Endocrine system 8

physiology

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In this sheet we will discuss the role of pancreas in food metabolism.

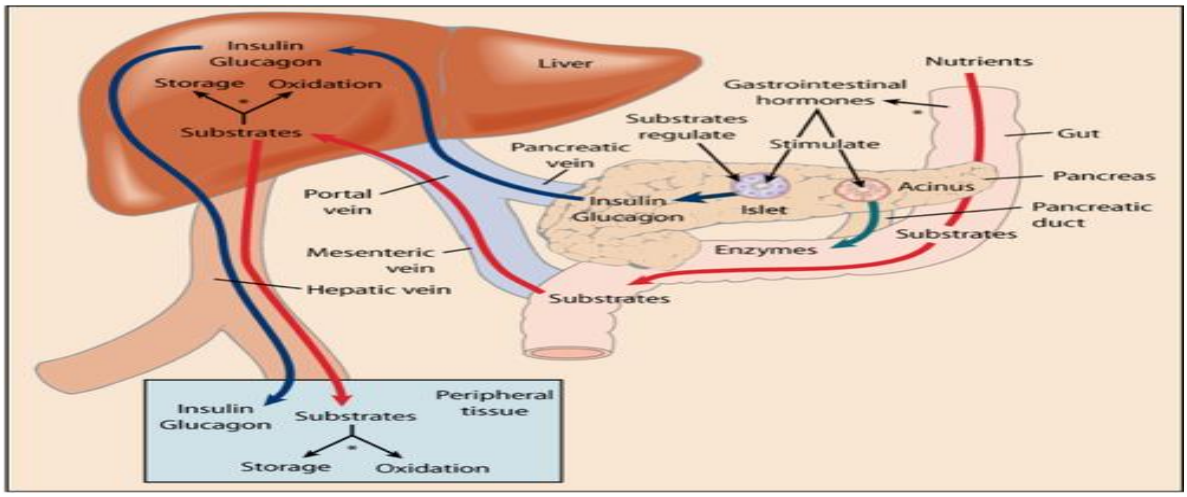
- As you know pancreas is a **mixed** organ , it's considered as an endocrine gland as well as an exocrine gland, which means that it produces enzymes(exocrine activity) and hormones(endocrine activity).
- Pancreas has a very important role in the metabolism of carbohydrates, proteins and lipids.
- The secretion of hormones from the pancreas is stimulated by:
    1. Food intake
    2. Gastrointestinal hormones.

The food as well as the gastrointestinal hormones are released into the portal vein then transported into the liver , then the hormones (mainly insulin and glucagon) affect food metabolism.After the food is metabolized in the liver it's transported into the peripheral tissues, then these substrates feedback the pancreatic islets to modulate the pancreatic hormones mainly insulin and glucagon.

feel a bit confused? It's okay, read this revision((This was NOT mentioned by the doctor in the video))

**As we said, food ingestion and GIT hormones stimulate the secretion of pancreatic enzymes into the duodenum and digestion of nutrients occurs there producing substrates. Notice that gastrosplenic vein from the stomach, superior mesenteric from the ascending colon & the inferior mesenteric from the descending colon all of them and their tributaries drain into the portal vein, and consequently to the liver. *Food ingestion and GIT hormones also stimulate the secretion of pancreatic hormones (mainly glucagon and insulin) that affect the metabolism of different elements; carbohydrates, lipids and proteins. *Now, the substrates, pancreatic enzymes and hormones travel through the portal vein into the liver. *Within the liver, these hormones affect the metabolism of the substrates, after metabolism, the metabolic end products travel through peripheral arteries into peripheral tissues. *These metabolic end products in the peripheral tissues affect the secretory function of the endocrine*

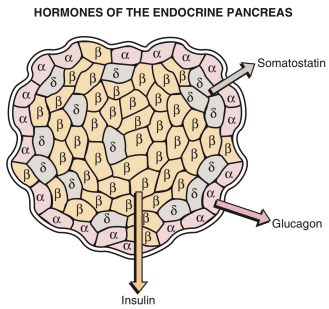
part of the pancreas by feedback mechanisms affecting the secretion of insulin and glucagon.



- Hormones of the pancreas are secreted by cells called: **Islets of Langerhans,** they comprise 1-2% of the mass of the pancreas and are scattered throughout the organ.

