Endocrine

434 Physiology team presents to you:

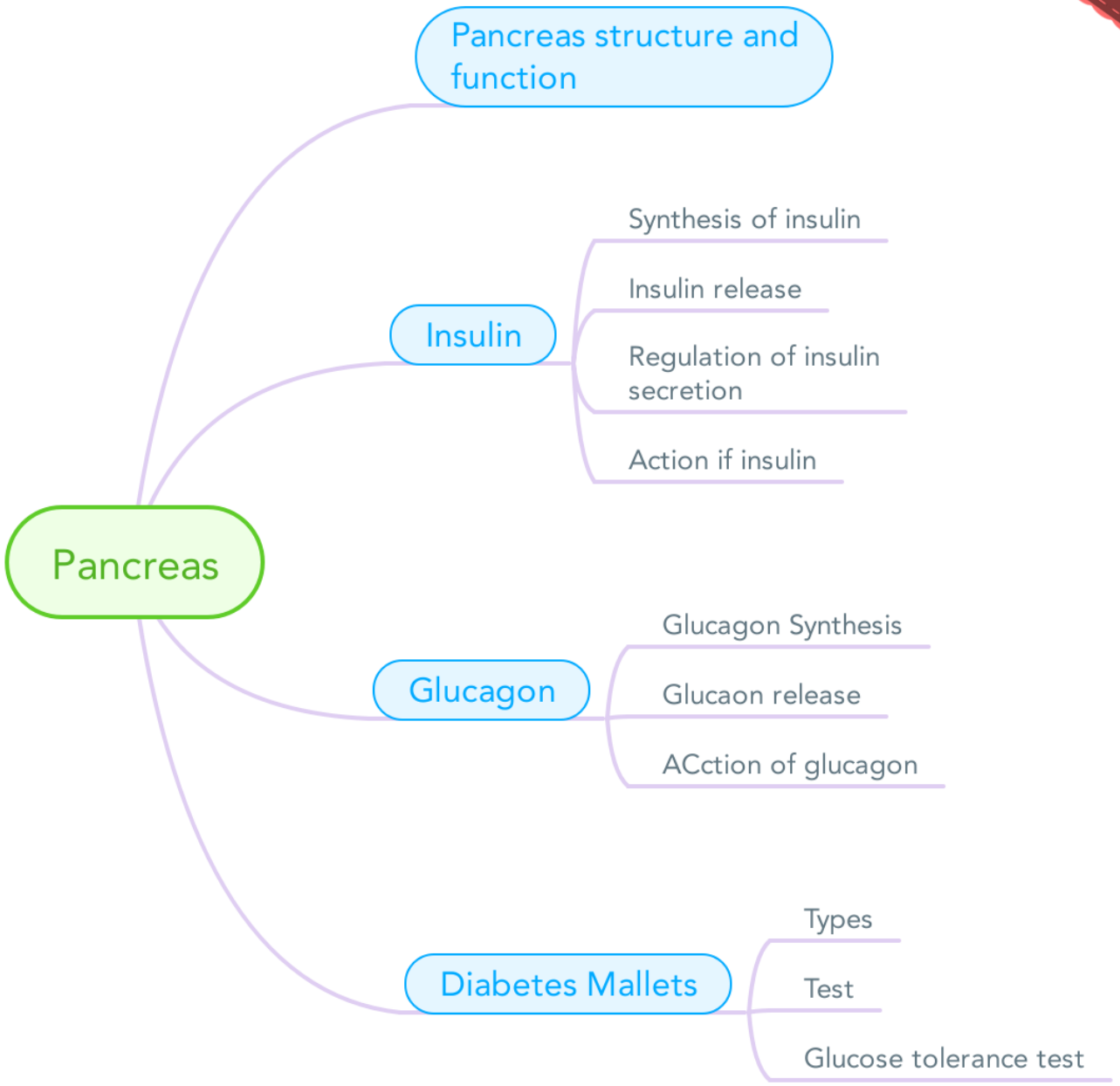
Pancreas

- Important
- Further explanation

Contents:

Please check out this link before viewing the file to know if there are any additions/changes or corrections. The same link will be used for all of our work Physiology Edit

Mindmap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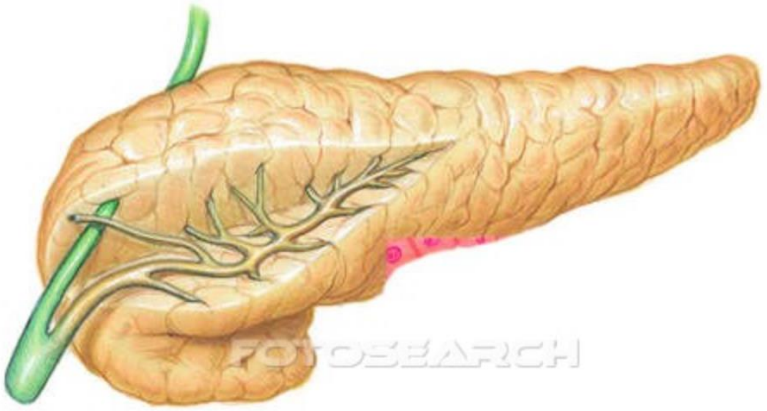
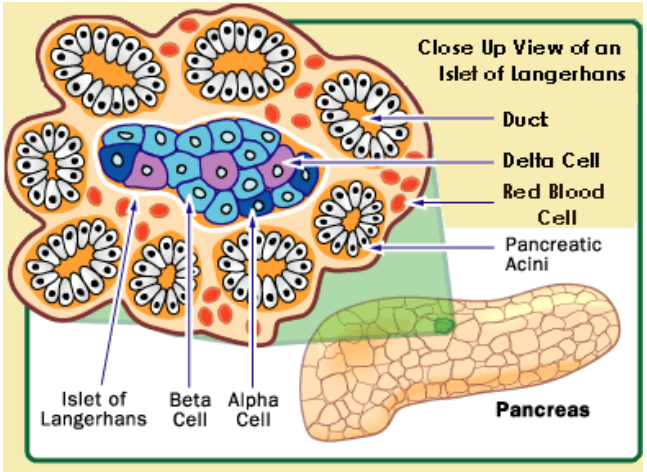
Pancreas



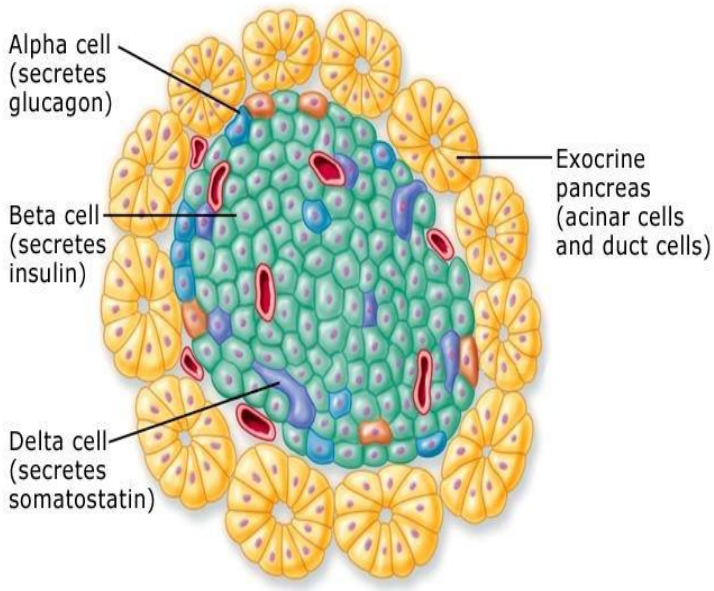


- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach
- Strategic location
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets **(islets of Langerhans)** produce hormones involved in regulating fuel storage and use.

