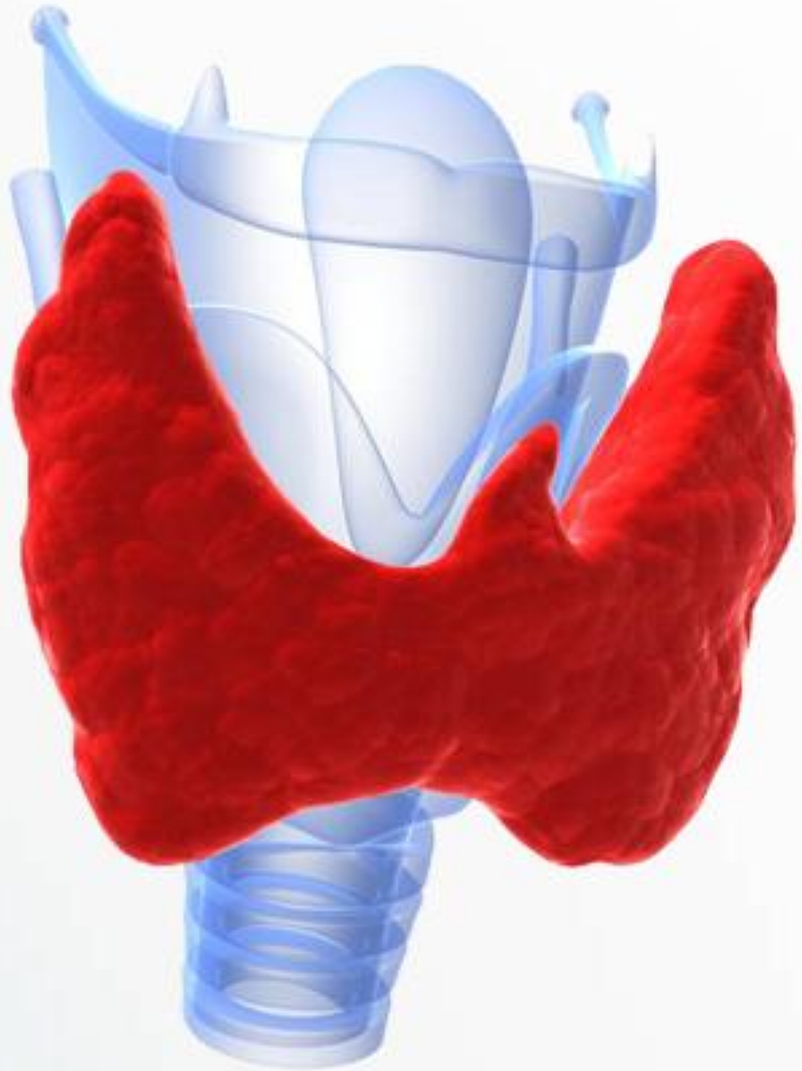
Physiology team



14 Physiology of the pancreas

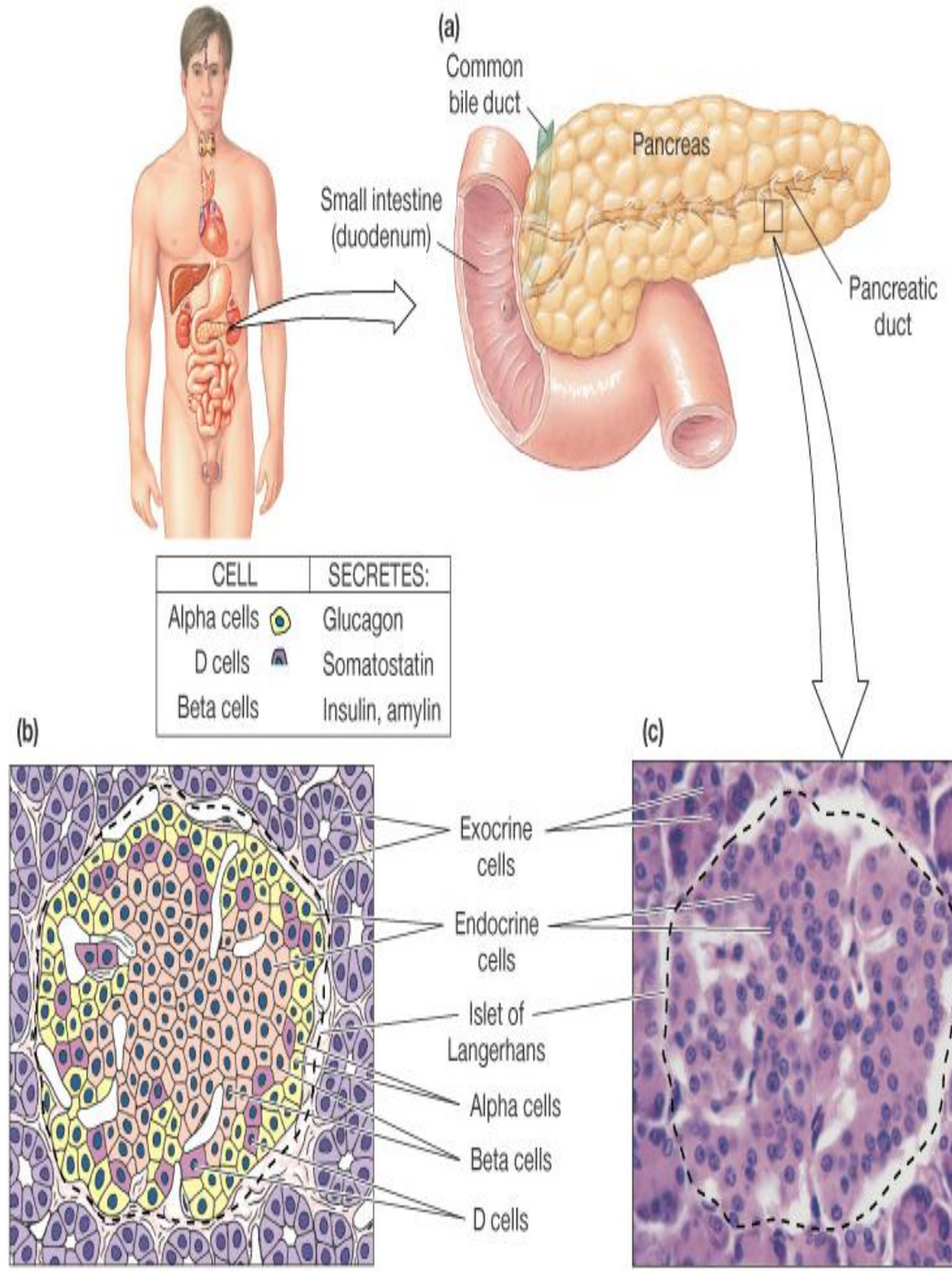
Sources:
Female slides
guyton

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 :

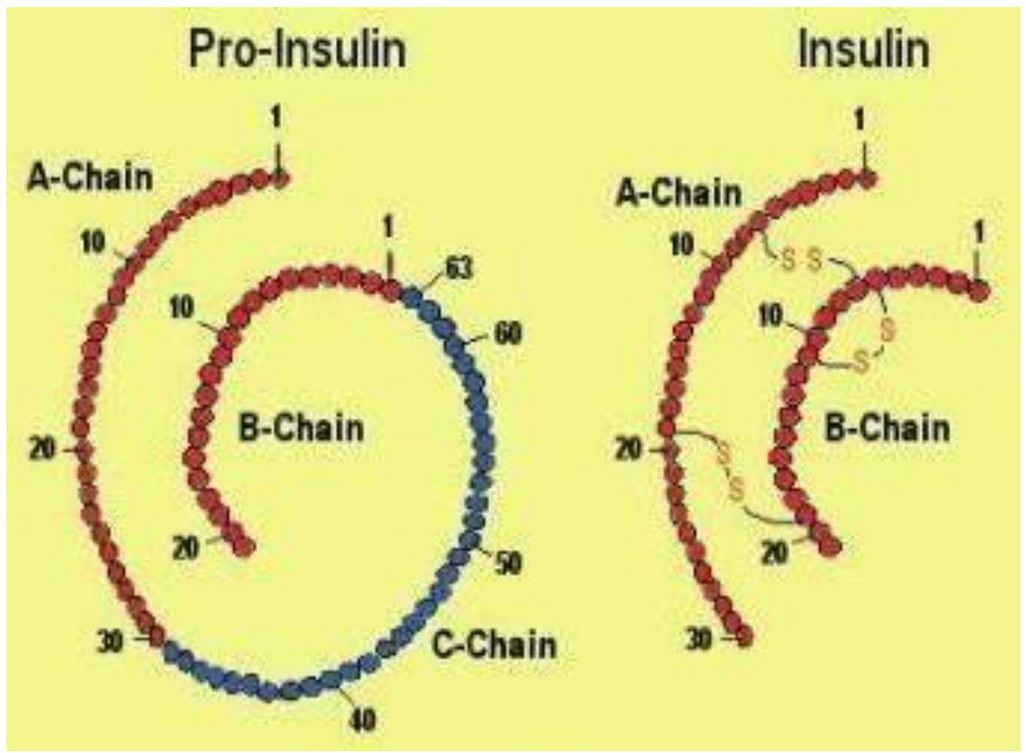
- 1-2 million islets.
- Beta (β) cells produce insulin (70%).
- Alpha (α) cells produce glucagon (20%).
- Delta (δ) cells produce somatostatin (5%).
- F cells produce pancreatic polypeptide (5%).



Insulin structure and synthesis:

- Structure:

- Hormone of nutrient abundance.
- It is composed of two amino acid chains (alpha and beta) connected to each other by disulfide linkage (when the two amino acids chains spilt apart, the functional activity of the insulin molecule is lost).



- Synthesis:

Insulin is synthesized in beta cells. (short arm of chromosome 11).

