Physiology Team

ENDOCRINE BLOCK

LECTURE 14 & 15

PHYSIOLOGY OF PANCREAS AND INSULIN

DONE BY:
Sarah Alabdualqader
Tahani AlShaibani
Rawan Al-Taleb

REVISED BY:
Fahad Al-Rashed

OBJECTIVES

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Not Given :|

MIND MAP

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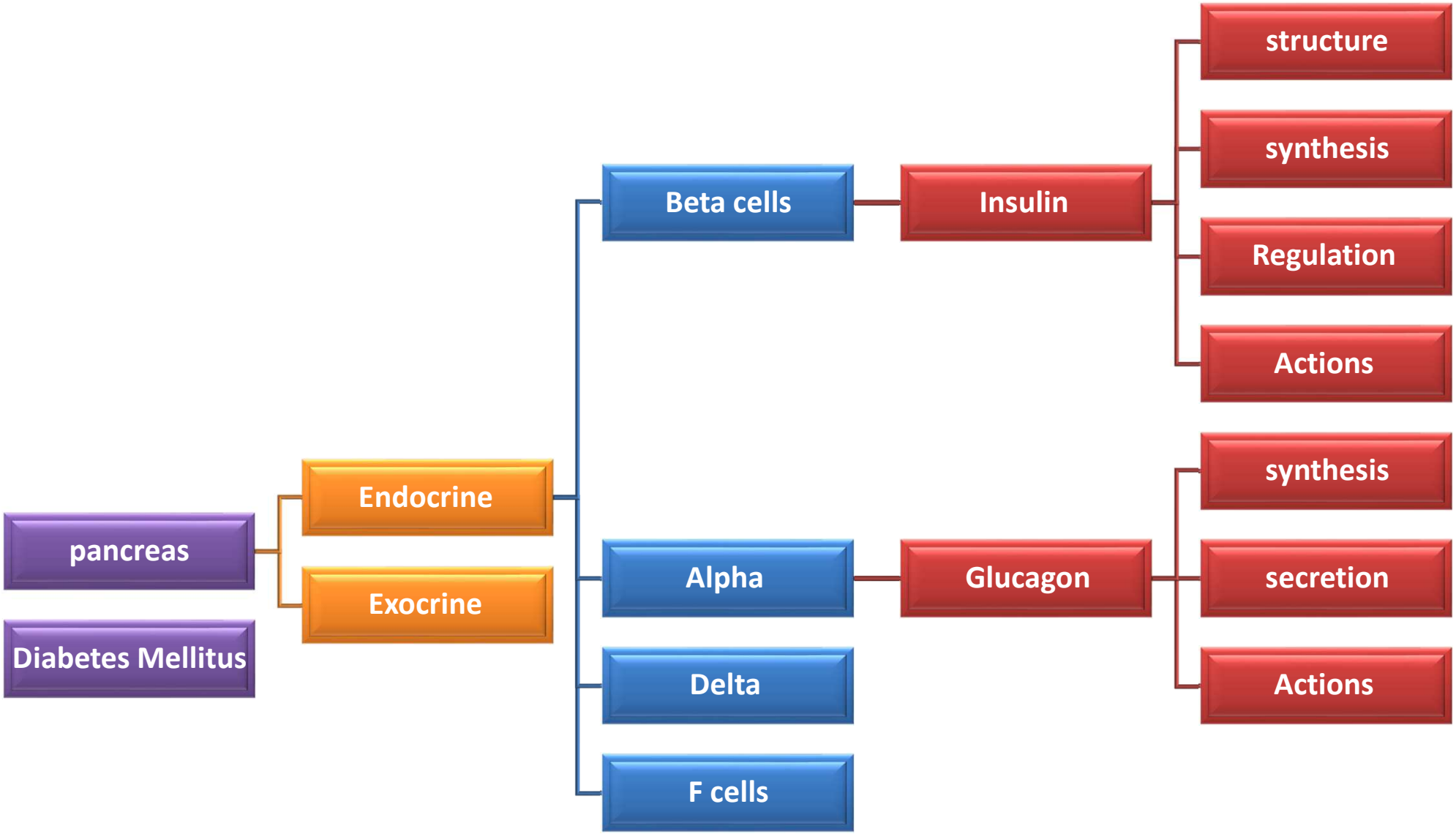

■ Slides ■ Important ■ Females' Notes ■ Explanation ■ Males' Notes

Pancreas

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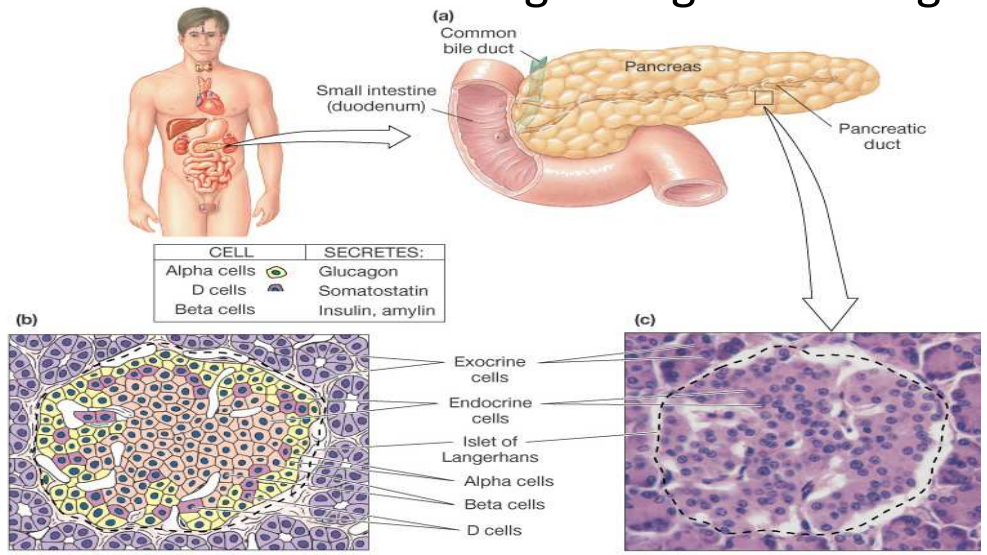
- A triangular gland, which has both exocrine and endocrine cells, located behind the stomach
- Strategic location
- Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- Pancreatic islets (islets of Langerhans) produce hormones involved in regulating fuel storage and use.

Islets of Langerhans high amount in the tail:

- 1-2 million islets
- Beta (β) cells produce insulin (70%)
- Alpha (α) cells produce glucagon (20%)
- Delta (δ) cells produce somatostatin (5%)
- F cells\ PP Cells produce pancreatic polypeptide (5%) it's function still unknown



- B cells stands for beautiful lady who likes to attract attention so it is located in the center. Beautiful lady is surrounded by males! Which are alpha cells. D cells stands for dogs you can find it everywhere. Beautiful lady likes money which are glucose, amino acids and fatty acids (nutrient). So beta cells is stimulated when there is nutrient. Once it is stimulated, it can secret insulin.
- Alpha cells are activated only in crisis (stress, exercise).
- D cells inhibits alpha and beta cells by releasing somatostatin.

Insulin

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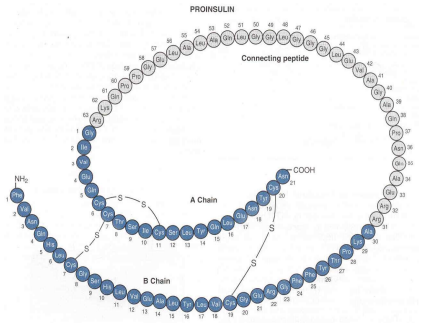
- Hormone of nutrient abundance
- A protein hormone consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).
- Has a plasma half-life of 6 minutes.