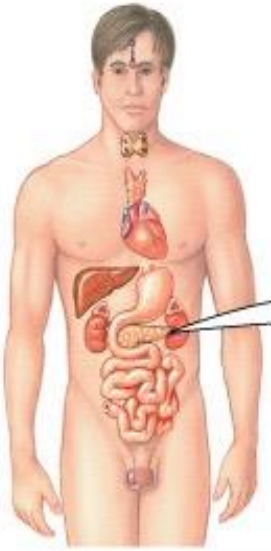
Islets of Langerhans

We have about 1-2 million islets in our pancreas!

These islets are divided into group of cells:



- Beta (β) cells produce insulin (70%)
- Alpha (α) cells produce glucagon (20%)
- Delta (δ) cells produce somatostatin (5%)
- F cells produce pancreatic polypeptide (5%)



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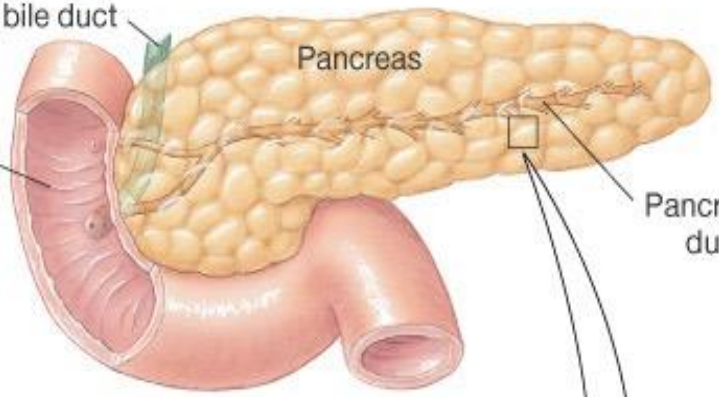
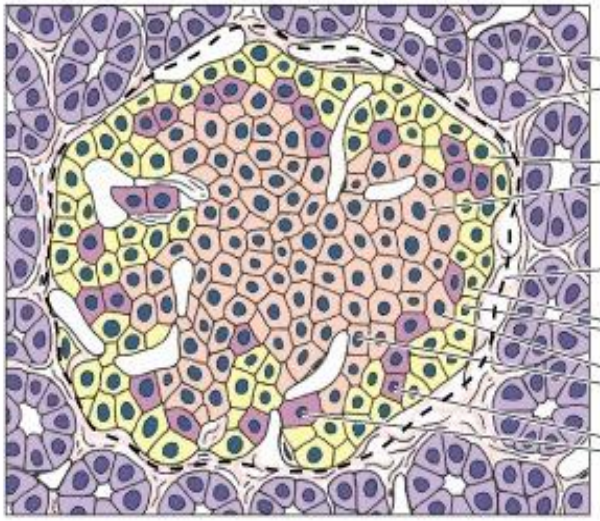


CELL	SECRETES:
Alpha cells	Glucagon
D cells	Somatostatin
Beta cells	Insulin, amylin

(b)



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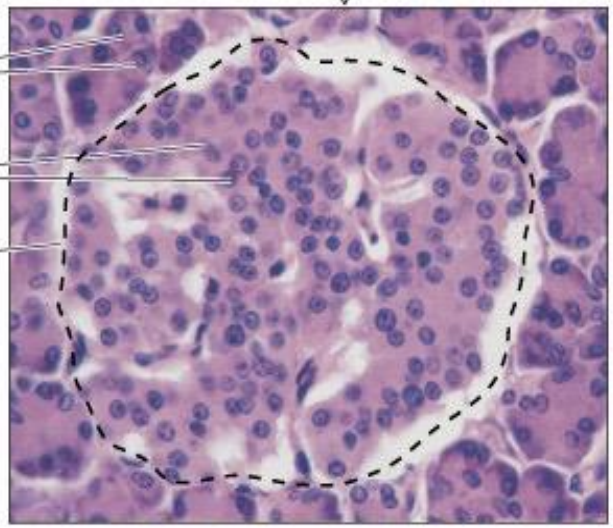
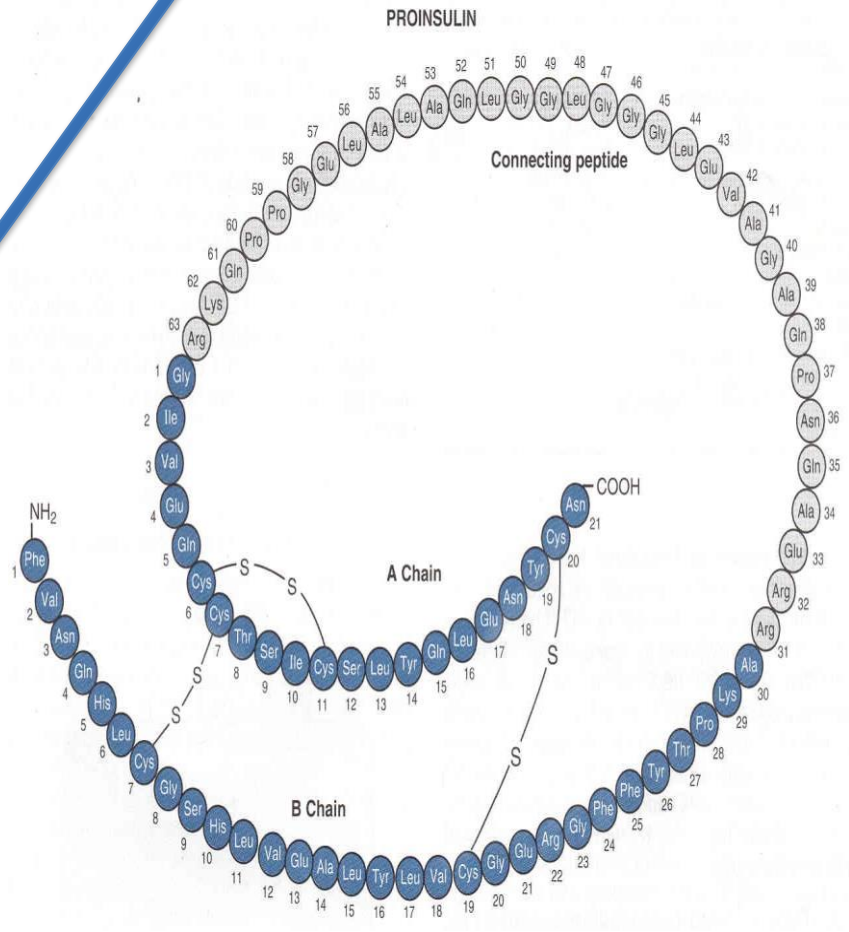


Insulin

In the next slide we will explain what does this (شخابيط) mean.