Types of cells presented in the islets of Langerhans:

Cell type	%	the hormone secreated .
Alpha	20%	Glucagon,Proglucagon
Beta	75%	Insulin,Proinsulin,C peptide,Amylin
Delta	3-5%	Somatostatin
Epsilon	<1%	Ghrelin
F cells	<2%	Pancreatic polypeptide



Somatostatin: Remember that this hormone is also secreted from the hypothalamus.

Ghrelin: remember that this hormone is also produced by the stomach as well as the intestine, it increases the appetite.

- Preclinical data indicates that Amylin which is produced along with Insulin as a neuroendocrine hormone that complements the

period after dinner or lunch

action of insulin in postprandial glucose homeostasis via several mechanisms .These include:

1. Suppression of postprandial glucagon secretion.
2. Slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption.

Postprandial means:
After a meal.

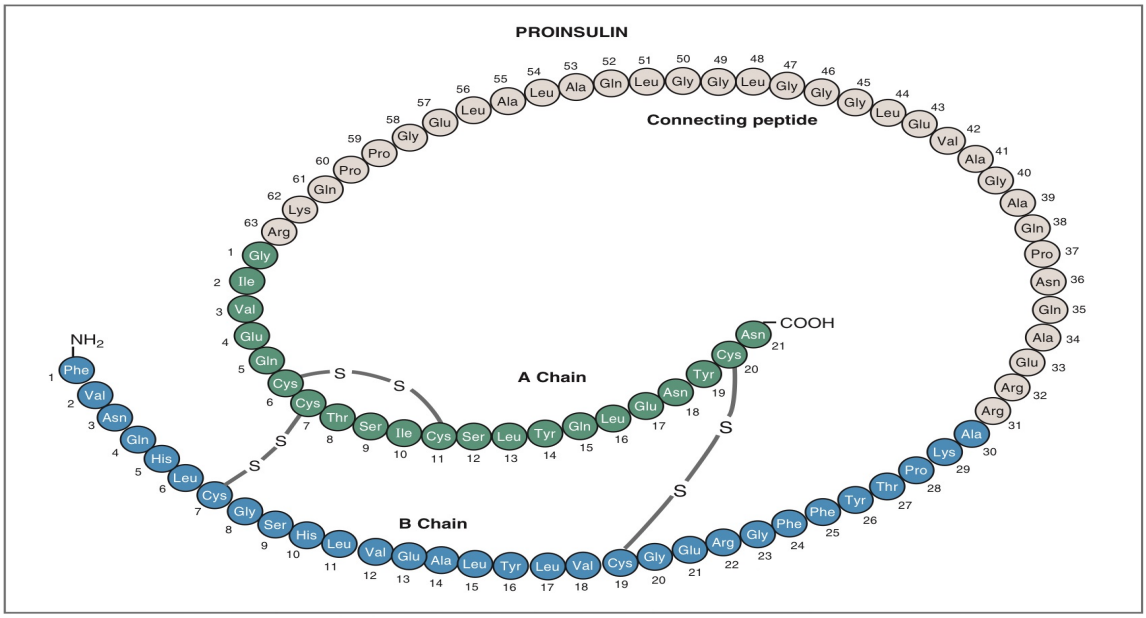


Fig. 9.28 Structure of porcine proinsulin. The connecting peptide (C peptide) is cleaved to form insulin. (Modified from Shaw WN, Chance RR: Effect of porcine proinsulin in vitro on adipose tissue and diaphragm of the normal rat. Diabetes 17:737, 1968.)

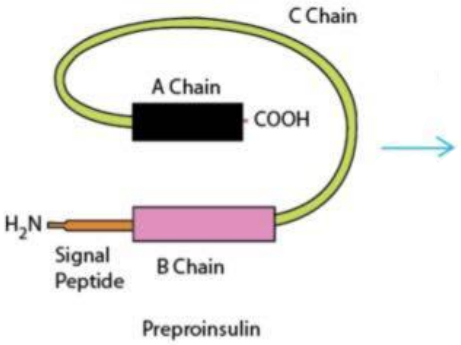
- This figure gives an idea about the structure of insulin:

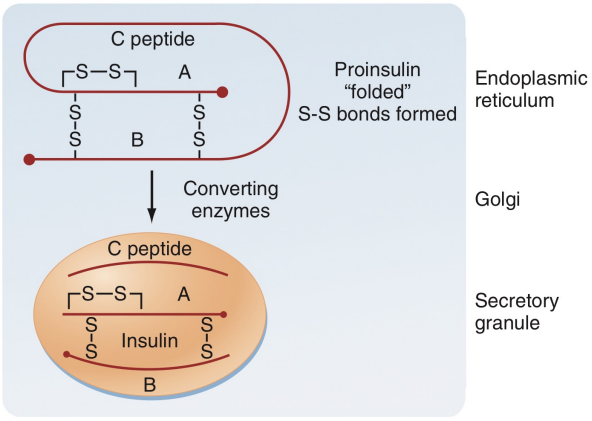
  It is a protein hormone.

  a. Insulin is connected with a C peptide.
  b. It's composed of two chains:
     I. A chain which is 21 amino acids.
     II. B chain which is 30 amino acids and it's the **active chain**.
  c. The two chains are connected with each other through disulfide bridges.

d. There's also a disulfide bridge in the A chain, in which we don't know the function of it.

