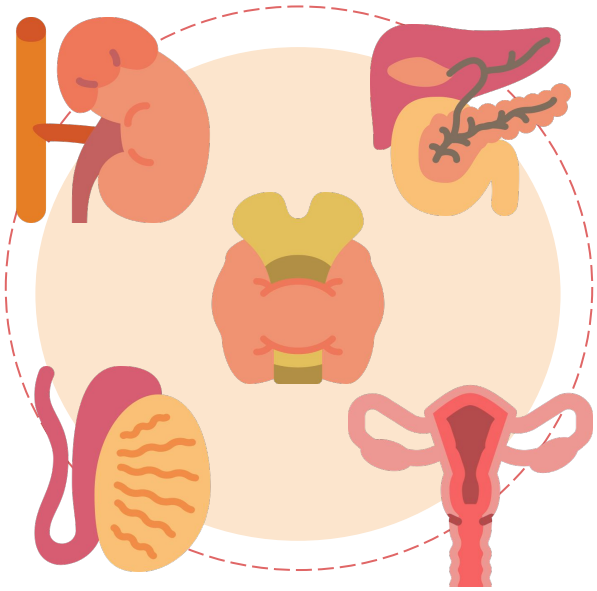


Pancreas & Insulin

Objectives:

- Describe the cellular arrangements and functional components of the pancreas.
- List the hormones secreted by the pancreas.
- Outline the regulation of insulin secretion.
- Describe the mechanism of action of insulin.
- Describe actions of pancreatic somatostatin.
- Outline the physiological and biochemical actions of insulin.
- Describe the consequences of insulin deficiency.
- Describe mechanism of action of glucagon.
- Outline regulation of glucagon secretion.
- Outline the physiological and biochemical actions of glucagon.
- Outline the effects of other hyperglycemic hormones.

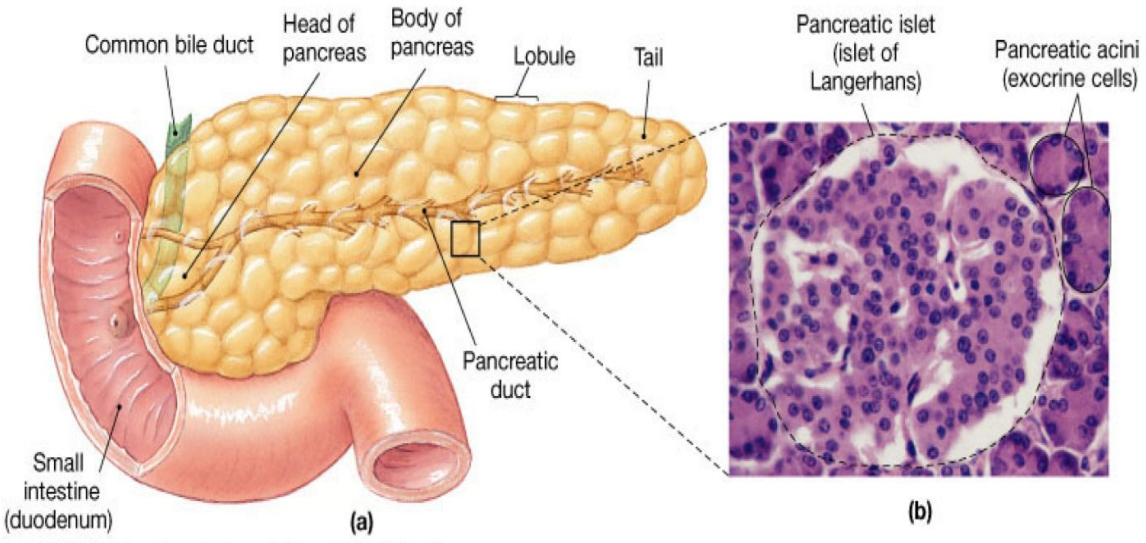
Done by :

➔ **Team leaders:** Rahaf AlShammari, Abdulelah AlDossari
➔ **Team members:**
- Fahad Alfaiz
- Ghaida Saad Alsanad, Rawan mishal
- Rakan Alsalhy, Wejdan albadrani
- Faisal AlQarni, Afnan AlMustafa
- Abdulaziz Aldukhayel, Norah Alkadi