- Hormone of nutrient abundance
- A protein hormone consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).
- Has a plasma half-life of 6 minutes.

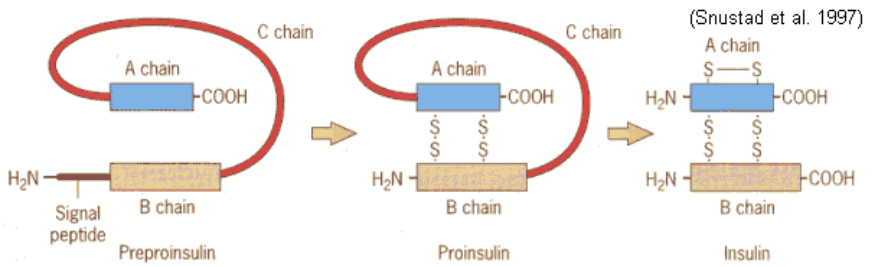
  "short half-life"



Synthesis of insulin

Basically, as we said that insulin is a polypeptide hormone which means that its formed from mRNA!
After mRNA is translated in ribosomes it becomes protein which is preproinsulin, the protein enters the endoplasmic reticulum & the signal peptide gets removed which turns it into proinsulin.
Proinsulin consists of three subunits (A , B , C) this protein travels to Golgi apparatus where its modified by cutting the C subunit and keeping A&B subunits conjugating with each other by disulfide bond!

This A&B subunits is our Insulin.



DNA (chromosome 11) in β cells

↓

mRNA

↓

Preproinsulin (signal peptide, A chain,
B chain, and peptide C)

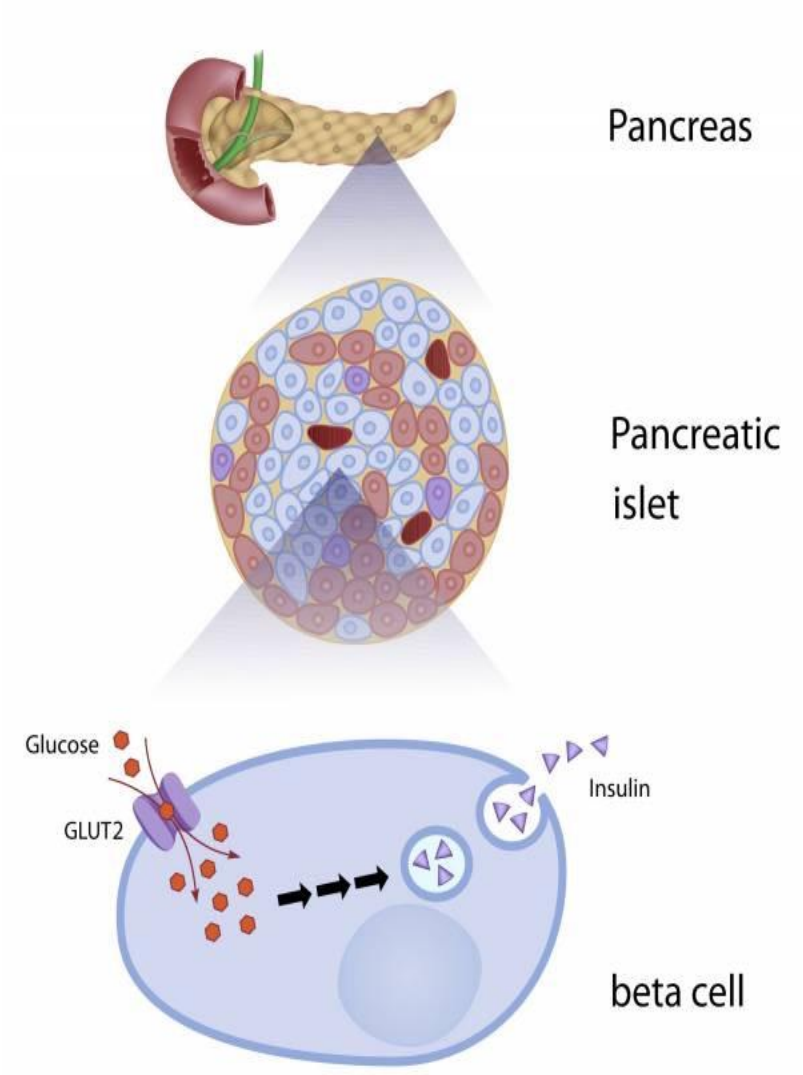
↓

proinsulin

↓

insulin

- Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
- Threshold of glucose-stimulated insulin secretion is 100 mg/dl.
- Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene
- Glucose is the primary stimulator of insulin secretion!