Insulin Synthesis

- 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

DNA (chromosome 11) in β cells

↓

mRNA

↓

Preproinsulin (signal peptide, A chain, b chain and peptide C which connecte A with B) synthesized in the ribosomes

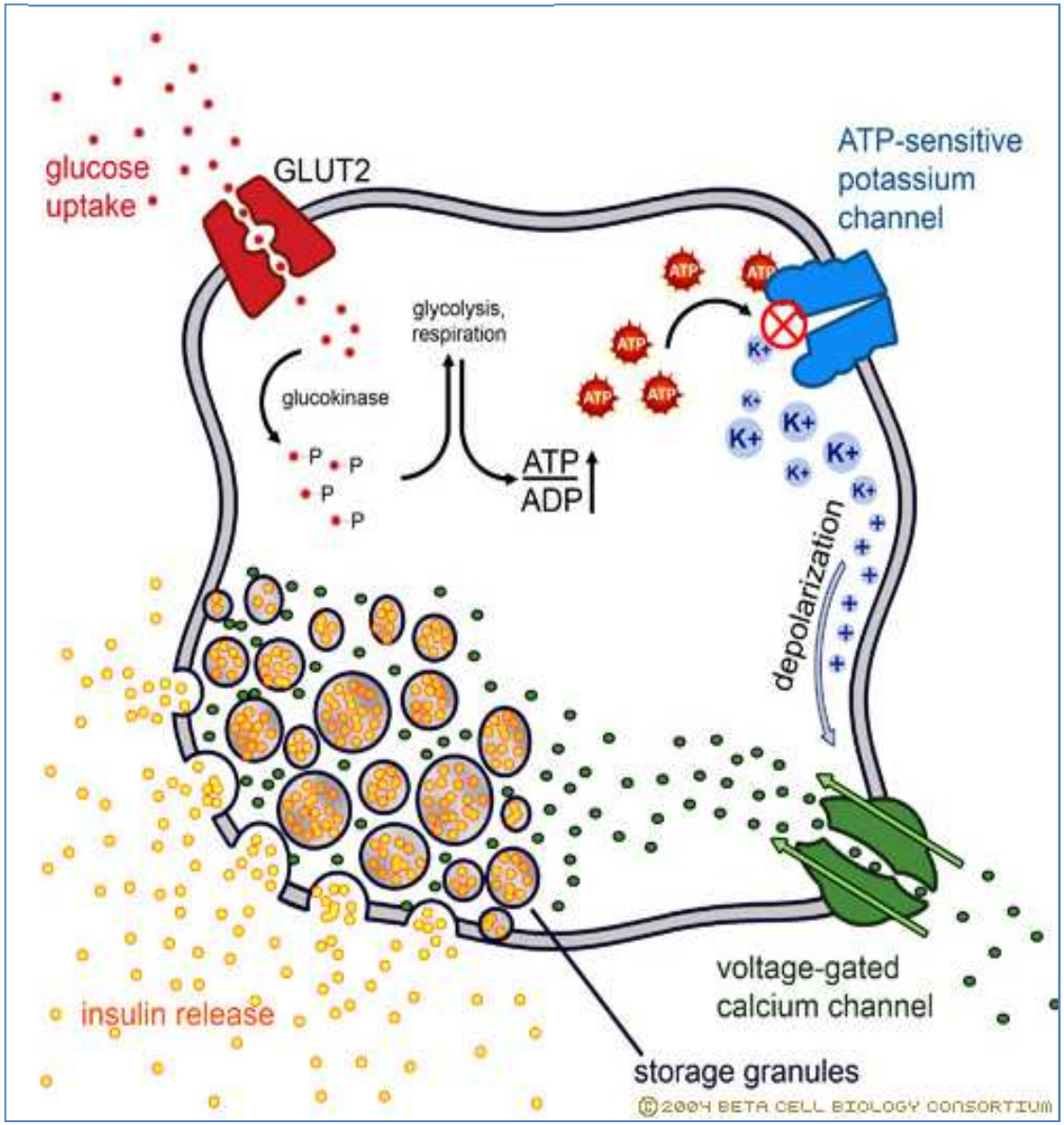
↓

Proinsulin. (in the rER the signal is cleaved so we will have A, B and C chain connected by disulfide bonds)

↓

Insulin (in golgi apparatus, the C peptide (connecting) is cleaved so we will have A and B connected together (Insulin) and c peptide (separated)

Insulin release



- the major stimulus is glucose
- receptor: GLUT 2 (allows glucose to go inside and outside the cell; in two ways. This receptor is found in beta cells, kidney, liver & intestine)
- when glucose enter the cell it will be phospholerated. After phospholpration glycolysis and then it produces energy (ATP)
- another gate on the cell membrane which is ATP-sensitive K channel. This gate allows K to go outside the cell. However, this gate is sensitive for ATP when there is a high amount of ATP it will be blocked and prevents K efflux and causes depolarization.
- since the cell is depolarized, a voltage-gated Ca channel will open allowing Ca to go inside the cell.
- Ca will push the storage granules toward the cell membrane and by exocytosis it releases insulin and the C peptide