Colour index:
- Important
- ;)
- Extra

وَأَن لَّيْسَ لِلْإِنسَانِ إِلَّا مَا سَعَىٰ

introduction



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

Islets of Langerhans

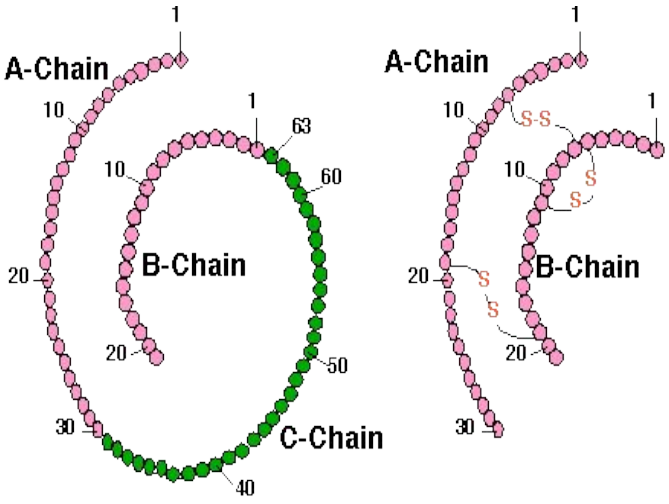
(α)cells= glucagon (20%)	(β) cells = insulin (70%)	(δ) cells = somatostatin (5%)	(F) cells = pancreatic polypeptide (5%)
In the periphery	In the center	Scattered	

universal inhibitors

1-2 million islets

Insulin structure

- 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 (51AA) and C peptide (29 AA).
- Has a plasma half-life of 6 minutes.



Insulin Synthesis

DNA (chromosome 11) in β cells

↓

mRNA

↓

Preproinsulin (signal peptide, A chain, B chain, and peptide C) In the Ribosomes

↓

proinsulin *

↓

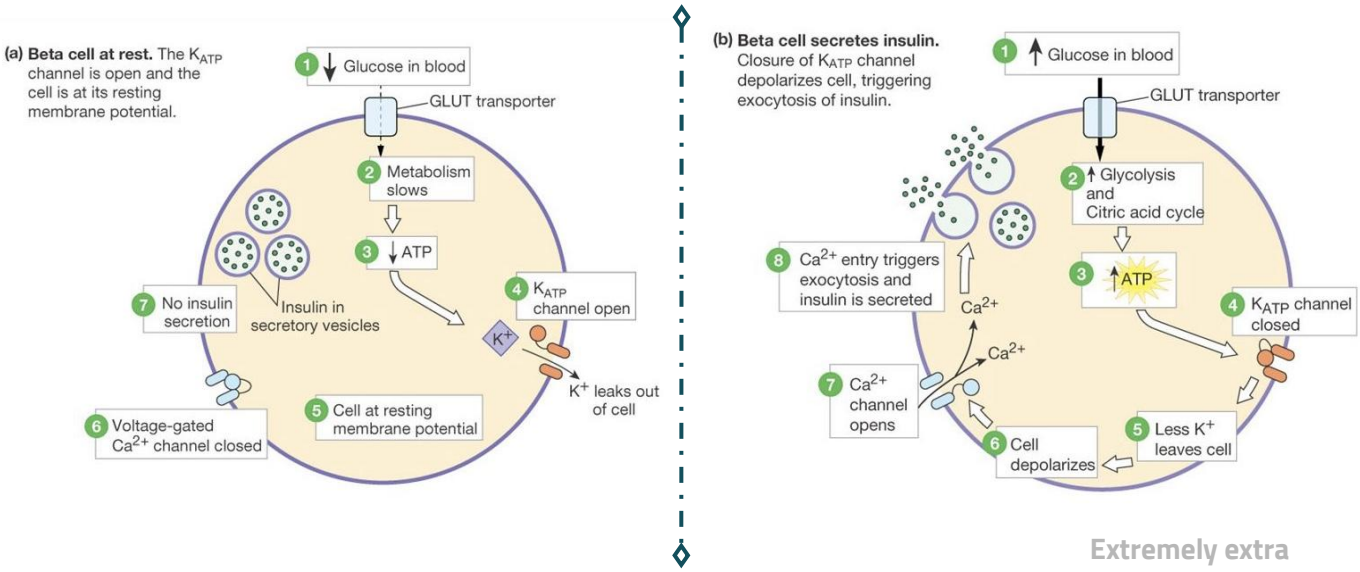
insulin (Active)
+free c-peptide

- 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.