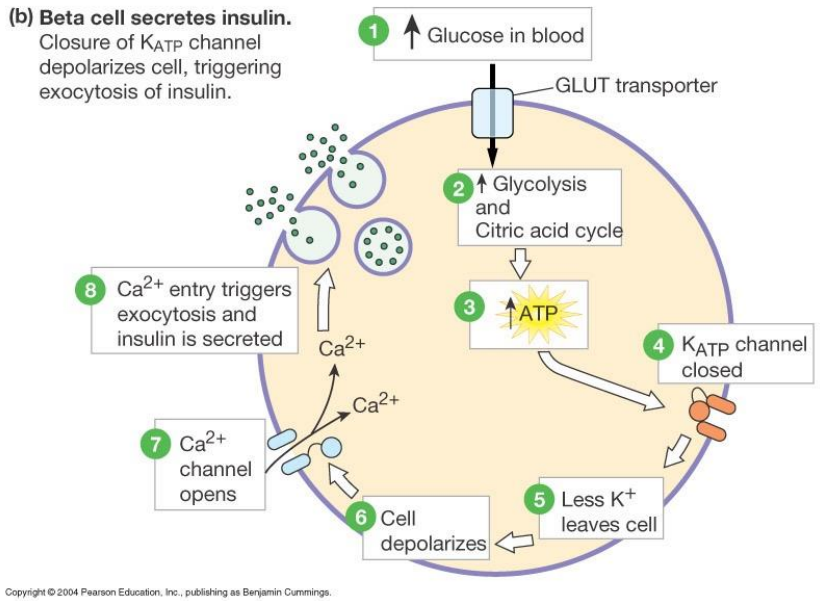


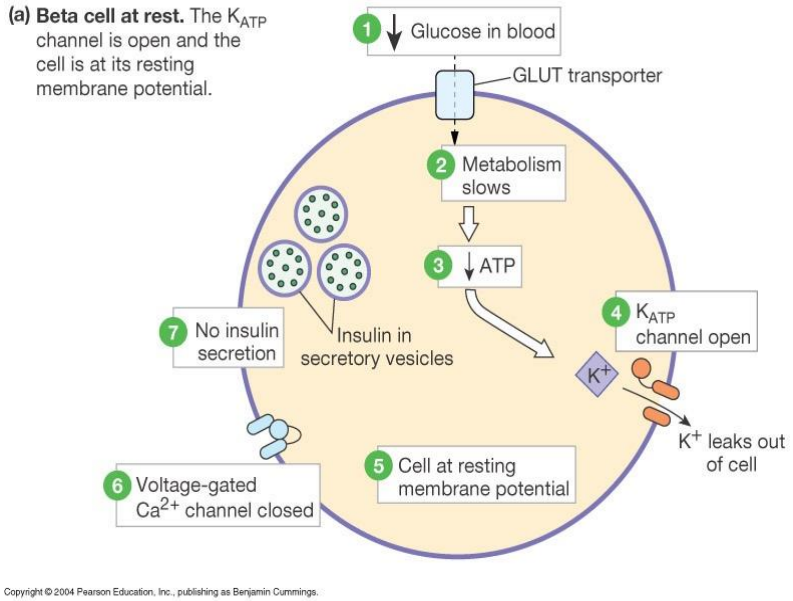
Insulin release

We have two situation which deal with insulin in our body!

Weather Glucose is high or Glucose is low.

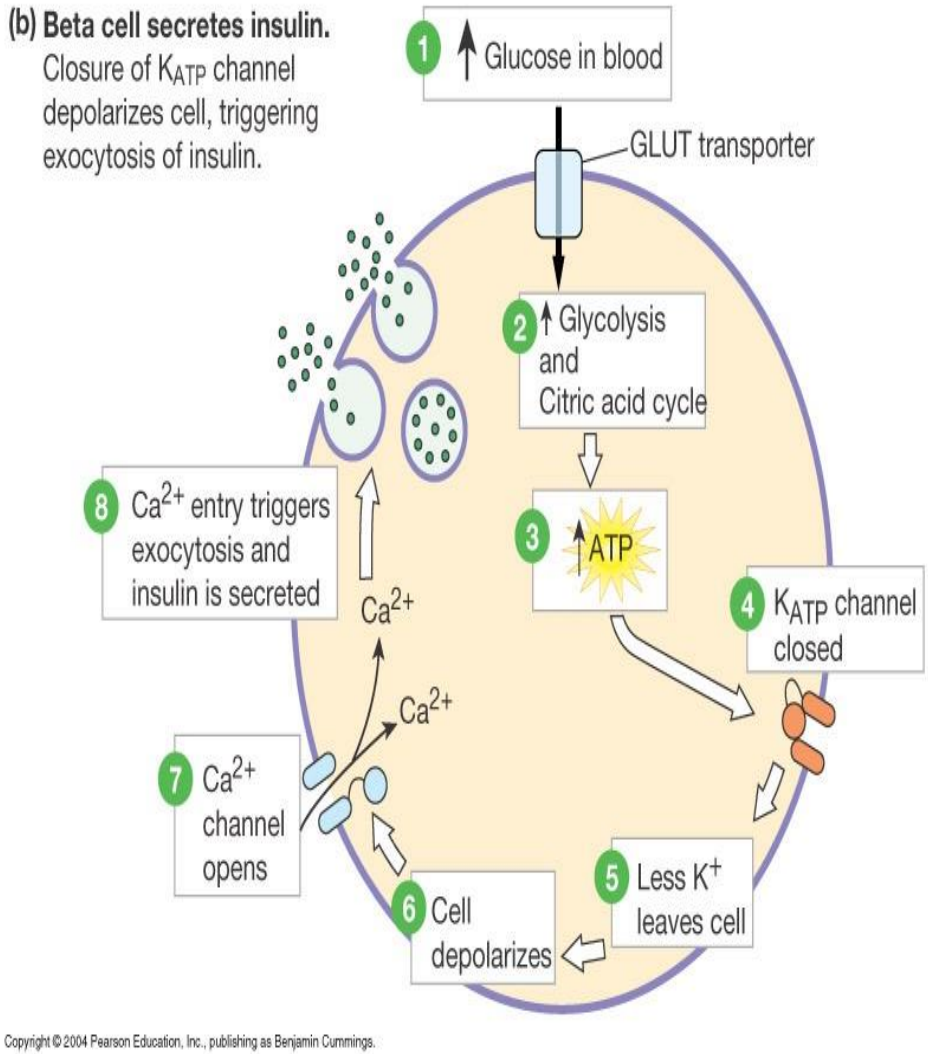
Look to the two pictures below and the explanation will be on the next slide.





In case of too much glucose in our blood.

1. Glucose enters B cell by facilitated diffusion via **GLUT-2.**
2. Glucose is phosphorylated to glucose-6-phosphate **by <u>Glucokinase</u> *((rate limiting enzyme))**
3. Oxidation of glucose-6-phosphate generates ATP. (by glycolysis)
4. ATP acts on ATP-sensitive K+ channel , closing it. (sulfonylurea drug for diabetics works by closing this channel → ↑ insulin)
5. Reduced exit of K+ depolarizes membrane.
6. Depolarization opens voltage-gated Ca+2 channels.
7. Ca+2 enters B cell.
8. Ca+2 triggers exocytosis of insulin vesicles.
9. Insulin is secreted



*Mnemonic: GLUT-2 <u>LIK</u>es insulin (GLUT-2 is found in): L → Liver, I → Intestine, K → Kidney + Pancreas

Stimulators

1) ↑ Blood glucose concentration
"major Control"
2) ↑ Blood amino acid conc.
3)Food intake → increases gastrointestinal hormones & Parasympathetic stimulation

Inhibitors

Sympathetic stimulation (and epinephrine)

Islet B cells

Release insulin

↓ Blood glucose
↓ Blood fatty acids
↓ Blood amino acid
↑ Protein synthesis
↑ Fuel storage

Regulation of Insulin Secretion

Stimulators of insulin secretion	Inhibitors of insulin secretion
↑ Serum glucose	↓ Glucose
↑ Serum amino acids	↓ Amino acids
↑ Serum free fatty acids	↓ Free fatty acids
↑ Serum ketone bodies	
Hormones	Hormones
Gastroinhibitory peptide (GIP)	Somatostatin
Glucagon	Epinephrine (α-receptor)
Gastrin	
Cholecystokinin (CCK)	
Secretin	
Vasoactive intestinal peptide (VIP)	
Epinephrine (β-receptor)	
Parasympathetic nervous system	Sympathetic nervous system stimulation