Insulin release

Not Important

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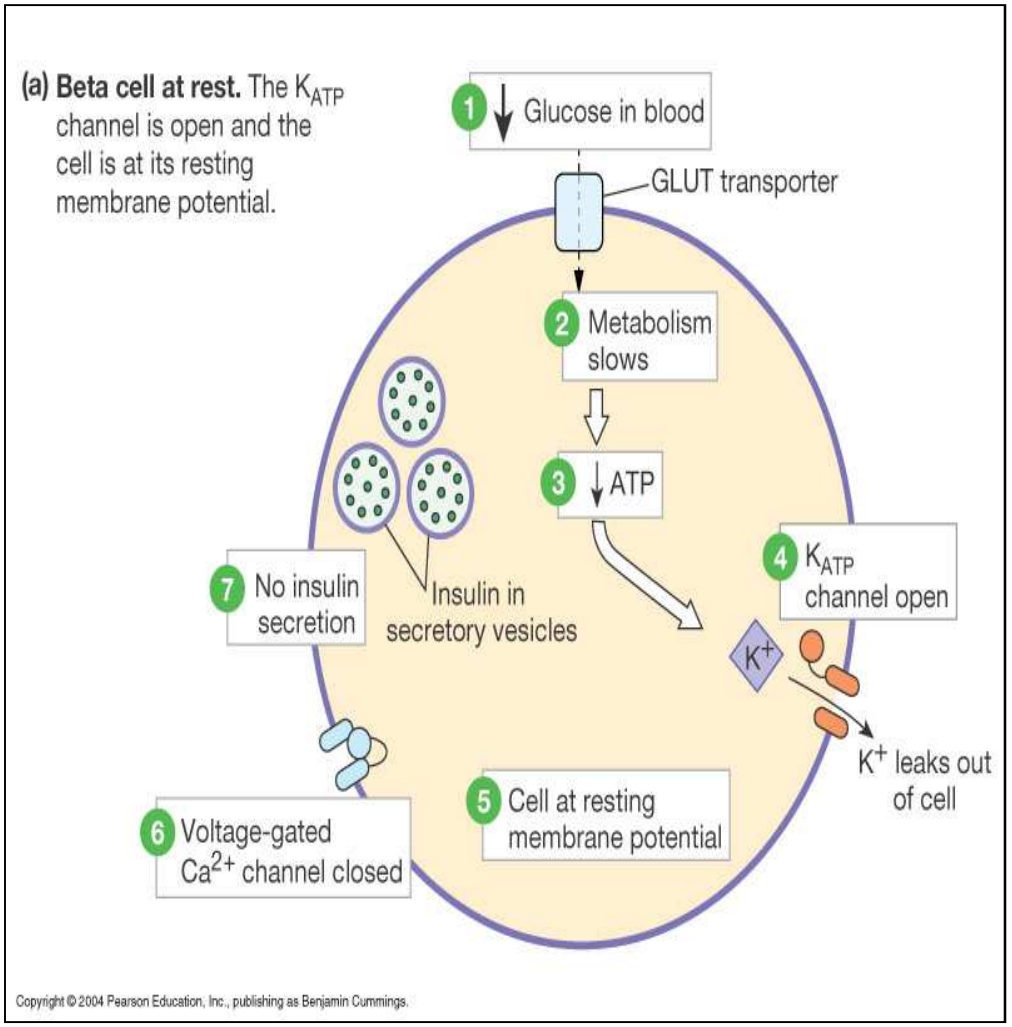
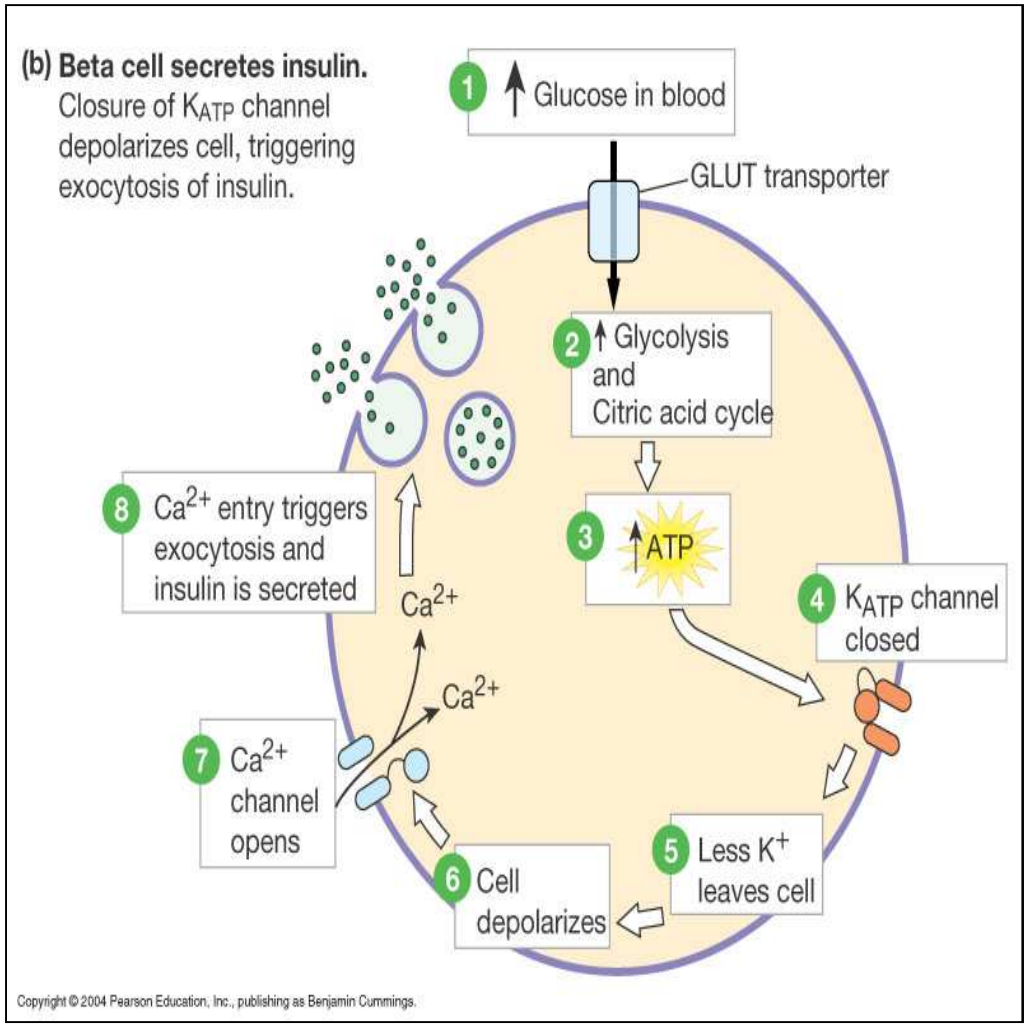
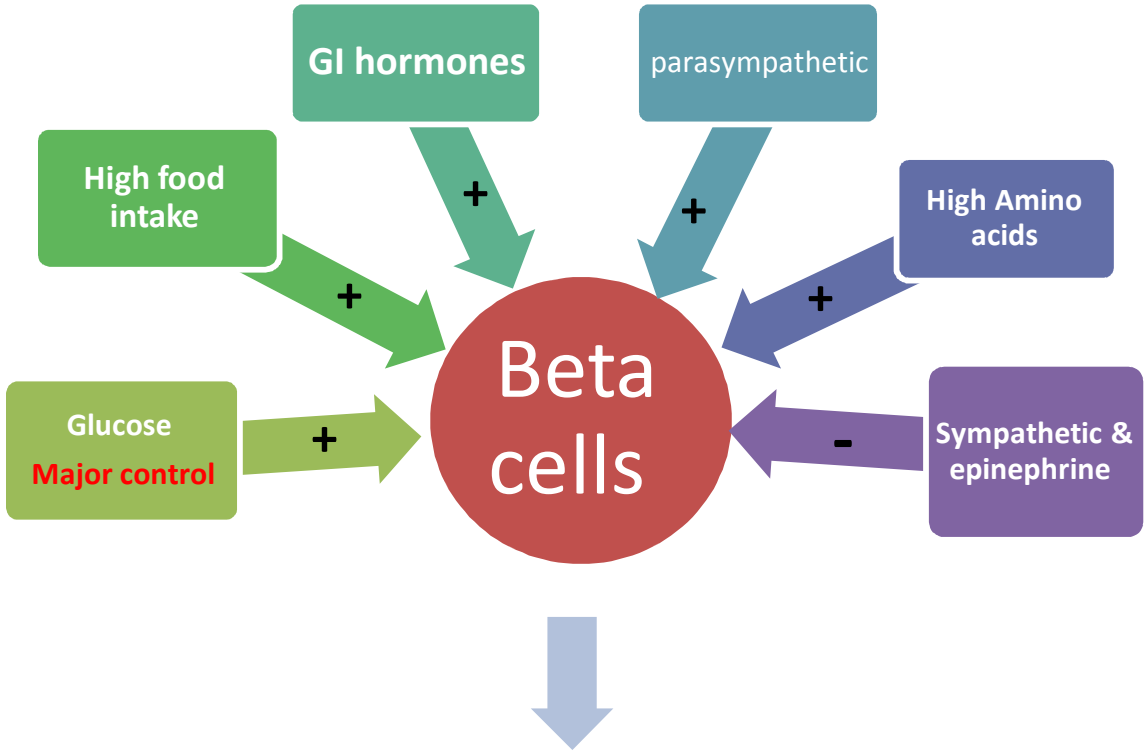
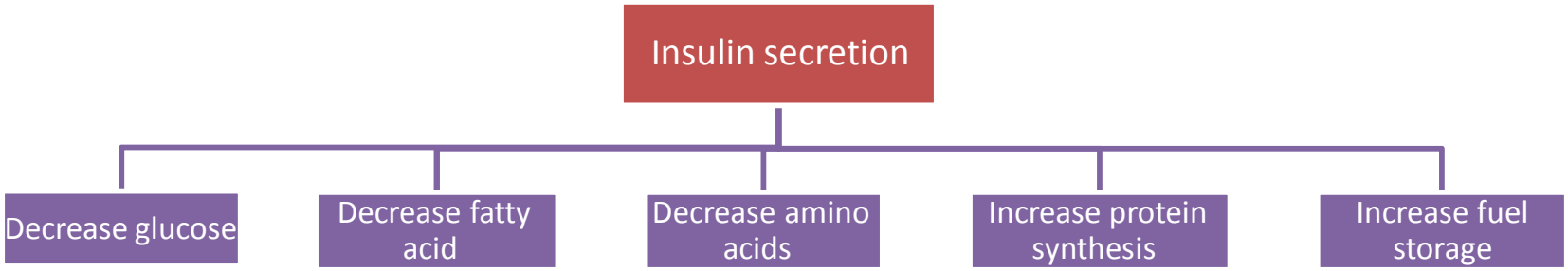