*in RER →
1- cutting of signal peptide
2- connect A+B chain by Disulfide bond → Proinsulin
(C-peptide is important for the folding of insulin to keep the a+b chain opposite to each other so they can form the disulfide bond)
In Golgi →
- Proinsulin is packed it into vesicles
- Cleavage of the c peptide → active insulin

Regulation Of Insulin Secretion

Glucose is the primary stimulator of insulin secretion:

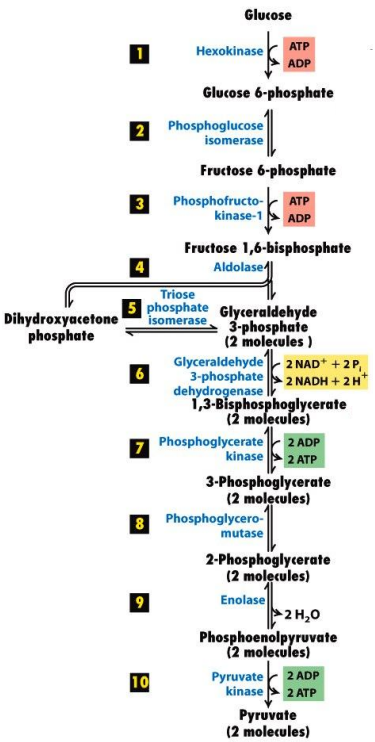


***How insulin is released ?**

Insulin release is stimulated by all types of fuel, but the Master regulator of insulin is glucose level.
Entry of glucose into the beta cell is independent of insulin.

1. Glucose enters the beta cell by GLUT2 receptors.
2. Glucose will be converted to glucose 6 phosphate by glucokinase, to trap the glucose inside the cell. **(Trapping is the RATE LIMITING STEP)***
3. Next step is glycolysis "see the picture" => results in conversion of ADP to ATP.
4. Increase ATP inside the cell => block the k channel, that normally secretes k out of the cell **(ATP sensitive k channel)**.
5. Increase k level in beta cell => Depolarization (-90 => -50)
6. Depolarization results in opening of the Ca channel (voltage gated Ca channel).
7. Increase Ca entry.
8. Ca moves the insulin vesicles into the membrane.
9. Exocytosis.
   (All this happens within seconds)

Extremely extra



*****Trapping of glucose is **the rate limiting** step, while oxidation of glucose which will result in production of ATP is a **key factor for insulin regulation.**

What is the importance of insulin release steps? Site of action for different drugs.

- Sulfonilurea : drug used for type two diabetes, act as ATP, closes the potassium channel.
- Diazoxide: drug used in cases of increased insulin, tumor for example. Prevent ATP blocking effect on the potassium channel, keep the channel open and prevent the insulin release.

Factors controlling insulin secretion

Stimulators Of Insulin Secretion

- Increase serum glucose.
- Increase serum amino acids.
- Increase serum free fatty acids.
- Increase serum ketone bodies.
- Hormones:
  - Gastroinhibitory peptide(GIP).
  - Glucagon.
  - Gastrin.
  - Cholecystokinin(CCK).
  - Secretin.
  - Vasoactive intestinal peptide (VIP)
  - Epinephrine**(β-receptor)**.
- Parasympathetic nervous system.

Insulin inhibit glucagon release **But** glucagon stimulate the release of insulin.

Inhibitors Of Insulin Secretion

- Decrease glucose.
- Decrease amino acids.
- Decrease free fatty acids.
- Hormones:
  - Somatostatin.
  - Epinephrine**(α-receptor)**.
- Sympathetic nervous system.

In stress, you need more glucose in your blood. So, sympathetic will decrease insulin to increase glucose. Beta cells have both alpha 2 and beta 2 receptors:

- Alpha 2 stimulation results in decrease insulin release + increase glucose .
- Beta 2 stimulation results in increase insulin release + decrease glucose.

Beta cells have more alpha 2 receptors. Therefore, the net effect of sympathetic stimulation is **decrease insulin + increase glucose.**

Intake of glucose + AAs have more effect than glucose alone.

Which one will increase insulin level in blood more, oral or IV glucose? **ORAL** glucose. Why? Because of the Incretin, group of hormones released from the GI system that stimulate further release of insulin. They are Natural antidiabetic.

Insulin Receptor

- 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.