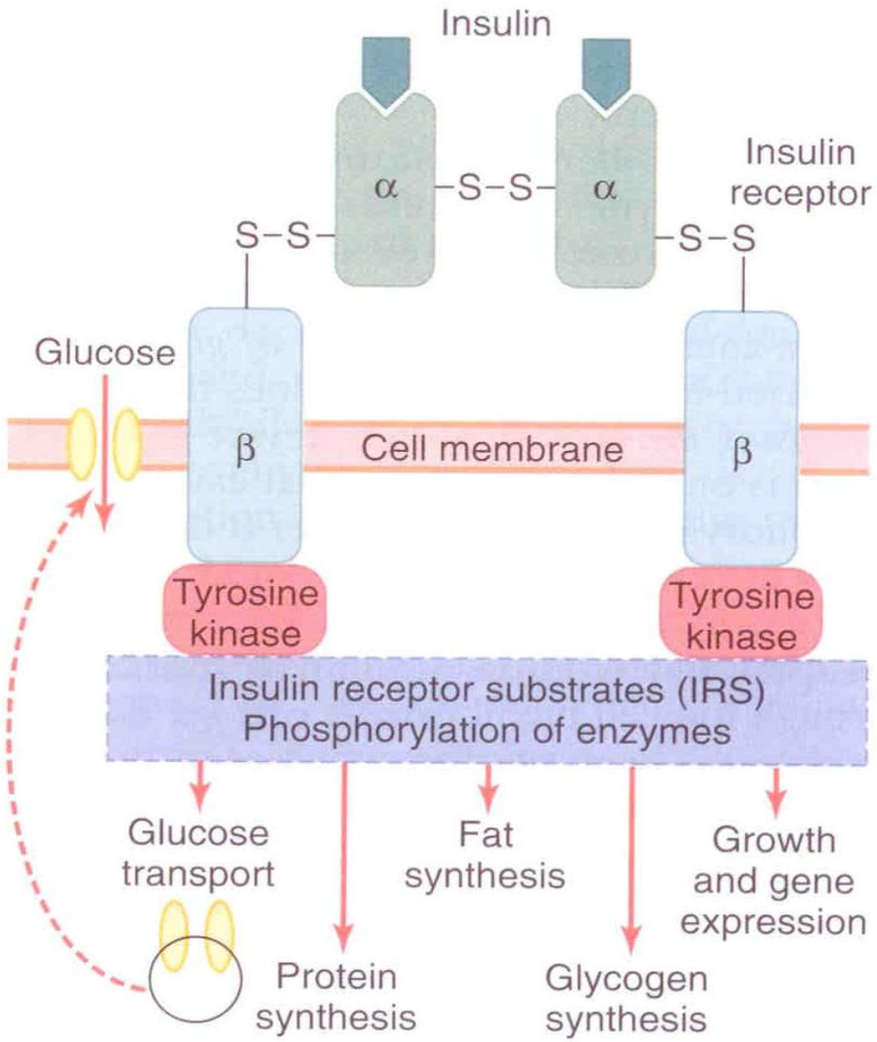
1. Translation of the insulin RNA by ribosomes attached to ER lumen to form preproinsulin (signal peptide, A chain, B chain and C chain).
2. Cleaved in the ER to form a proinsulin (A chain, B chain and C chain).
3. Most of proinsulin is further cleaved in the golgi apparatus to form insulin (A chain and B chain connected by disulfide linkages).
4. The insulin and C peptide are packaged in the secretory granules and secreted in equimolar amounts.

* Measurement of C peptides levels can be used in insulin-treated diabetic patients to determine how much of their own natural insulin they are still producing.

- Insulin has a plasma half-life of 6 minutes and degraded mainly in the liver by insulinase.
- Insulin synthesis is stimulated by glucose or feeding and decreased by fasting.
- Glucose rapidly increases translation of insulin mRNA and slowly increases transcription of the insulin gene.

Insulin receptors :

- The insulin receptor is combination of four subunits held together by disulfide linkages. (Two alpha subunits that lie entirely outside the cell membrane and two beta subunits that penetrate through the membrane, protruding into the cell's cytoplasm)
- The insulin receptor belongs to large class of tyrosine kinase receptors.
- When insulin binds to the receptor it will lead to autophosphorylation → activation of local tyrosine kinase.
- Insulin- receptor substrate: the name of the enzyme which insulin works on.



Insulin secretion:

- Glucose is the primary stimulator of insulin secretion.
- Threshold of glucose –stimulated insulin secretion is 100 mg/dl
- we have four receptor for glucose transportation one of the insulin dependent :

• GLUT1 (erythrocytes, brain).
• GLUT2 **(beta cells ,liver,small intestines, kidney, pancreas) → remember this (B cells LIKes insulin)**
• GLUT3 (brain) (The brain cells depend entirely on glucose for energy.)
• **GLUT4**, insulin sensitive transporter (muscle, adipose tissue)

Cont. :