Factors controlling insulin secretion





Regulation of insulin secretion

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Regulators 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

Insulin receptor

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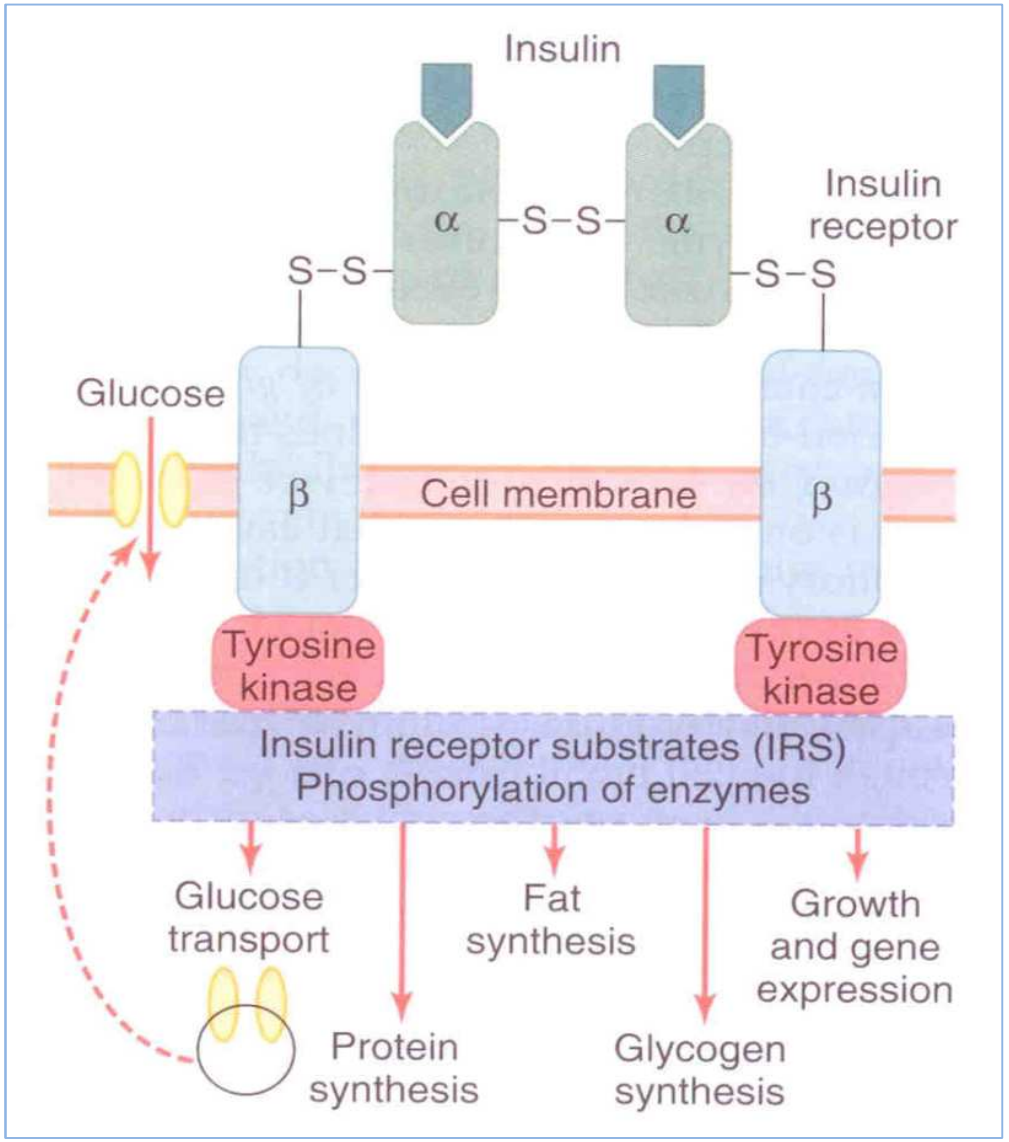
- the insulin receptor is a transmembrane receptor
- belongs to the large class of tyrosine kinase receptors
- Made of two alpha subunits and two beta subunits

Insulin binds to the extracellular portion of the alpha subunits of the insulin receptor. This, in turn, will autophosphorylates the beta subunits. Which in turn induce tyrosine kinase activity which will begins a cascade of cell phosphorylation that either increase or decrease the activity of some enzyme, including insulin receptor substrate for example the glucose receptor (GLUT4) are moved to the cell membrane to assist glucose entry

- From Guyton and Hall textbook

Read More



Actions of insulin

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introduction

- Insulin ensures that excess nutrients are stored as glycogen in liver, as fat in adipose tissue and as protein in muscle. These stored nutrients are then available during subsequent periods of fasting to maintain glucose delivery to brain, muscle and other organs .
- The hypoglycemic action of insulin is the result of coordinated responses that simultaneously stimulate glucose oxidation and inhibit gluconeogenesis.
- Insulin appears to have a direct effect on hypothalamic satiety center independent of the changes in produces in blood glucose concentration

Nutrient	Effect of insulin on blood level
Glucose	Decreased
Fatty acids	
Ketoacids	
Amino acids	
K+	

Actions of insulin

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Raapid (seconds)	Intermediate (minutes)	Delayed (hours)
Increases transport(entrance) of glucose, amino acids, K+ , fatty acids and ketone into insulin-sensitive cells	Increases protein synthesis Inhibits protein degradation Increase of glycolytic enzymes and glycogen synthase Inhibits phosphorylase and gluconeogenic enzymes	Increases mRNAs for lipogenic and other enzymes

Actions of insulin .. cont.

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Action of insulin on Adipose tissue	Action of insulin on Muscle	Action of insulin on Liver
1-Increases glucose entry. 2- increases fatty acid synthesis and storage . 3-increases glycerol phosophate synthesis. 4-increases triglyceride deposition. 5-increases lipoprotein lipase. 6-inhibits of hormone-sensitive lipase. 7- increase K uptake. *inhibits the mobilization and oxidation of fatty acids	1- increases glucose entry. 2- increases glycogen synthesis. 3- increases amino acid uptake. 4- increases protein synthesis in ribosomes. 5- inhibits protein catabolism. 6- inhibits release of gluconeogenic aminco acids. 7- increases ketone uptake. 8- increases K uptake.	1- inhibits ketogenesis. 2- increases protein synthesis. 3- increases lipid synthesis. 4- inhibits gluconeogenesis. 5-Increases glycogen synthesis and glycolysis. _indirectly enterance of glucose and prevent it from going out .

- However insulin in general will induce cell growth, they even say that the anabolic effect of insulin and GH are synergistic.
- Lipoprotein lipase is an enzyme present in the capillary wall and splits circulating triglycerides into fatty acids which is necessary for their transport into fat cells

Glucose Transport

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- GLUT1 (on cell membrane of erythrocytes, brain cells - Blood brain barrier -)
- GLUT2(is 2 ways receptors) (on cell membrane of liver, pancreas, small intestines cells)
- GLUT3 (on cell membrane of brain cells – Neurons -)
- **GLUT4, insulin sensitive transporter (on cell membrane of muscle, adipose tissue cells)**

NOTES:

- Oral insulin treatment will cause the concentration of insulin in blood to be higher than i.v insulin due to gastric release in oral insulin treatment.
- brain , RBCs and liver don't need insulin for glucose transport.
- GLUT 4 that on muscle cell membrane are stimulated by insulin or exercise (so we recommend DM patients to do exercises after eating meals that contain high glucose concentration) .