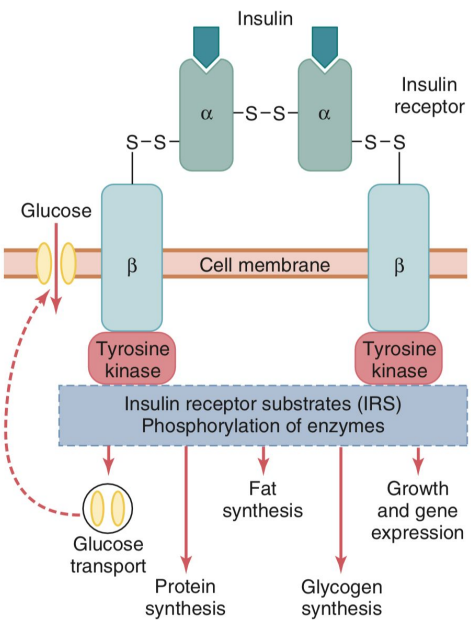


Figure 79-3. A schematic of the insulin receptor. Insulin binds to the α subunit of its receptor, which causes autophosphorylation of the β-subunit receptor, which in turn induces tyrosine kinase activity. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates, that mediate the effects on glucose, fat, and protein metabolism. For example, glucose transporters are moved to the cell membrane to assist glucose entry into the cell.

Glucose regulation and metabolism terms

Terms	Definitions
Gluconeogenesis	Synthesis of glucose from noncarbohydrate precursors, Lactic acid, glycerol, amino acids, liver cells synthesis glucose when carbohydrates are depleted.
Glycogenesis	Formation of glycogen, glucose stored in liver and skeletal muscle as glycogen, important energy reserve.
Glycogenolysis	Breakdown of glycogen (polysaccharide) into glucose molecules (monosaccharide).
Glycolysis	Breakdown of glucose into pyruvate by cells for the production of ATP.

Actions of insulin important

Rapid (seconds)	Intermediate (minutes)	Delayed (hours)
Stimulate transport of glucose, amino acids, K+ into insulin-sensitive cells. +phosphate	- Stimulate protein synthesis , glycolytic enzymes and glycogen synthase. - Inhibit protein degradation, phosphorylase and gluconeogenic enzymes. Phosphorylase: break the phosphate group and causes the release of glucose .	Stimulate mRNAs for lipogenic and other enzymes. Promote growth, independent of growth hormone (very important). لا يقل أهمية عن هرمون النمو. because it act on the nucleus, increase mitosis, maturation and synthesis of enzymes..

Action of insulin on

important

Adipose tissue

- Stimulate glucose entry by increasing GLUT-4 availability.
- Stimulate glucose use and glycolysis.
- Stimulate fatty acid synthesis.
- Stimulate triglyceride deposition.
- Stimulate α glycerol phosphate synthesis.
- Stimulate Esterification of fat.
- Stimulate lipoprotein lipase.
  - Lipoprotein formed in the liver, secreted into the blood. Lipoprotein lipase will break the lipoprotein and the lipids will enter the cells.
- Stimulate K uptake.
- Inhibit hormone-sensitive lipase.
  - Hormone break down the lipids.

Muscle

- Stimulate glucose entry by increasing GLUT-4 availability .
- Stimulate glucose use and glycolysis.
- Stimulate glycogen synthesis.
- Stimulate amino acid uptake.
- Stimulate protein synthesis in ribosomes.
- Stimulate ketone uptake.
- Stimulate K uptake.
- Inhibit protein catabolism.
- Inhibit release of gluconeogenic amino acids.

General

Stimulate cell growth.

Entry of glucose is independent of insulin in **LIVER and "EXERCISING" MUSCLES**

Glucose Enter the liver by GLUT2, independently of insulin.
So, what is the importance of insulin for the liver?
Insulin increase glucokinase, that phosphorylate glucose(trap it) and convert it to glucose 6 phosphate.
This decrease the concentration of glucose inside the cells => result in more entry of glucose.

"Insulin INDIRECTLY increases glucose entry into the liver"

Muscles take its energy during the day from the fat, only in the fed state it will use the glucose.
If there is insulin it will use glucose, if no insulin the adipose tissue is the source.
تذكروا اللي عنده سكر دائماً يجي مع (muscle wasting)
فهو ينحف لأنه ما فيه جلوكوز يدخل، يستخدم الفات والبروتين.

Liver

- Stimulate glucose use and uptake.
- Stimulate glycolysis.
- Stimulate glycogen synthesis.
- Stimulate protein synthesis.
- Stimulate lipid synthesis.
- Inhibit gluconeogenesis.
- Inhibit ketogenesis.
- Inhibit glycogenolysis.
- Inhibit urea cycle activity.

- Why do we advise diabetics to exercise?

Only during exercise, the muscles uptake glucose independently of insulin.

- How?

Glucose needs it's receptors(GLUT4) to enter the cell, if there is no insulin there is no expression of GLUT4 on the cell membrane. But only in exercise, the contracting muscles express the GLUT4.