High blood glucose

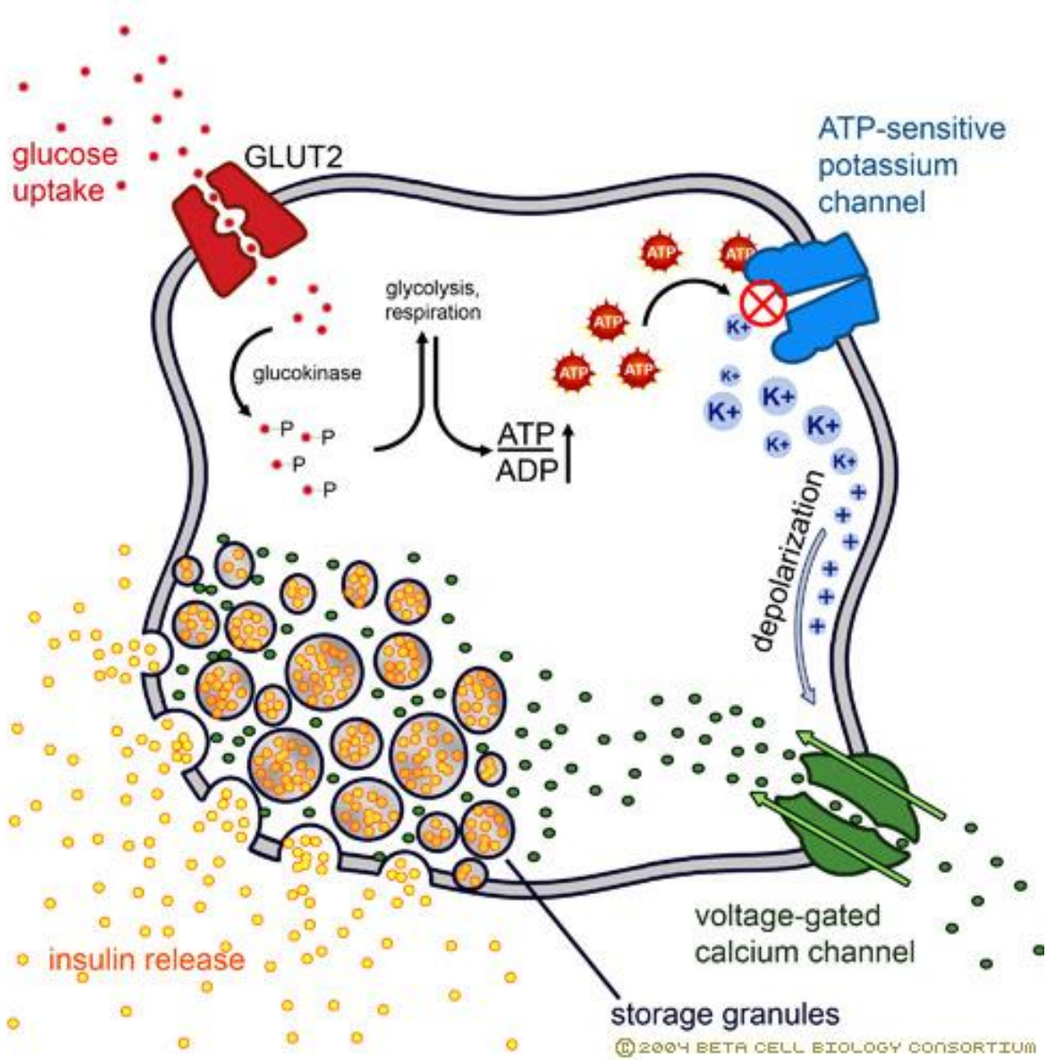
1.Transport of glucose into the beta cells by GLUT2 receptor. (facilitated diffusion)

2.One glucose inside the cell, glucose is phosphorylated to glucose-6-phoaphate by glucokinase (to prevent glucose from getting out of the cells and decrease its concentration) , and glucose-6-phosphate is subsequently oxidized → production of ATP.

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

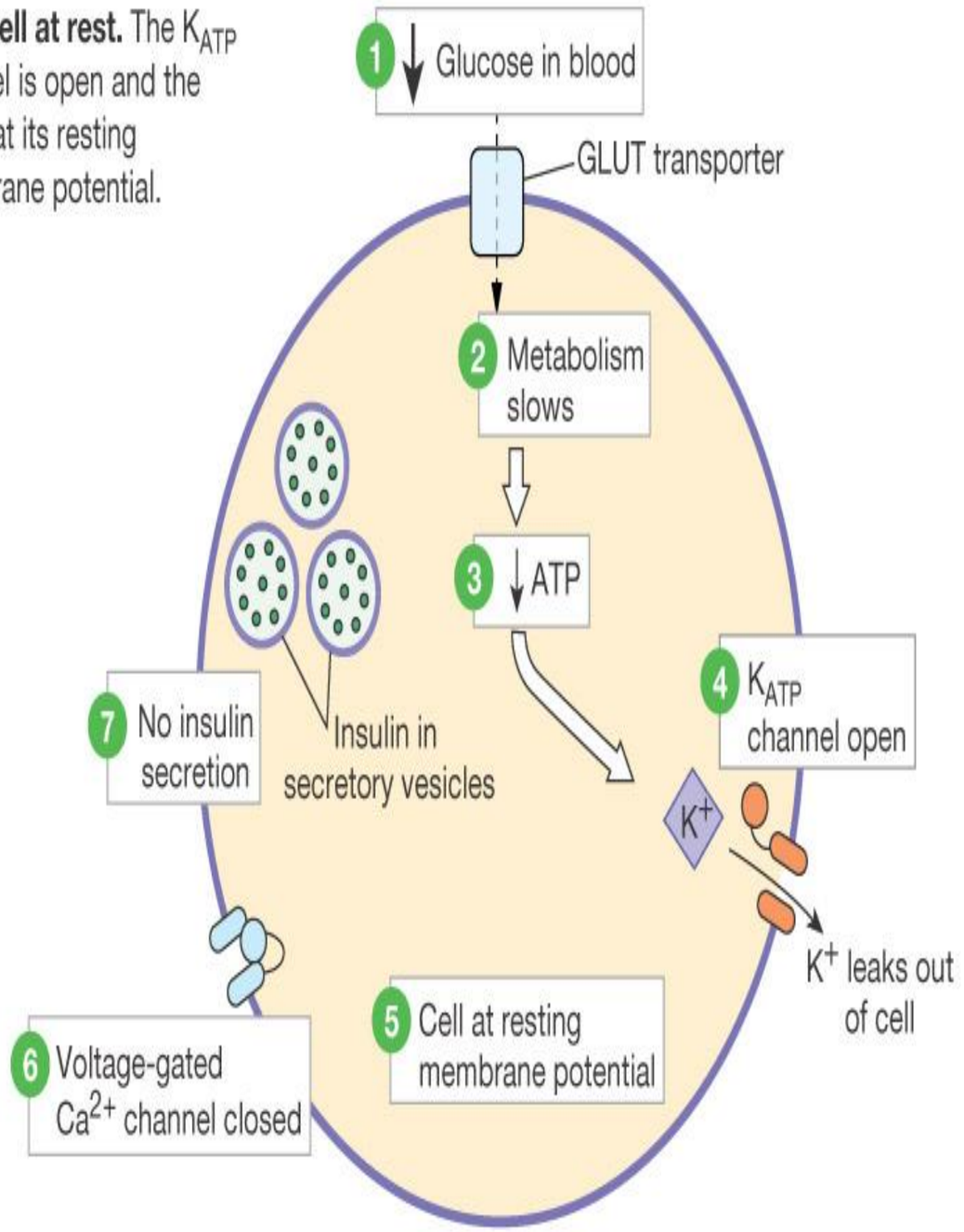
4.The depolarization caused by ATP opens voltage-gated calcium channel → Ca+2 flows into the beta cells down its concentration gradient.