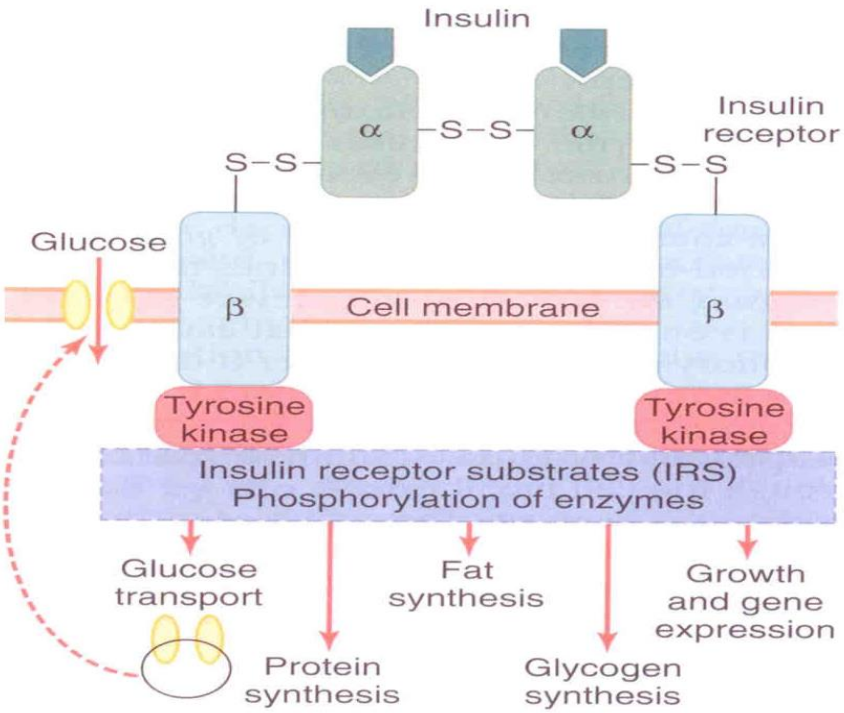
↑ AA stimulates both insulin & glucagon release

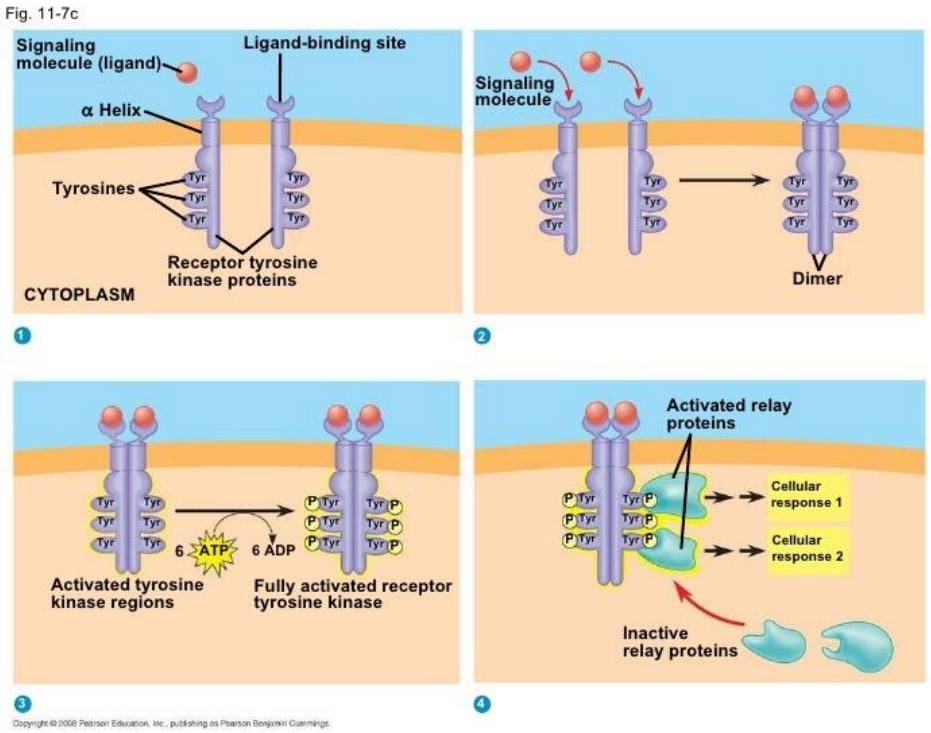
GLUCOSE PLAYS A MAJOR ROLE IN INSULIN REGULATION!

Dr. Manan's explanation:
Sympathetic NS generally inhibits insulin release. When it acts on α receptors it inhibits insulin secretion but when it acts on β receptors it stimulates insulin release, however β cells have more α receptors which makes the net result of SNS: inhibition of insulin secretion.

Insulin Receptor

A wonderful video that explains how does this receptor works
https://www.youtube.com/watch?v=ObrsQl-vPA4





- the insulin receptor is a transmembrane receptor
- belongs to the large class of **tyrosine kinase receptors**
- Made of two alpha subunits and two beta subunits

Actions of insulin

- Rapid (seconds)

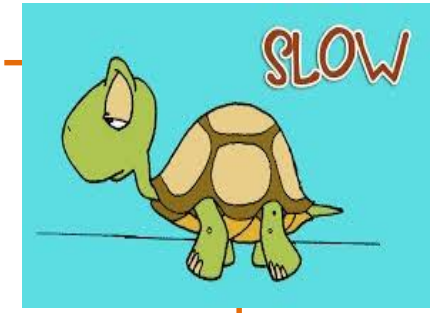
(+) transport of glucose, amino acids, K+ into insulin-sensitive cells

Intermediate (minutes)

(+) protein synthesis
(-) protein degradation
(+) of glycolytic enzymes and glycogen synthase
(-) phosphorylase and gluconeogenic enzymes

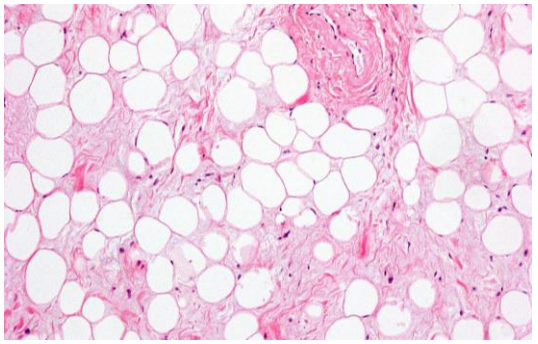
Delayed (hours)