- *When the two amino acid chains are split apart, the functional activity of insulin is lost.* ***What is Pro-insulin? It is insulin with another peptide (C-peptide/C chain).*** *And to form mature insulin the C-peptide is removed, and B peptide remains connected with A-peptide (Pro-insulin has a biological activity that is equal to just 10% of insulin's activity). Read this paragraph from Guyton to understand what's coming next: Pro-insulin is first synthesized in the beta cells as preproinsulin , which is then cleaved in the endoplasmic reticulum into pro-insulin consisting of three chains of peptides, A ,B , and C .Most of the pro-insulin is further cleaved in Golgi apparatus to form (1) insulin , composed of the A and B chains connected by disulfide linkage and (2) the C peptide.*





- Insulin and C peptide are secreted with each other, and are packaged in granules and secreted in equimolar amounts, along **with small amounts of proinsulin.**

Equimolar means: Equal number of moles.

Very important points:

- In vivo, proinsulin has a biologic potency that's only about 10% of that of insulin.

- It's of clinical significance that Insulin and C peptide are co-secreted in equal amounts.
- 50% to 60% of the insulin produced by the pancreas is extracted by the liver without ever reaching the systemic circulation. In contrast, the liver doesn't extract C peptide.
- Because C peptide is secreted in equimolar concentrations with insulin, and is not extracted by the liver, β-cell insulin secretion can be calculated.
- Another advantage of measuring C peptide is that the standard insulin radioimmunoassay doesn't distinguish between endogenous and exogenous insulin, making it an ineffective measure of endogenous β cell function in an insulin treated diabetic patient, *these diabetic patients may take exogenous insulin (injected insulin) as treatment. The problem is that the standard insulin radioimmunoassay method of measurement doesn't distinguish between the exogenous insulin and the endogenous insulin, so we can't know the exact amount of insulin secreted by this patient's pancreas! Here comes the significance of C peptide which tells us about the exact amount secreted by the pancreas, because exogenous Insulin has no C peptide and all the C peptide that is going to be measured is completely endogenously secreted by the pancreas*

The regulation of glucose levels in the plasma (Glucose Homeostasis):

- Glucose levels in the body should be controlled minute by minute, it is extremely important to maintain glucose concentration normally in the body and there are hormones responsible for this regulation.
- There is short-term regulation and there is a long-term regulation.

-Short term regulation:

I. Mainly exerted by two hormones: *Insulin and Glucagon*.

a. Insulin is the only HYPOGLYCIMIC hormone (it's the only one capable of reducing glucose level).

b. Glucagon is the most important HYPERGLYCEMIC hormone (it increases glucose level).

-Long term regulation:

II. These hormones contribute to the maintenance of a stable blood glucose as well as mobilizing glucose when necessary.

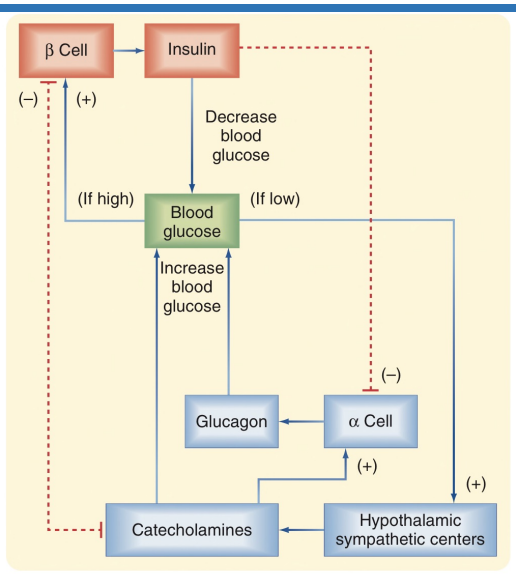
a. Catecholamines.
b. GH (Growth Hormone)
c. Adrenal corticosteroids
d. Thyroid hormones

- Cortisol comes in the second place after glucagon,these two hyperglycemic hormones are essential because when you are fasting these hormones will work to produce glucose from non-carbohydrate sources in order to raise glucose level in the plasma preventing death.