5.Influx of calcium stimulates fusion of the docked insulin-containing vesicles with the cell membrane and secretion of insulin by exocytosis.

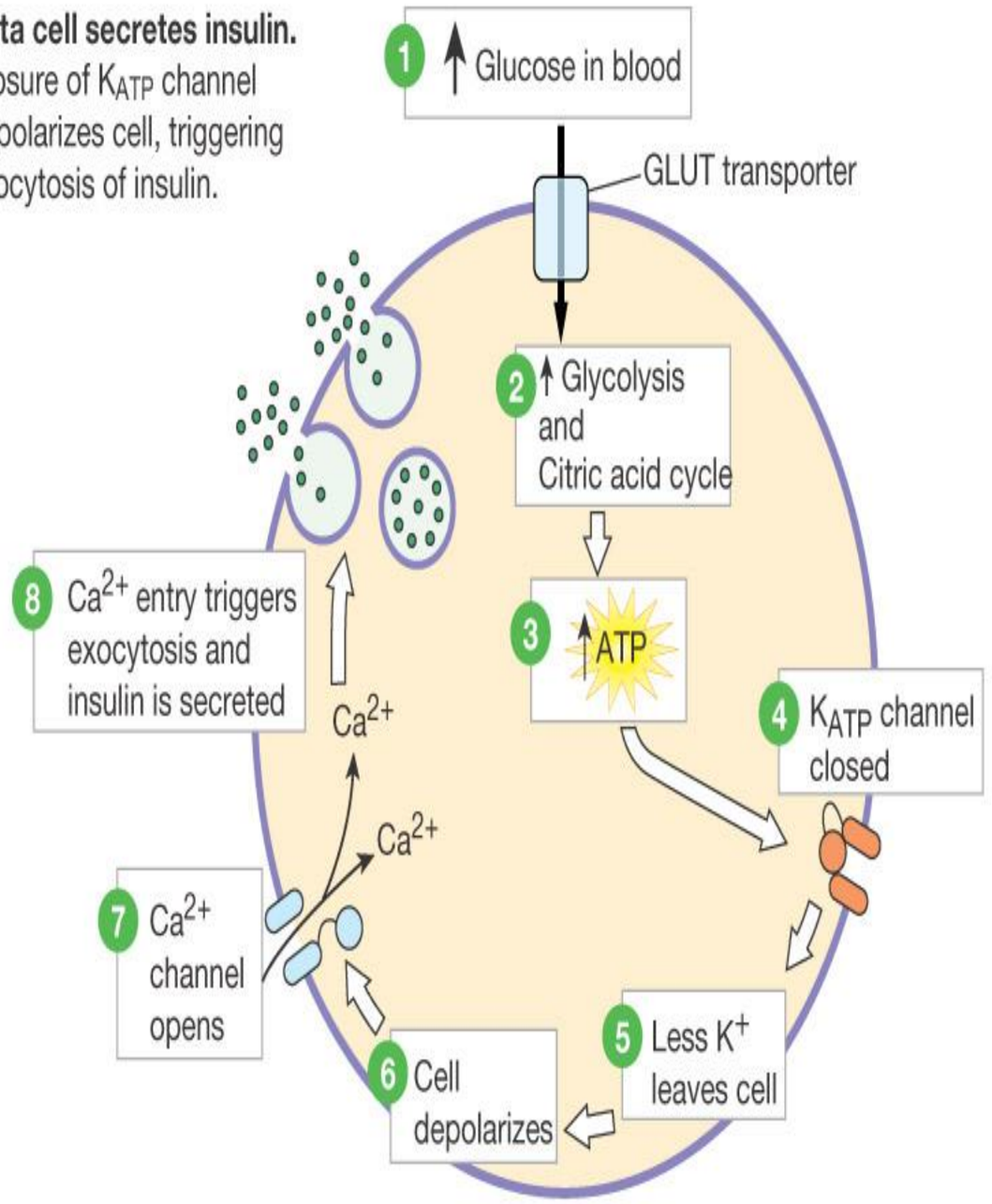


Sulfonylurea drugs stimulate insulin secretion by binding to the ATP-sensitinve potassium channel and blocking their activity . This results in a depolarizing effect triggers insulin secretion , making these drugs useful in stimulating insulin secretion in patients with type II diabetes.

