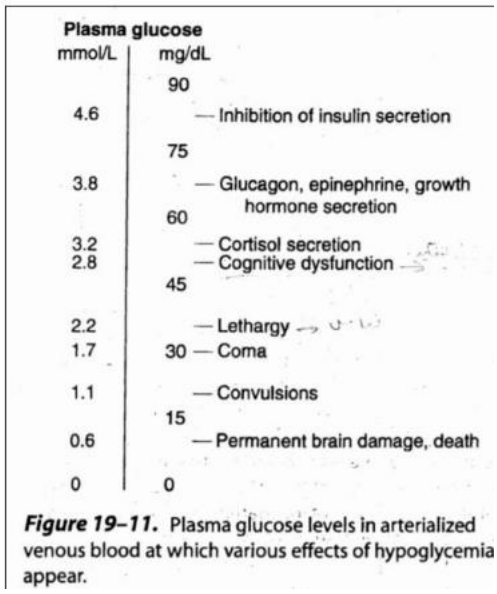


Figure 19–11. Plasma glucose levels in arterialized venous blood at which various effects of hypoglycemia appear.

***TYPES OF DIABETES:**
there are two types of diabetes :
• TYPE 1 → insulin-dependent diabetes mellitus/juvenile diabetes this type is genetic. The problem resides in the pancreas where it is caused by a lack of insulin secretion. The usual onset occurs at the age of children's
• TYPE 2 → non-insulin dependent diabetes mellitus /maturity onset diabetes. is caused by reduced sensitivity of target tissues to the metabolic effects of insulin.

the hyperosmolar hyperglycemic state is a metabolic complication of diabetes mellitus (DM) characterized by severe hyperglycemia, extreme dehydration, hyperosmolar plasma, and altered consciousness. It most often occurs in type 2 DM

also, genetic factors play a role in Diabetes type 2.

TABLE 78–2
Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

Feature	Type I	Type II
Age at onset	Usually <20 years	Usually >40 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

*Insulin-dependent diabetes (IDDM). Juvenile diabetes.
*Non-insulin-dependent diabetes (NIDDM). Maturity-onset diabetes.

**before we start the comparison between diabetes type 1&2, at the beginning of the lecture, we talked about downregulation in which the insulin either normal or high → this is type 2 diabetes mellitus.

As shown in the table above:
1. Age usually young in type one, while old in type 2.
2. Body mass is low to normal in type 1 while obese in type 2.
3. Plasma insulin is low or absent in type 1' that's why they take inulin injections' while normal to high in type 2.
4. Plasma GLUCOSE increased in both.
5. Insulin sensitivity is normal in type 1 while reduced in type 2.
6. Therapy, insulin is a must for type one diabetes while it's a final choice for type 2, what do you conclude?

There are alternative medications like diet and exercise.
• OR we can give them drugs to:
1. increase the function of insulin sensitizers in the liver cells
2. to increase the function of insulin in the peripheral tissues
3. to increase the insulin secretion by the pancreas
4. to decrease the absorption of glucose.

• If the drugs, diet, and exercises didn't affect, insulin will be given to type 2 diabetes mellitus patients.