To get a brief idea about the role of each one of the previously mentioned hormones, read these notes while looking at the following figure carefully:

Summary of Glucose-Counterregulatory Controls

	Glucagon	EPI	Cortisol	GH
Glycogenolysis	X	X		
Gluconeogenesis	X	X	X	X
Lipolysis		X	X	X
(Inibition) Blockade of Glucose Uptake			X	X



• **Fig. 39.11** Integrated regulation of blood glucose by insulin and the counterregulatory factors glucagon and catecholamines (norepinephrine, epinephrine).

1) Glucagon: stimulates Gluconeogenesis and glycogenolysis (glycogen degradation).

2) Cortisol: stimulates long gluconeogenesis, lipolysis and inhibits glucose uptake so that glucose remains in the blood. (Notice that Cortisol has no role to play in glycogenolysis; glucagon does). *Cortisol has permissive action with glucagon in stimulating gluconeogenesis.

3) Adrenaline (Epinephrine): Stimulates Gluconeogenesis, glycogenolysis and lipolysis. *Adrenaline has permissive hormonal interaction with glucagon in stimulating lipolysis. -Remember that Adrenaline does not function at its full capacity if thyroxin is not present.→ permissive effect.

(Remember that permissiveness refer to the effect of one hormone on a second whereby the second can exert its full normal effect that is normally associated with it.).

4) GH: has actions similar to cortisol but most probably cortisol is more potent and stronger than GH in providing glucose.

Now how does Insulin function??

- The structure of Insulin's receptor: It is composed of 4 subunits:
  i. 2 alpha subunits that lie entirely outside the cell membrane (The DR said that they're on the membrane)connected with each other and with the beta subunits through disulfide bridges.

ii. 2 beta subunits (penetrating through the cell membrane and protruding into the cell cytoplasm). there is No disulfide linkage lying directly between the two beta subunits).

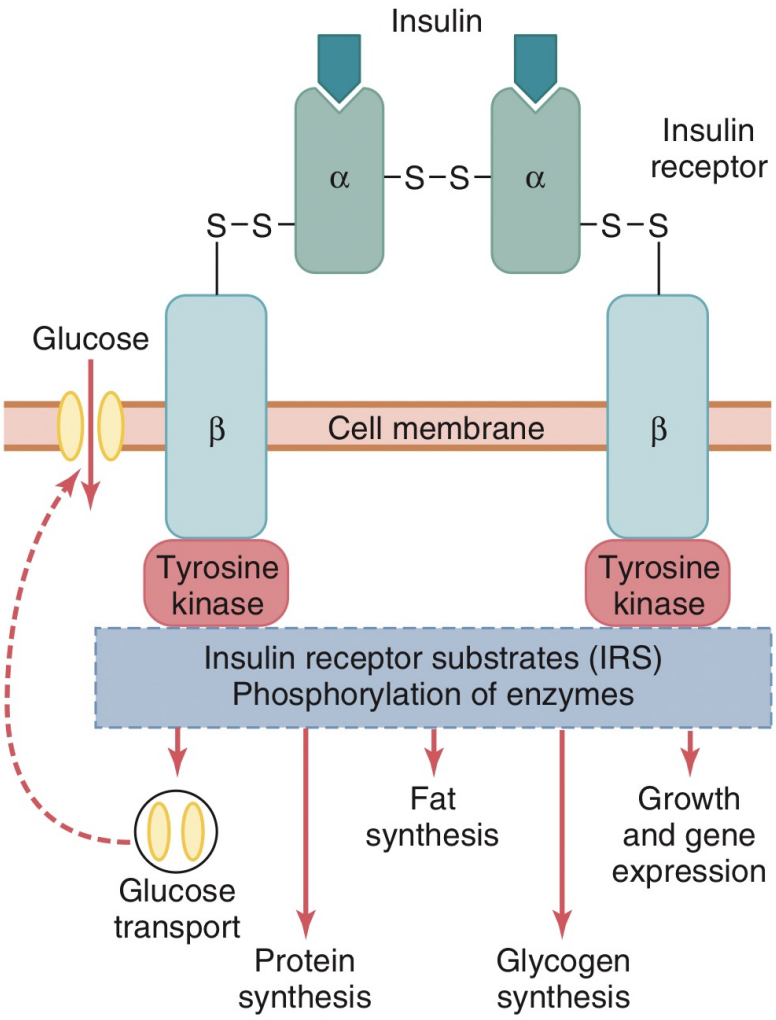
Once the insulin binds to the alpha subunits this binding is transmitted through betas to the tyrosine kinase, usually the second messengers in the end of the betas are inactive ,but when insulin binds to the alphas and this binding is transmitted into the second messengers (the tyrosine kinases)which in turn activate the phosphorylation of different enzymes.