(a) **Beta cell at rest.** The K_{ATP} channel is open and the cell is at its resting membrane potential.



(b) **Beta cell secretes insulin.** Closure of K_{ATP} channel depolarizes cell, triggering exocytosis of insulin.



Regulation of insulin secretion :

Stimulators of Insulin secretion	Inhibitors of insulin secretion
↑ Serum Glucose. ↑ Serum amino acids. ↑ Serum fatty acids. ↑ Serum ketone bodies. Hormones: • Gastroinhibitory peptide (GIP) • Growth Hormone • Glucagon • Gastrin • Cholecystokinin (CCK) • Secretin • Vasoactive intestinal peptide (VIP) • Epinephrine (β-receptor) • Estrogen and Progesterone • Parasympathetic nervous system	↓ Glucose. ↓ Amino acids. ↓ Free fatty acids. Hormones: • Somatostatin • Leptin • Norepinephrine (α-receptor)

Diabetic patients → they give them drugs work like GI hormone but their degradation takes more time to increase their effect on insulin secretion

Actions of Insulin

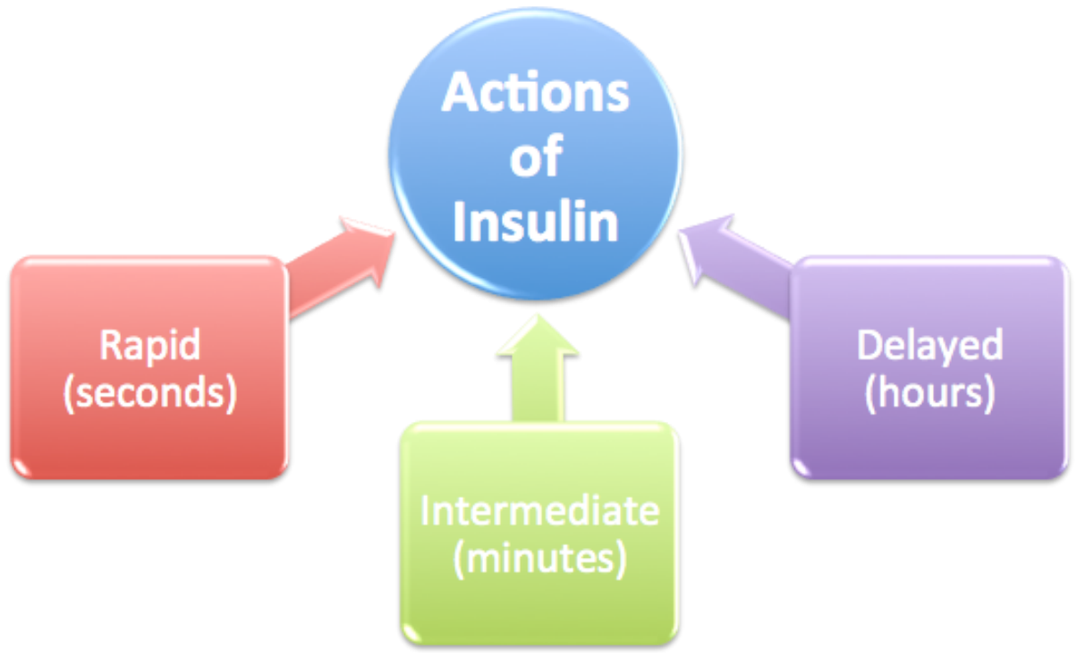
In general, it has 4 actions:

1- Decrease blood glucose via glycogen synthesis & inhibition of gluconeogenesis.

2- Increase fat synthesis & inhibit fat catabolism. (If there was an excess of carbohydrate intake)

3- increase protein synthesis & inhibit protein catabolism.

4- Growth, as it interacts synergistically with Growth hormone and increase protein synthesis.



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

(+) mRNAs for lipogenic and other enzymes

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

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

(+) glucose entry
(+) fatty acid synthesis
(+) glycerol phosphate synthesis
(+) triglyceride deposition
(+) lipoprotein lipase
(-) of hormone-sensitive lipase, this enzyme function in releasing of fatty acid into the blood.
(+) K uptake

The excess of fatty acids in the plasma associated with insulin-deficiency promotes liver conversion of some fatty acids into phospholipids and cholesterol. This high lipid concentration promotes the development of atherosclerosis in people with serious diabetes.