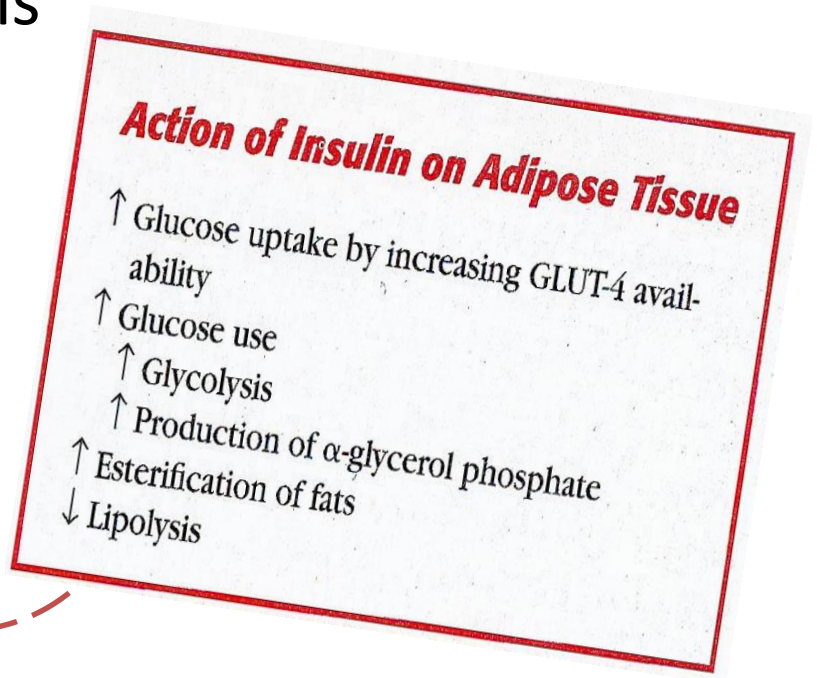
(+) mRNAs for lipogenic and other enzymes



Action of insulin on Adipose tissue

- (+) glucose entry
- (+) fatty acid synthesis
- (+) glycerol phosphate synthesis
- (+) triglyceride dep0sition
- (+)lipoprotein lipase
- (-) of hormone-sensitive lipase
- (+) K uptake





Action of insulin on Muscle

(+) glucose entry

(+) glycogen synthesis

(+) amino acid uptake

(+) protein synthesis in ribosomes

(-) protein catabolism

(-) release of gluconeogenic amino acids

(+) ketone uptake

(+) K uptake

Action of Insulin on Muscle

↑ Glucose uptake by increasing GLUT-4 availability
↑ Glucose use
↑ Glycogenesis, ↓ glycogenolysis
↑ Glycolysis
↑ Amino acid uptake (particularly branched-chain amino acids)
↑ Protein synthesis, ↓ proteolysis

Action of insulin on Liver

(-) ketogenesis

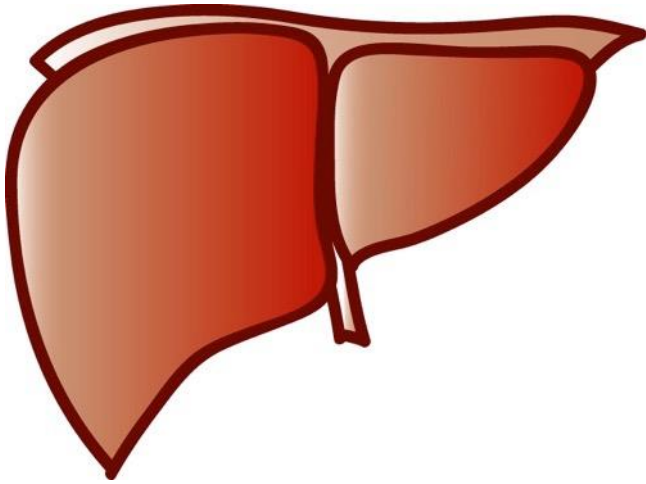
(+) protein synthesis

(+) lipid synthesis

(-)gluconogenesis,

(+) glycogen synthesis,

(+) glycolysis.



Actions of Insulin on Liver

↑ Glucose uptake (if blood glucose level is high)
↑ Glucose use
↑ Glycogenesis, ↓ glycogenolysis
↑ Glycolysis, ↓ gluconeogenesis
↑ Fatty acid synthesis and very-low-density lipoprotein formation, ↓ ketogenesis
↓ Urea cycle activity

And in Genereal it promotes Cell growth

Glucose Transport

Name	location
• GLUT1	• erythrocytes, brain *Insulin independent
• GLUT2	• liver, pancreas, small intestines, kidney *insulin independent
• GLUT3	• Brain *Insulin independent
• GLUT4*	• muscle, adipose tissue * insulin sensitive transporter

Glucagon

- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent
- Produced by α cells in the pancreas

- The effect of glucagon is opposite to that of insulin
- Glucagon vs glycogen: Glucagon causes the liver to convert stored glycogen into glucose (hence its function +glucose)

SYNTHESIS of glucagon:

DNA in α cell (chromosome 2) → mRNA → Preproglucagon → proglucagon → glucagon

Glucagon Actions

- Its major target is liver:
  - Glycogenolysis
  - Gluconeogenesis
  - Lipid oxidation (fully to CO_2 or partially to produce keto acids "ketone bodies").
  - Release of glucose to the blood from liver cells
- It also acts on adipose tissue but does NOT act on muscles.

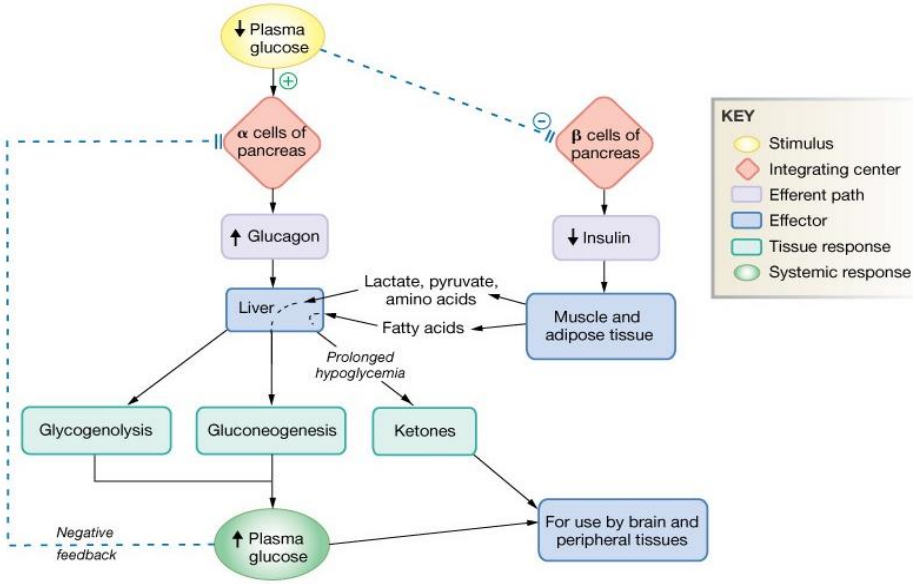


Image shows Glucagon Action on Cells

Effects on Glucagon Secretion

Stimuli	Inhibitors
↓ Blood Glucose	↑ Blood Glucose
↑ Serum amino acids (arginine, alanine)	Somatostatin
Sympathetic NS, Stress, Exercise	Insulin