- **Why DM patients loss Wight ?**
  Due to decrease in synthesis of protein and lipids.
- **hyperkalemia ?**
  in these patient we give them insulin due to its rapid action by increasing the transport of potassium into the cells.

- glucagon increases insulin secretion while insulin decreases glucagon secretion .

Summery of insulin action

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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

Action of Insulin on Adipose Tissue

↑ Glucose uptake by increasing GLUT-4 availability
↑ Glucose use
  ↑ Glycolysis
  ↑ Production of α-glycerol phosphate
↑ Esterification of fats
↓ Lipolysis

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

Glucagon

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- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent
- Produced by α cells in the pancreas
- Use cAMP \ Adenylyl cyclase system (second massager).

❖ Glucagon Action:

- Its major target is liver:
  - Increase Glycogenolysis
  - Increase Gluconeogenesis
  - Increase Lipid oxidation (fully to CO2 or partially to produce keto acids "ketone bodies").
  - Inhibits glycolysis.
  - Release of glucose to the blood from liver cells

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❖ Synthesis of Glucagon:

DNA in α cells (chromosome 2)

↓

mRNA

↓

Preproglucagon

↓

proglucagon

↓

glucagon

❖ Stimuli of Glucagon:

Stimuli for Glucagon Secretion

↓ Blood glucose

↑ Serum amino acids (arginine, alanine)

Sympathetic nervous system stimulation

Stress

Exercise

Inhibitors of Glucagon Secretion

Somatostatin

Insulin

↑ Blood glucose

- Glucagon stimulate insulin secretion while insulin inhibit glucagon secretion

Diabetes

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- ✓ 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	Polydipsia	Polyphagia
Excessive urination	Excessive thirst	Excessive hunger
Next Slide (FYK)	In these patients, the kidneys produce excessive amounts of urine in an attempt to flush blood sugar. This depletes the body of water, triggering feelings of dehydration and intense thirst.	comes with dropping blood sugar

How does hyperglycemia cause excessive urine production?

Illustration is on the next slide!!

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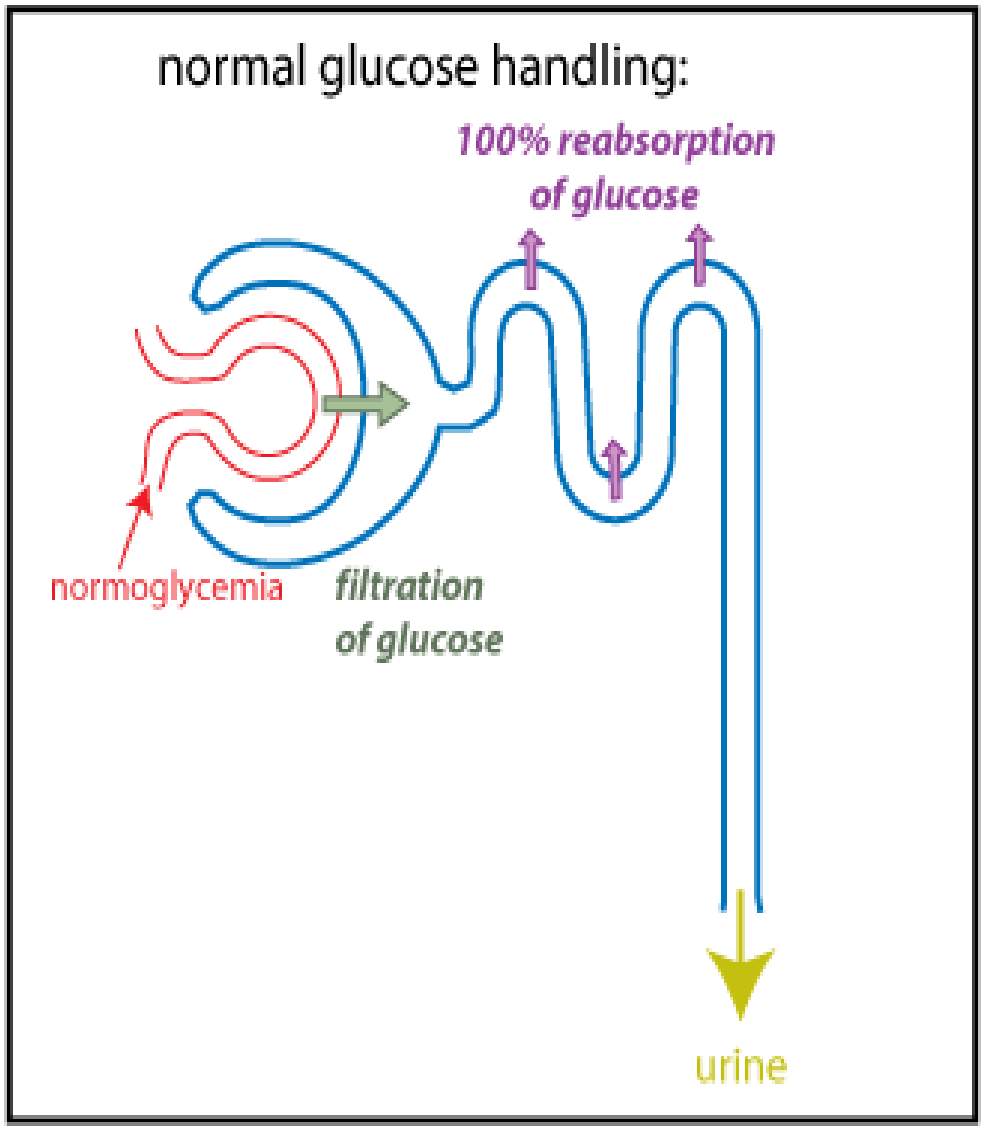
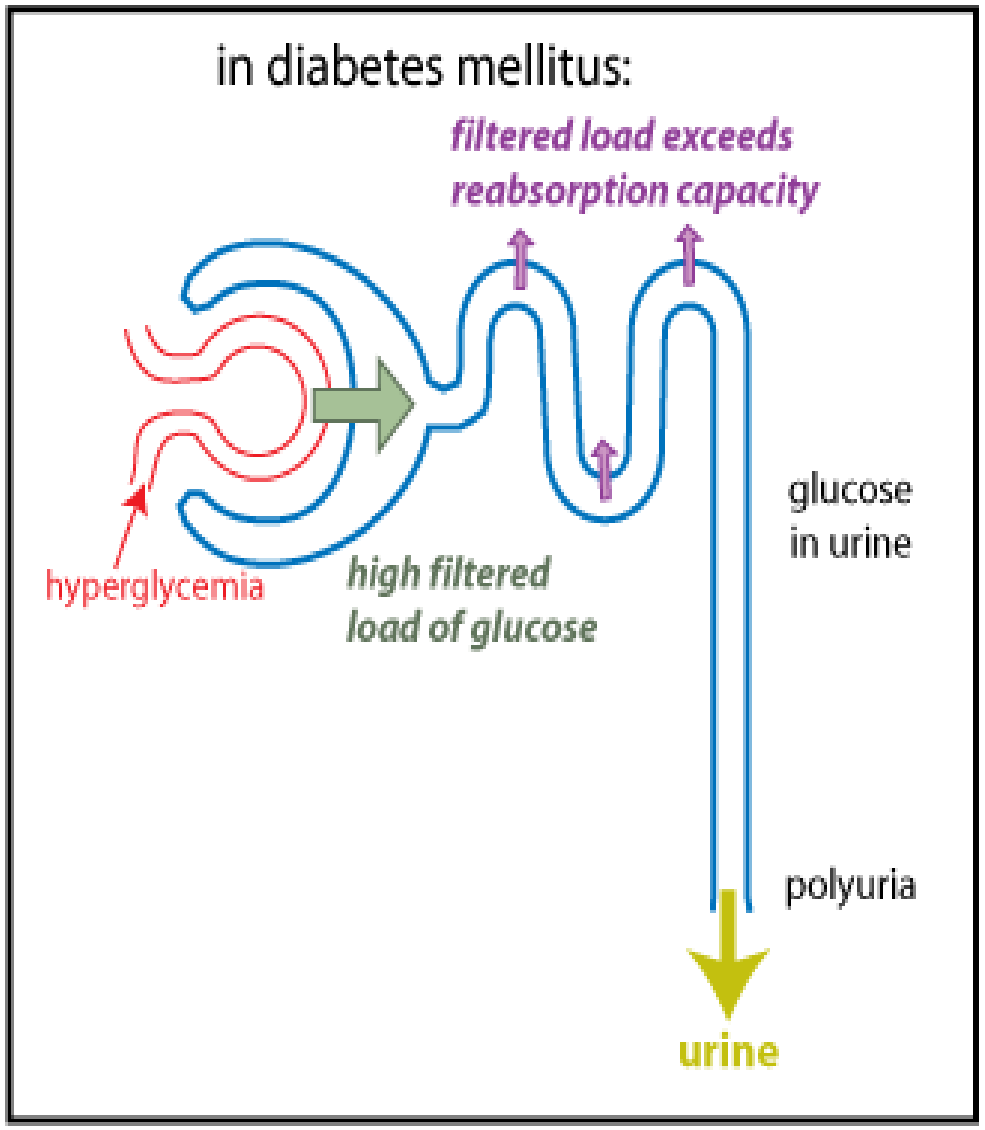
To answer this, we need to understand a little bit about how the kidney works. Each kidney contains about a million functional units called nephrons (see figure). The first step in the production of urine is a process called filtration (green arrow). In filtration, there is bulk flow of water and small molecules from the plasma into Bowman's capsule (the first part of the nephron). Because of the nonspecific nature of filtration, useful small molecules such as glucose, amino acids, and certain ions end up in the forming urine, which flows into the kidney tubules. To prevent the loss of these useful substances from the body, the cells lining the kidney tubules transfer these substances out of the forming urine and back into the extracellular fluid. This process is known as reabsorption (purple arrows).