-Mechanism of insulin action on cell:(These steps are taken from Guyton and Hall since the Dr didn't explain them clearly)

1) To initiate its effects on the target cell, insulin first binds with Alpha subunits outside the cell membrane.

2) Because of the linkages between the alpha and beta subunits, the portions of beta subunits protruding towards the cytoplasm become auto-phosphorylated. (Insulin receptor is an example of enzyme linked receptor).

3) Auto-phosphorylation of the beta subunits activates the local tyrosine kinase (The second messenger) which, in turn, causes phosphorylation of multiple other intracellular enzymes, so that insulin can exert its effects.



- Functions of insulin:
  i. Activation of glucose transporters, for the entry of glucose to cells.
  ii. Insulin produces two other second messengers IP3 and DAG, these mostly play a role in the entry of amino acids as well as minerals(potassium , phosphate and magnesium)
  iii. Stimulates protein synthesis.
  iv. Stimulates fat synthesis.
  v. Inhibits gluconeogenesis
  vi. Promotes growth and gene expression (remember that growth does not occur in the absence of insulin even if GH is present).

- Factors affecting Insulin secretion:

Stimulatory Factors	**Inhibitory Factors**
1) Increased glucose concentration 2) Increased amino acid concentration 3) Increased fatty acid and ketoacid 4) concentration 5) Glucagon 6) Cortisol 7)Glucose-dependent insulinotropic peptide (GIP) 8) Potassium 9) Vagal stimulation;acetylcholine 10) Sulfonylurea drugs (e.g.,tolbutamide, glyburide) 11) Obesity	1) Decreased blood glucose 2) Fasting 3) Exercise 4) Somatostatin α-Adrenergic agonists 5) Diazoxide

- Notes:
  1. The most important stimulatory factor is the glucose, but it has to be metabolized (to generate ATP) before it stimulates the insulin secretion. When ATP increases potassium channels close which is followed by depolarization and increased calcium levels then insulin secretion.

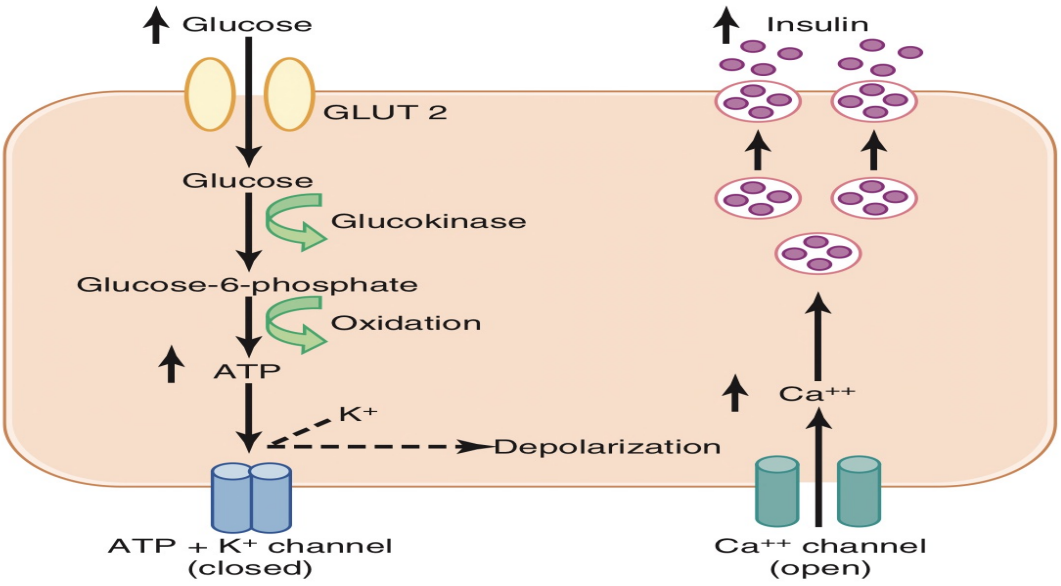
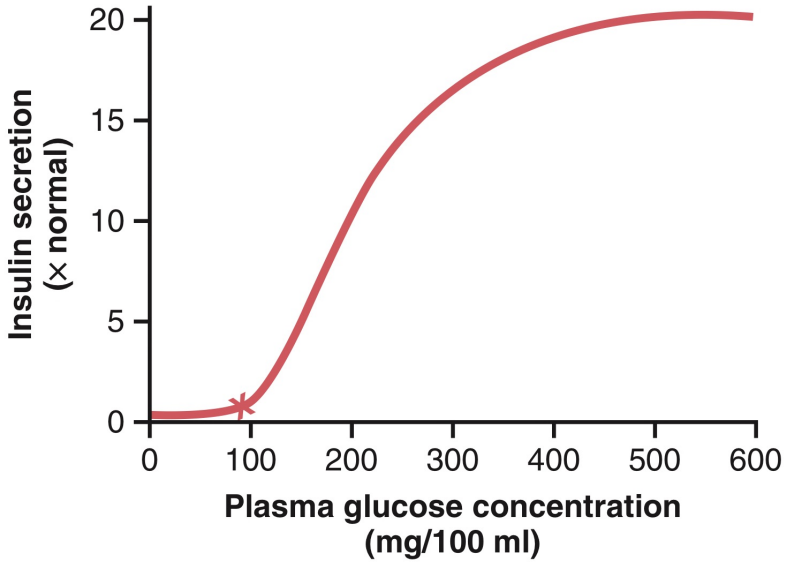