Comparison Between Glucagon and Insulin

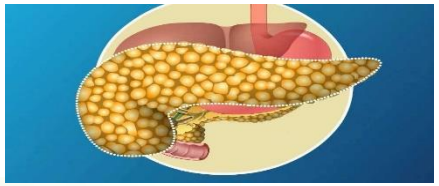


Table 22-5: Glucagon

Cell of origin	Alpha cells of pancreas
Chemical nature	29-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	4–6 minutes
Factors affecting release	Stimulated by plasma [glucose] < 200 mg/dL, with maximum secretion below 50 mg/dL; ↑ blood amino acids.
Target cells or tissues	Liver primarily
Target receptor/second messenger	G protein-coupled receptor linked to cAMP
Whole body or tissue action	↑ Plasma [glucose] by glycogenolysis and gluconeogenesis; ↑ lipolysis leads to ketogenesis in liver
Action at molecular level	Alters existing enzymes and stimulates synthesis of new enzymes
Feedback regulation	↑ Plasma [glucose] shuts off glucagon secretion
Other information	Member of secretin family along with VIP, GIP, and GLP-1

Table 22-3: Insulin

Cell of origin	Beta cells of pancreas
Chemical nature	51-amino acid peptide
Biosynthesis	Typical peptide
Transport in the circulation	Dissolved in plasma
Half-life	5 minutes
Factors affecting release	Plasma [glucose] > 100 mg/dL; ↑ blood amino acids; GI hormones (feedforward reflex) and parasympathetic amplify. Sympathetic inhibits.
Target cells or tissues	Liver, muscle, and adipose tissue primarily; brain, kidney, and intestine not insulin-dependent
Target receptor	Membrane receptor with tyrosine kinase activity; pathway with insulin-receptor substrates
Whole body or tissue action	↓ Plasma [glucose] by ↑ transport into cells or ↑ metabolic use of glucose
Action at cellular level	↑ Glycogen synthesis; ↑ aerobic metabolism of glucose; ↑ protein and triglyceride synthesis

Diabetes

- Diabetes is probably the most important metabolic disease.
- It affects every cell in the body and affects carbohydrate, lipid, and protein metabolism.
- characterized by the polytriad:
  - **Polyuria** (excessive urination)
  - **Polydypsia** (excessive thirst)
  - **Polyphagia** (excessive hunger)

Note that:
- Alpha cells produce glucagon
- Beta cells produce insulin

Types of Diabetes

Type 1 diabetes
Affects children
Cause: inadequate insulin secretion
Treatment : insulin injection

Type 2 diabetes
Affects adults
Cause: defect in insulin action
Treatment: diet or OHA

Diabetes Mellitus Type I

- Caused by an immune-mediated selective destruction of β cells
- β cells are destroyed while α cells are preserved:
- No insulin —> high glucagon —> high production of glucose and ketones by liver —>
- high glucose & ketones —> osmotic diuresis
- keto acids —> diabetic ketoacidosis

Diabetes Mellitus: Type II

- More common in some ethnic groups
- Insulin resistance keeps blood glucose too high
- Chronic complications: atherosclerosis, renal failure & blindness

Symptoms of Diabetes Mellitus

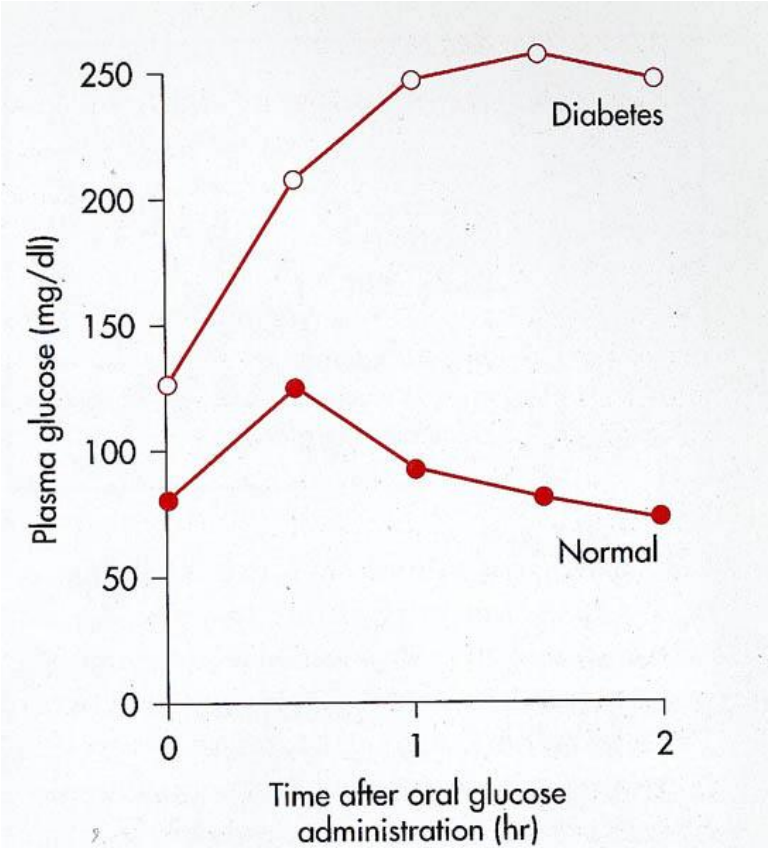
Hyperglycemia
Polyuria
Polydipsia
Polyphagia
Ketoacidosis (IDDM)
Hyperlipidemia
Muscle wasting
Electrolyte depletion

Glucose Tolerance Test

- Both the FPG* and OGTT* tests require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.
- The oral glucose tolerance test (OGTT):
  - FPG test
  - Blood is then taken 2 hours after drinking a special glucose solution
- Following the oral administration of a standard dose of glucose, the plasma glucose concentration normally rises but returns to the fasting level within 2 hours.
- If insulin activity is reduced, the plasma glucose concentration takes longer than 2 hours to return to normal and often rises above 200 mg/dl.
- Measurement of urine glucose allows determination of the renal threshold for glucose.

*fasting plasma glucose (FPG) / *Oral Glucose Tolerance Test

- The following results suggest different conditions:
- **Normal values:**
- FPG <100 mg/dl
- 2hr PPG < 140 mg/dL
- **Impaired glucose tolerance**
- 2hr PPG = 140 - 199 mg/dL
- **Impaired fasting glucose**
- FPG = 100-125
- **Diabetes**
- FPG ≥ 126 mg/dl
- 2hr PPG levels ≥200 mg/dL



Summary

table 7-8 Cell Types of the Islets of Langerhans

Type of Cell	Location	Function
Beta	Central islet	Secrete insulin
Alpha	Outer rim of islet	Secrete glucagon
Delta	Intermixed	Secrete somatostatin and gastrin

table 7-7 Comparison of Insulin and Glucagon

	Stimulus for Secretion	Major Actions	Overall Effect on Blood Levels
Insulin (tyrosine kinase receptor)	↑ Blood glucose ↑ Amino acids ↑ Fatty acids Glucagon GIP Growth hormone Cortisol	Increases glucose uptake into cells and glycogen formation Decreases glycogenolysis and gluconeogenesis Increases protein synthesis Increases fat deposition and decreases lipolysis Increases K^+ uptake into cells	↓ [glucose] ↓ [amino acid] ↓ [fatty acid] ↓ [ketoacid] Hypokalemia
Glucagon (cAMP mechanism)	↓ Blood glucose ↑ Amino acids CCK Norepinephrine, epinephrine, ACh	Increases glycogenolysis and gluconeogenesis Increases lipolysis and ketoacid production	↑ [glucose] ↑ [fatty acid] ↑ [ketoacid]

ACh = acetylcholine; cAMP = cyclic adenosine monophosphate; CCK = cholecystokinin; GIP = glucose-dependent insulinotropic peptide.