Under normal circumstances, 100% of the glucose that is filtered is reabsorbed. Glucose reabsorption involves transport proteins that require specific binding. In a diabetic that has hyperglycemia, the filtered load of glucose (amount of glucose filtered) can exceed the capacity of the kidney tubules to reabsorb glucose, because the transport proteins become saturated. The result is glucose in the urine. Glucose is a solute that draws water into the urine by osmosis. Thus, hyperglycemia causes a diabetic to produce a high volume of glucose-containing urine


normal glucose handling:
100% reabsorption of glucose
normoglycemia
filtration of glucose
urine


in diabetes mellitus:
filtered load exceeds reabsorption capacity
hyperglycemia
high filtered load of glucose
glucose in urine
polyuria
urine

Types of Diabetes:

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Important

Type 1 DM	Type 2 DM
Affects children	Affects adults
Cause: inadequate insulin secretion	**Cause:** defect in insulin action (Resistance to the insulin action)
Treatment : insulin injection	**Treatment :** diet or OHA* **OHA:** oral hypoglycemic agents

Diabetes Mellitus:

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Inadequate secretion of insulin

Defects in the action of insulin

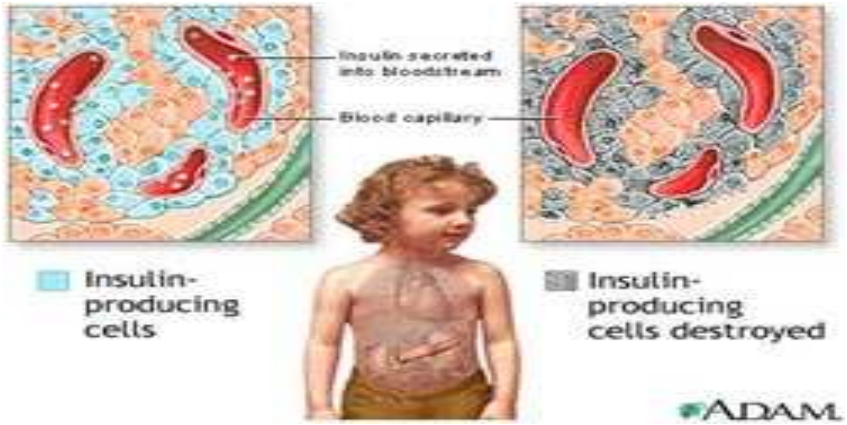
Metabolic disturbances

(hyperglycemia and glycosuria)

There is no "mild" type of diabetes. Type 2 is just as serious as type 1 if not properly controlled.

Type 1 diabetes

- 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.
  - glucose & ketones ↑ → osmotic diuresis.
  - keto acids ↑ → diabetic ketoacidosis



Type 2 diabetes

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

Glucose Tolerance Test (GTT)

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- Both the Fasting Plasma Glucose Test (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):**
  - ✓ We do FPG test first.
  - ✓ Then blood is 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.

The following results suggest different conditions:

Normal values:

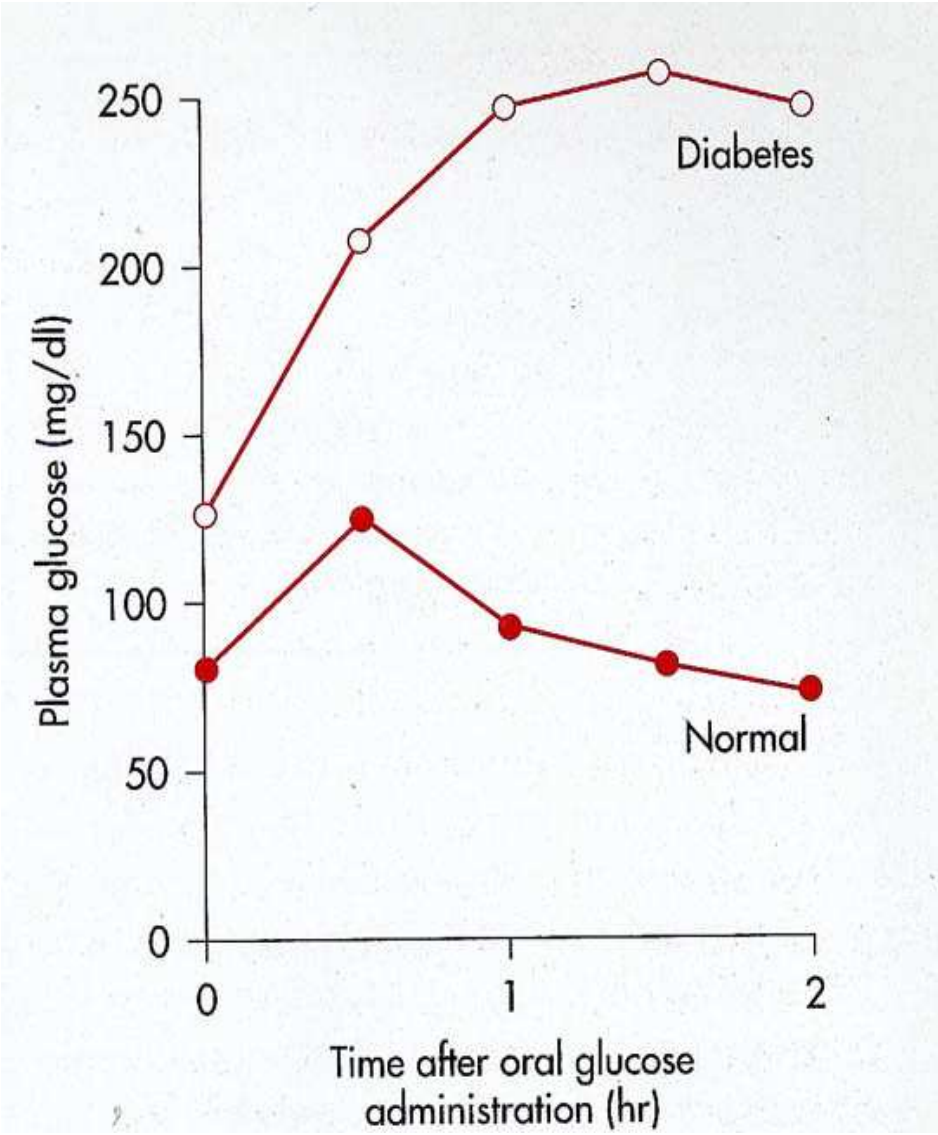
- FPG <100 mg/dl
- 2hr PPG < 140 mg/dL

Impaired glucose tolerance:

- 2hr PPG = 140 - 199 mg/dL

Diabetes:

- FPG ≥ 126 mg/dl
- 2hr PPG levels ≥ 200 mg/dL



Symptoms of Diabetes Mellitus

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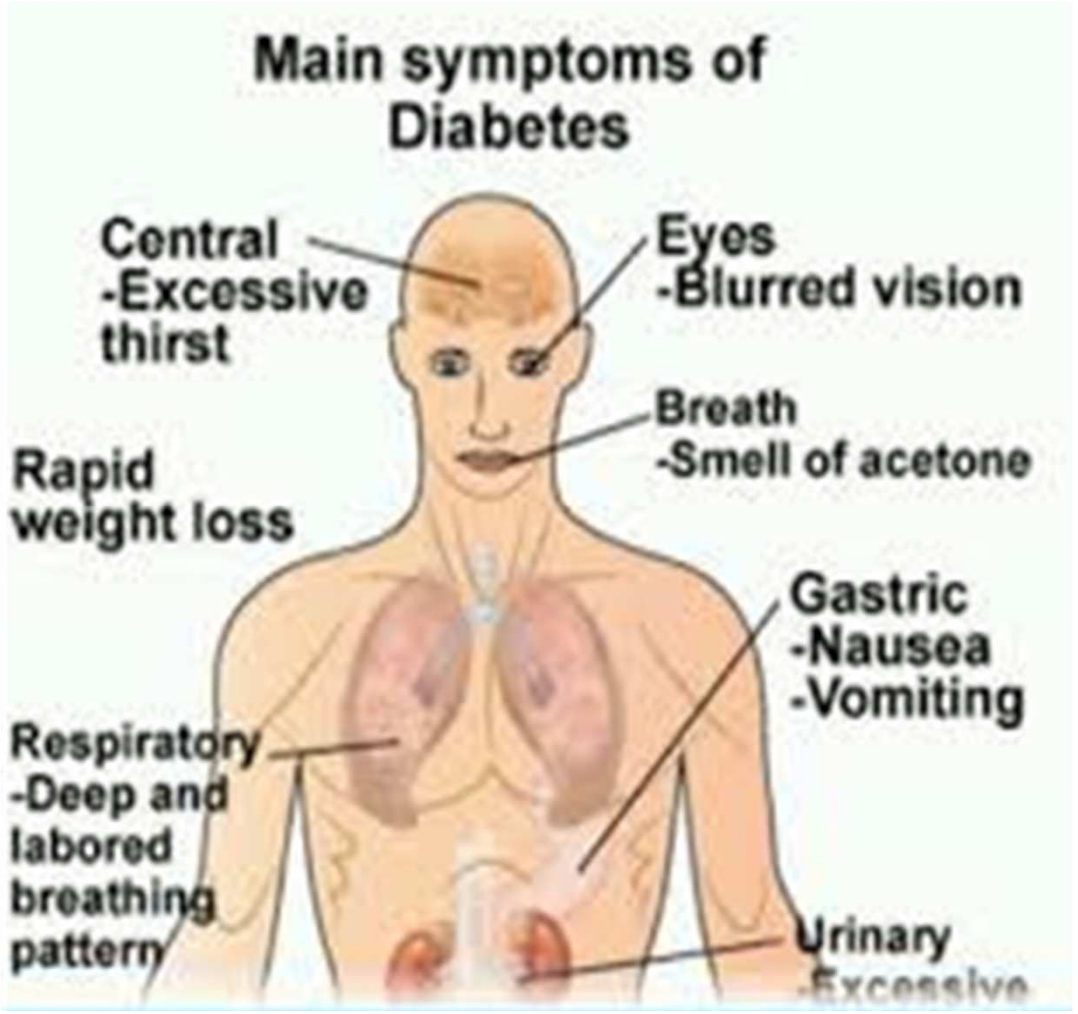
Symptoms of Diabetes Mellitus

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



Diabetes Mellitus (DM)

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Organs/tissue involved	Organ/tissue responses to insulin deficiency	Resulting condition of:		Signs and symptoms
		Blood	Urine	
	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria	**Polyuria** - dehydration - soft eyeballs
	Glycogenolysis		Osmotic diuresis	**Polydipsia** Fatigue Weight loss **Polyphagia**
	Protein catabolism and gluconeogenesis			
	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria Loss of Na^+, K^+; electrolyte and acid-base imbalances	Acetone breath Hyperpnea Nausea/vomiting/ abdominal pain Cardiac irregularities Central nervous system depression; coma

 = Muscle  = Adipose tissue  = Liver

SUMMARY

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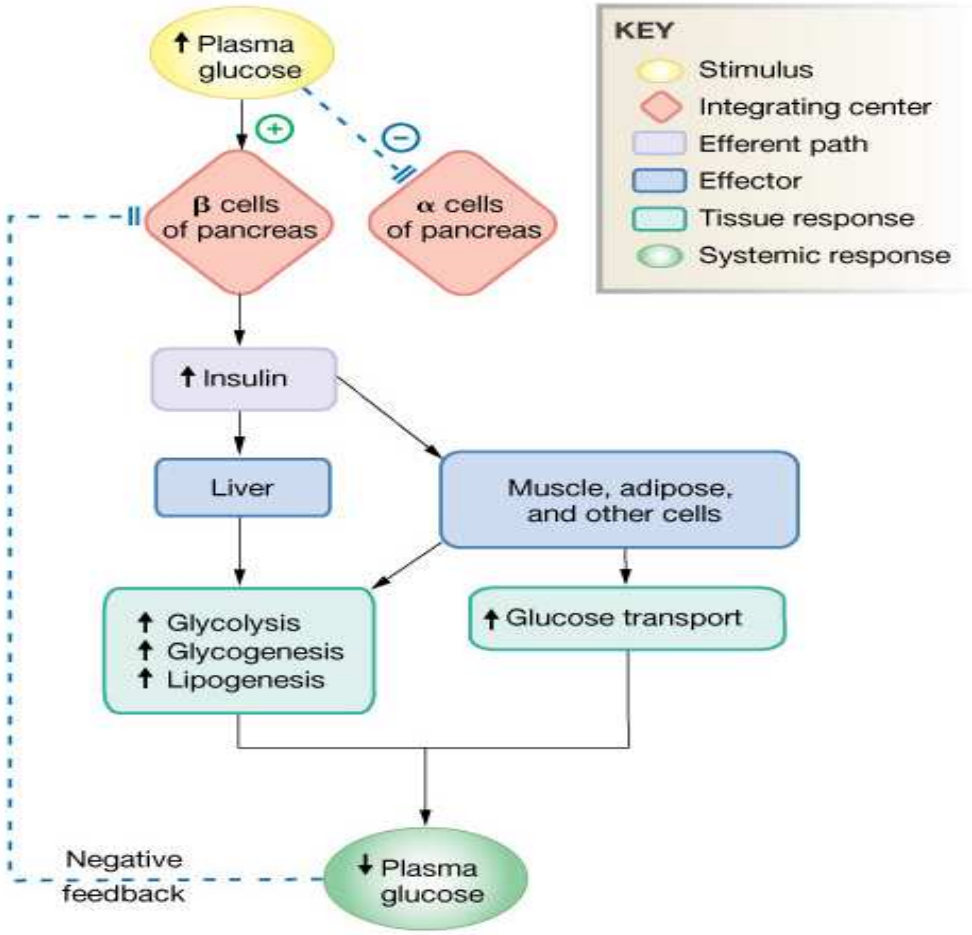
- Pancreas has both exocrine and endocrine cells
- The endocrine part consists of millions of Islets of Langehans
- Beta cells are the major cell type the islets of langrhans, it secrets Insulin
- Alpha cells secret Glucagon while Delta cells secret somatostation
- Insulin is Hormone of nutrient abundance
- Insulin consists of two amino acid chains linked by disulfide bonds
- Insulin is Synthesized as part of proinsulin and then excised by enzymes releasing functional Insulin
- Insulin synthesis is stimulated by glucose
- The major control on the synthesis of Insulin is Glucose
- Diabetes mellitus is a disease caused by deficiency or diminished effectiveness of endogenous insulin.
- **Type 1 diabetes mellitus**: results from the body's failure to produce sufficient insulin.
- **Type 2 diabetes mellitus:** results from resistance to the insulin, often initially with normal or increased levels of circulating insulin.
- pregnant women who have never had diabetes before but who have high blood glucose levels during pregnancy are said to have **gestational diabetes.** It may precede development of type 2 (or rarely type 1) diabetes.
- Patients with Type 1 DM always need insulin treatment and are prone to ketoacidosis.