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

(+) glucose entry
(+) glycogen synthesis
(+) amino acid uptake
(+) protein synthesis in ribosomes
(-) protein catabolism
(-) release of gluconeogenic amino acids
(+) ketone uptake
(+) K uptake

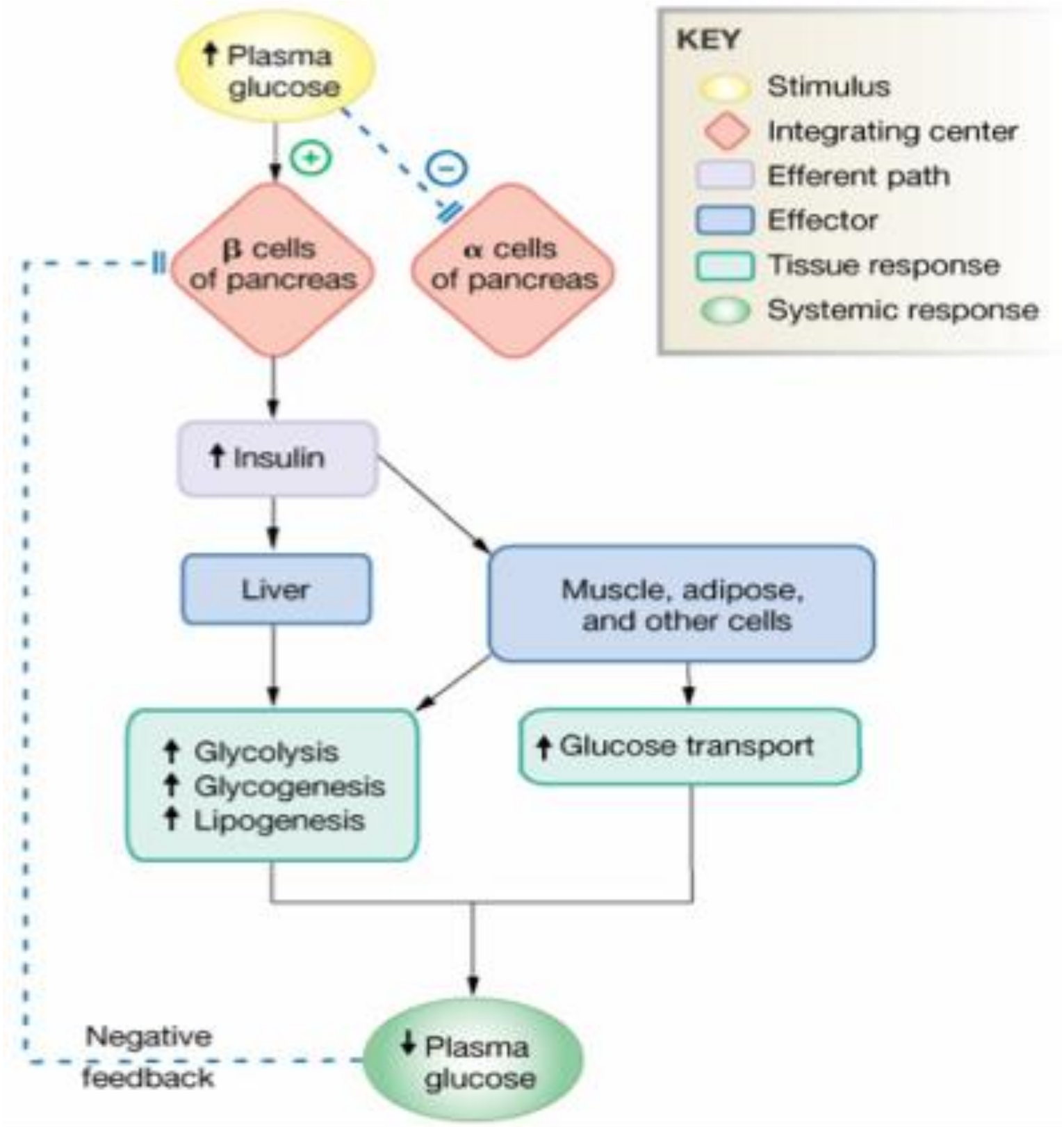
Actions of Insulin on Liver

↑ 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

(-) ketongenesis
(+) protein synthesis
(+) lipid synthesis
(-) gluconeognesis
(+) glycogen synthesis
(+) glycolysis.

There will be no increase in Glucose entry, because Liver cells have GLUT2 which is not sensitive to insulin as GLUT4. (in adipose tissue and muscle)

Overall


↑ Plasma glucose
β cells of pancreas
α cells of pancreas
KEY
Stimulus
Integrating center
Efferent path
Effector
Tissue response
Systemic response
↑ Insulin
Liver
Muscle, adipose, and other cells
↑ Glycolysis
↑ Glycogenesis
↑ Lipogenesis
↑ Glucose transport
Negative feedback
↓ Plasma glucose

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 7-10 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.

SUMMARY

INSULIN	
Receptor	belongs to tyrosine kinase receptors
Half Life (Endogenous insulin)	5-6 minutes.
Mechanism of Insulin Release (4 minutes Video)	Click Here

Regulated By :	
Stimulates insulin release	**Inhibits insulin release**
▪ Increase serum glucose ▪ Increase serum amino acids ▪ Increase serum fatty acids ▪ Increase serum ketone bodies ▪ Parasympathetic NS ▪ Most of Gastric hormones ▪ glucagon	• Decrease serum glucose • Decrease serum amino acids • Decrease serum fatty acids • Somatostatin • Sympathetic NS