Figure 79-7. The basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

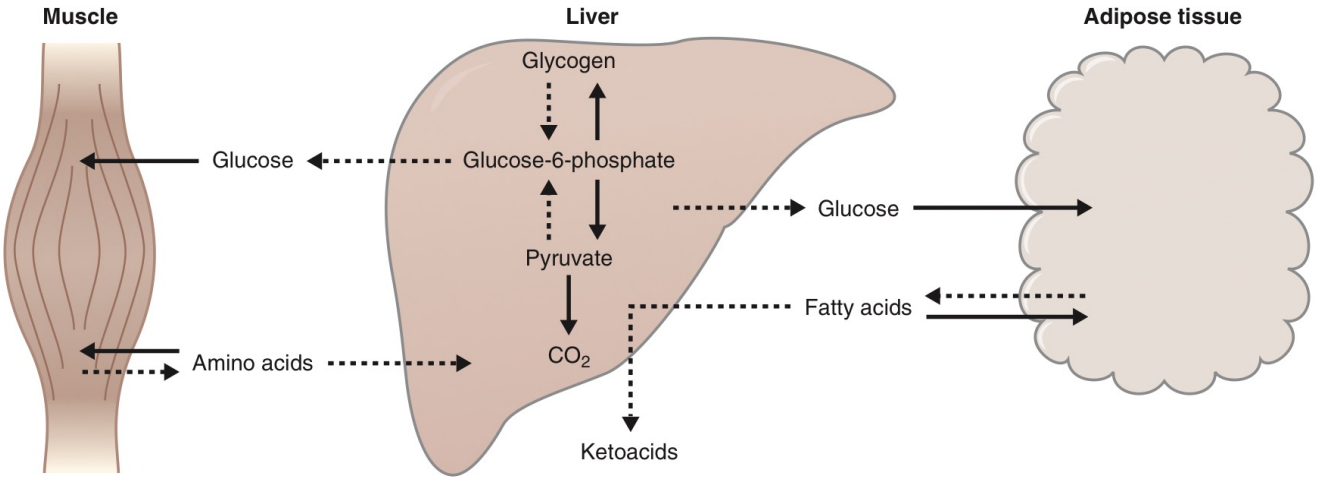


- At a level of blood glucose around 50 mg/dL there is almost no secretion of Insulin, while if the blood glucose level approaches 300 mg/dL then we will achieve the maximum concentration of

insulin in the blood. The increase in the insulin level stops when it reaches 500mg/dL .

- Just a reminder for the down regulation:
  In the down regulation, the number of the receptors as well as the affinity of them to insulin decrease, therefor, the level of insulin in the down regulation is higher than the control .
- Diabetic patient needs more insulin to reduce glucose (to reach the normal level) because of the low number of receptors as well as the affinity.>>>>which we called it diabetes 2.

Extra image from Costanzo Physiology textbook



Nutrient	Effect of Insulin on Blood Level
Glucose	Decreased
Fatty acids	Decreased
Ketoacids	Decreased
Amino acids	Decreased