Summary

table 7-10 Regulation of Insulin Secretion

Factors that Increase Insulin Secretion	Factors that Decrease Insulin Secretion
↑ Blood glucose	↓ Blood glucose
↑ Amino acids (arginine, lysine, leucine)	Somatostatin
↑ Fatty acids	Norepinephrine, epinephrine
Glucagon	
GIP	
Ach	

ACh = acetylcholine; GIP = glucose-dependent insulinotropic peptide.

table 7-9 Regulation of Glucagon Secretion

Factors that Increase Glucagon Secretion	Factors that Decrease Glucagon Secretion
↓ Blood glucose	↑ Blood glucose
↑ Amino acids (especially arginine)	Insulin
CCK (alerts alpha cells to a protein meal)	Somatostatin
Norepinephrine, epinephrine	Fatty acids, ketoacids
ACh	

ACh = acetylcholine; CCK = cholecystokinin.

Summary

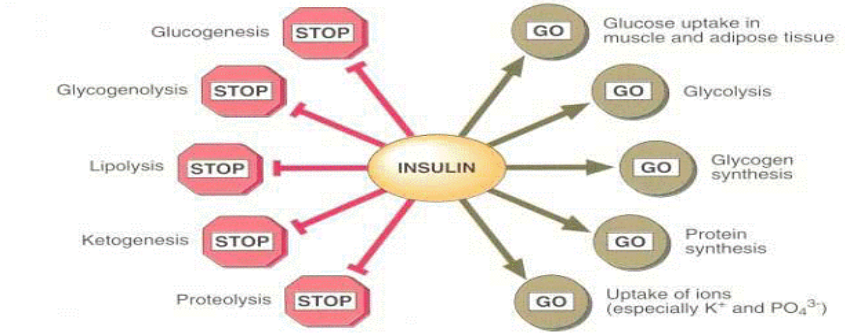


Fig. 2 **The actions of insulin.**

Insulin:

- insulin is composed of two amino acid chains (alpha and beta) connected to each other by disulfide linkage

The insulin receptor belongs to large class of tyrosine kinase receptors.

- Glucose is the primary stimulator of insulin secretion.

four receptor for glucose transportation: GLUT1,GLUT2,GLUT3,GLUT4

Insulin secretion:

1.high blood glucose →Transport of glucose into the beta cells by GLUT2 receptor. (facilitated diffusion) →glucose is oxidized to ATP.

2. ATP increases inside the cell this will lead to closure of ATP-sensitive K+ channel and trapping of K+ inside the cell.

3. The depolarization of cells open voltage-gated calcium channel →Ca+2 flows into the beta cells down its concentration gradient and cause secretion of insulin by exocytosis.

Summary

Glucagon

Glucagon is a hyperglycemic polypeptide hormone
It Uses cAMP \ Adenylyl cyclase system (second messenger).
Its major target is the liver

Diabetes:

Diabetes is metabolic disease. characterized by :

Polyuria (excessive urination)
Polydipsia (excessive thirst)
Polyphagia (excessive hunger).

- **Type 1 Diabetes:** Affects children Caused by inadequate insulin secretion Treatment : insulin injection
- **Type 2 diabetes:** Affects adults .Caused by defect in insulin action Treatment diet

Actions of Insulin

Rapid (seconds)
(+) transport of glucose, amino acids, K+ into insulin-sensitive cells

Intermediate (minutes)
(+) protein synthesis
(-) protein degradation
(+) of glycolytic enzymes and glycogen synthase
(-) phosphorylase and gluconeogenic enzymes

Delayed (hours)
(+) mRNAs for lipogenic and other enzymes

Answer key:1-B, 2-C, 3-A, 4-A, 5-A, 6-C, 7:A

MCQs

1- insulin synthesis is decreased by:
A. Glucagon
B. Fasting
C. Gastrin
D. Increase in free fatty acids

2- A slow action of insulin:
A. (+) protein synthesis
B. (-) protein degradation
C. (+) mRNAs for Fat formation
D. (+) transport of glucose

3- which of the following is an insulin effect on the liver:
A. (+) protein synthesis
B. (+) ketogenesis
C. (-) lipid synthesis
D. (-) glycolysis.

4- GLUT4 is located in:
A. muscle
B. brain
C. Liver
D. kidney

5- Which of the following is a characteristic of Type 1 diabetes
A. β cells are destroyed
B. α cells are destroyed
C. Affects adults
D. Insulin resistance

6- Which of the following results suggest a diabetic patient:
A. 2hr PPG = 130 mg/dL
B. FPG < 100 mg/dl
C. FPG = 126 mg/dl
D. HDL < 40 mg

7-Insulin has all of the following effects on adipose tissue except:
A. Decrease Glycerol phosphate synthesis
B. Increased triglyceride deposition
C. Increased potassium uptake
D. Inhibition of hormone sensitive lipase enzyme

SAQs

Q1: How is glucagon formed ?

Ans: Inside the alpha cells, genes encoding pancreatic preproglucagon, cleaving of preproglucagon produces proglucagon which is proteolytically processed to yield glucagon within alpha cells of the pancreatic islets.

Q2:Difference in the plasma glucose level between a normal vs diabetic patient after oral glucose administration:

Ans: normal; Starts below 100 mg/dl, after ingestion of glucose a slight rise in the level of glucose not persisting more than 2 hours. Then Glucose level goes back to normal.
diabetic: Starts above 110 mg/dl After ingestion of oral glucose, level of plasma glucose rises rapidly (above 150 mg/dl), and persist for a period longer than 2 hours.

Q3: How is the pancreas secrete insulin?

1-Glucose enters B cell by facilitated diffusion via GLUT-2.
2-Glucose is phosphorylated to glucose-6-phosphate.
3--Oxidation of glucose-6-phosphate generates ATP.
4-ATP acts on ATP-sensitive K+ channel , closing it.
5-Reduced exit of K+ depolarizes membrane.
6-Depolarization opens voltage-gated Ca+2 channels.
7-Ca+2 enters B cell.
8-Ca+2 triggers exocytosis of insulin vesicles.
9-Insulin is secreted

Thanks for checking our work

Good Luck

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