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



SUMMARY

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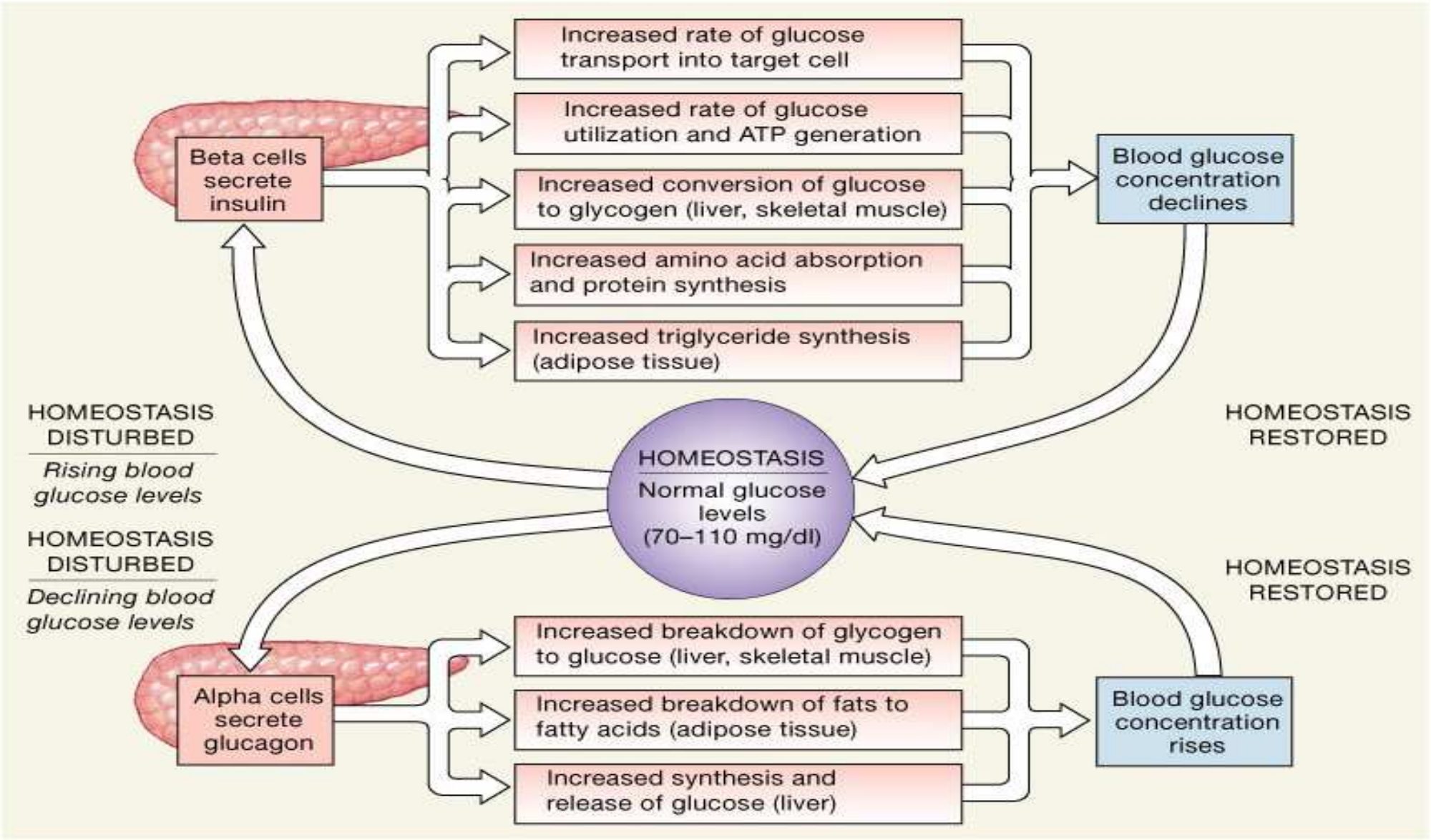

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QUESTIONS

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1. Which one of the following inhibits insulin secretion:

A) Sympathetic stimulation
B) High levels of amino acids
C) Parasympathetic stimulation
D) CCK

2. When insulin is secreted, which one of the following will happen:

A) Decrease in protein synthesis
B) Decrease in blood fatty acids
C) Increase in amino acids

3. What is the effect of ATP on the ATP sensitive K channel:

A) It allows more K to leave the cell
B) It prevents Ca from entering the cell
C) It prevents K from leaving the cell

4. What is the effect of insulin in hyperkalemia :

A) Causes hypokalemia
B) No effect
C) Increases k transport into the cells
D) A+C

5. What is the major stimulator for insulin secretion:

A) hyperglycemia
B) hypoglycemia
C) ketoacidosis
D) Glucagon

1	A
2	B
3	C
4	D
5	A

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6. Which one of the following organs don't depend on insulin for glucose transport :

A) Brain
B) muscle
C) RBCs
D) A+C

7. A fasting blood glucose test level of _____indicates diabetes.:

A) 50 mg/dl to 69 mg/dl
B) 70 mg/dl to 99 mg/dl
C) 100 mg/dl to 125 mg/dl
D) 126 mg/dl or higher on two separate tests

8. A fasting blood glucose test level of _____indicates prediabetes:

A) 50 mg/dl to 69 mg/dl
B) 70 mg/dl to 99 mg/dl
C) 100 mg/dl to 125 mg/dl
D) 126 mg/dl or higher on two separate tests

9. A fasting blood glucose test level of ____ is considered normal.:

A) 50 mg/dl to 69 mg/dl
B) 70 mg/dl to 99 mg/dl
C) 100 mg/dl to 125 mg/dl
D) 126 mg/dl or higher on two separate tests

6	D
7	D
8	C
9	B

THE END

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If there are any Problems or Suggestions,
Feel free to contact us:

Physiology Team Leaders

Mohammed Jameel & Shaimaa Al-Refaie

432Physiology@gmail.com

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