Actions:		
Rapid	**Intermediate**	**Delayed**
• Increase transport of glucose, amino acids, K+ into insulin-sensitive cells	▪ Increase protein synthesis and glycolytic enzymes and glycogen synthase ▪ Decrease protein degradation and phosphorylase and gluconeogenic enzymes	• Increase mRNAs for lipogenic and other enzymes

b. Mechanism of insulin secretion

- Glucose, the stimulant for insulin secretion, binds to the **Glut 2** receptor on the beta cells.
- Inside the beta cells, glucose is oxidized to **ATP,** which closes K^+ channels in the cell membrane and leads to **depolarization** of the beta cells. Similar to the action of ATP, **sulfonylurea drugs** (e.g., tolbutamide, glyburide) stimulate insulin secretion by closing these K^+ channels.
- Depolarization **opens Ca^{2+} channels,** which leads to an increase in intracellular $[Ca^{2+}]$ and then to **secretion of insulin.**

2. Insulin receptor

- is found on target tissues for insulin.
- is a tetramer with two α subunits and two β subunits.

a. The β **subunits** span the cell membrane and have **tyrosine kinase activity.** When insulin binds to the receptor, tyrosine kinase autophosphorylates the β subunits. The phosphorylated receptor then phosphorylates intracellular proteins.

b. The insulin-receptor complexes enter the target cells.

c. Insulin **down-regulates** its own receptors in target tissues.

- Therefore, the number of insulin receptors is **increased in starvation** and **decreased in obesity.**

3. Actions of insulin

- Insulin acts on the liver, adipose tissue, and muscle.

a. Insulin decreases blood glucose concentration by the following mechanisms:

(1) It **increases uptake of glucose** into target cells by directing the insertion of glucose transporters into cell membranes. As glucose enters the cells, the blood glucose concentration decreases.

(2) It **promotes formation of glycogen** from glucose in muscle and liver, and simultaneously inhibits glycogenolysis.

(3) It **decreases gluconeogenesis.** Insulin increases the production of fructose 2,6-bisphosphate, increasing phosphofructokinase activity. In effect, substrate is directed away from glucose formation.

b. Insulin decreases blood fatty acid and ketoacid concentrations.

- In adipose tissue, insulin **stimulates fat deposition** and **inhibits lipolysis.**
- Insulin **inhibits ketoacid formation** in the liver because decreased fatty acid degradation provides less acetyl CoA substrate for ketoacid formation.

c. Insulin decreases blood amino acid concentration.

- Insulin stimulates amino acid uptake into cells, increases protein synthesis, and inhibits protein degradation. Thus, insulin is **anabolic.**

d. Insulin decreases blood K^+ concentration.

- Insulin increases K^+ uptake into cells, thereby decreasing blood $[K^+]$.

4. Insulin pathophysiology—diabetes mellitus

- **Case study:** A woman is brought to the emergency room. She is hypotensive and breathing rapidly; her breath has the odor of ketones. Analysis of her blood shows severe hyperglycemia, hyperkalemia, and blood gas values that are consistent with metabolic acidosis.
- **Explanation:**

a. Hyperglycemia

- is consistent with insulin deficiency.
- In the absence of insulin, glucose uptake into cells is decreased, as is storage of glucose as glycogen.
- If tests were performed, the woman's blood would have shown increased levels of both amino acids (because of increased protein catabolism) and fatty acids (because of increased lipolysis).

b. Hypotension

- is a result of ECF volume contraction.
- The high blood glucose concentration results in a high filtered load of glucose that exceeds the reabsorptive capacity (T_m) of the kidney.
- The unreabsorbed glucose acts as an osmotic diuretic in the urine and causes ECF volume contraction.

c. Metabolic acidosis

- is caused by overproduction of ketoacids (β-hydroxybutyrate and acetoacetate).
- The **increased ventilation rate** is the respiratory compensation for metabolic acidosis.

d. Hyperkalemia

- results from the lack of insulin; normally, insulin promotes K^+ uptake into cells.

D. Somatostatin

- is secreted by the delta cells of the pancreas.
- inhibits the secretion of insulin, glucagon, and gastrin.

SUMMARY

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.

M C Q

A 39 year old man with untreated DM type1 is brought to the emergency room. An injection of insulin would be expected to cause an increase in his:
A) Urine glucose concentration.
B) Blood glucose concentration.
C) Blood K+.
D) Blood PH.

2. Which of the following is Intermediate action of insulin ?
A) Increase transport of glucose
B) Increase mRNAs for lipogenic and other enzymes
C) Increase of glycolytic enzymes and glycogen synthase
D) Increase transport of K+ into insulin-sensitive cells

3. Which of the following Glucose Transport is present in Erythrocytes ?
A) Glut1
B) Glut2
C) Glut3
D) Glut4

4. regarding pancreas choose the correct statement :
A) insulin is secreted via α cells
B) glycogen is secreted via β cells
C) somaotstain is secreted via Delta cells
D) "F" cells secret pre-insulin

5. which of the following need insulin to up-take Glucose
A) Pancreas
B) Adipose tissue
C) Liver
D) Brain

6. Insulin works on the cells Via :
A) tyrosine kinase
B) metabolites of complex phosphoinositols .
C) cAMP
D) cGMP

7. Insulin works as an anabolic factor for all the following except :
A- glycogen
B- amino acids
C- keton bodies
D- fatty acids

1: D. 2: C. 3:A. 4: C. 5: B. 6: A. 7: C

@PhysiologyTeam

Pht433@gmail.com

Done by :

Rahma Alshehri

Sara Habis

Latifa Fahad

Revised by:

Waleed AlRajban

Endocrine Block