Glucose transporter systems

Transporters	Present in
GLUT-1	Placenta, Blood brain barrier, RBCs(erythrocytes) , Kidneys and Colon.
GLUT-2	β cells of Pancreas, Liver, Epithelial cells of small intestines and Kidneys.
GLUT-3	Brain, Placenta and Kidneys.
GLUT-4	Insulin sensitive transporters (Skeletal Muscles, Cardiac muscles and Adipose tissue).
GLUT-5	Jejunum and sperm.

*Mnemonic: Beta Cells **LIK**es GLUT2 → **L**iver, **I**ntestine, **K**idney
*Why they name the receptor GLUT2? Because it has two ways.
Glucose can go in and out of the cell, according to the concentration gradient.

Insulin Summary

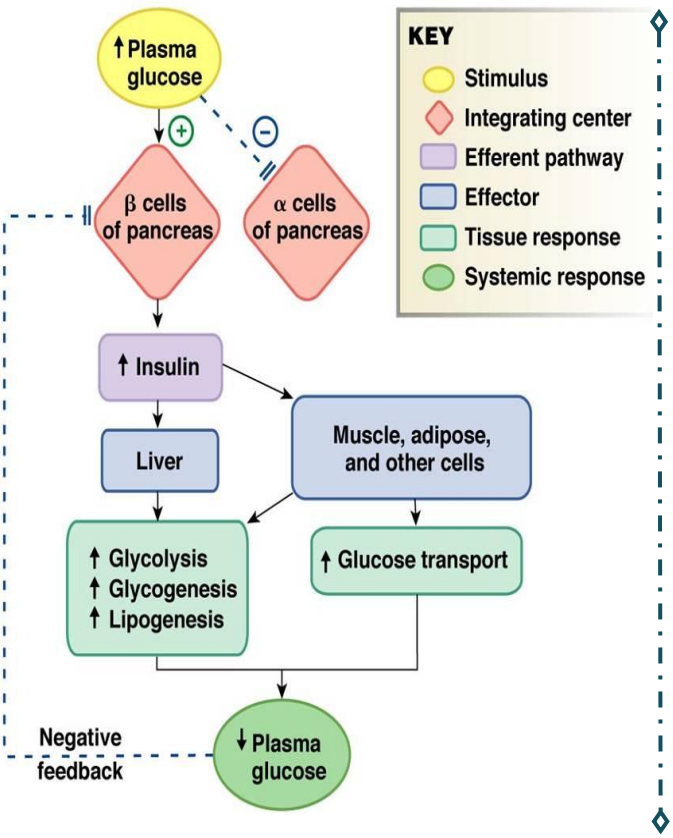


Table 22-3: Insulin

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

glucagon

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

Glucagon Synthesis

DNA in α cells (chromosome 2)

↓

mRNA

↓

Preproglucagon

↓

proglucagon

↓

glucagon

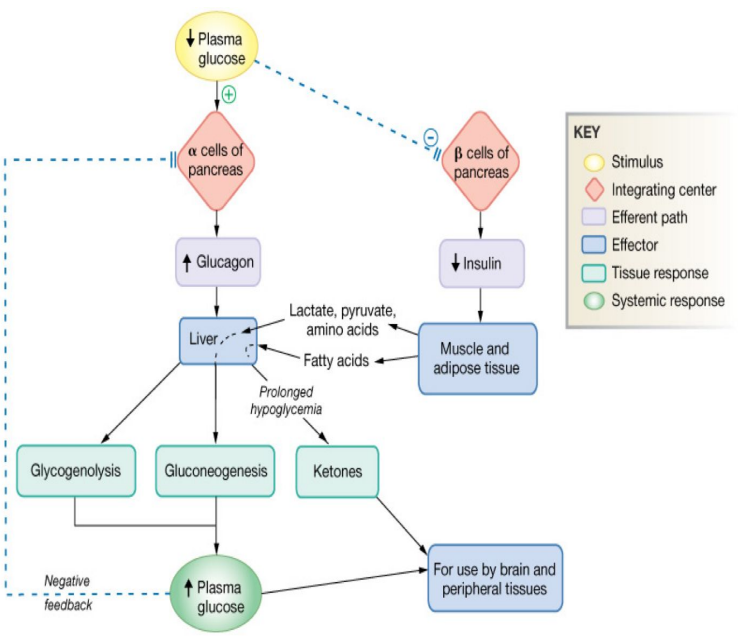
Factors Affecting Glucagon Secretion

Inhibitors	Stimuli
somatostatin	SNS stimulation
insulin	high Serum amino acids "arginine, alanine"*
high blood glucose	low blood glucose
	Stress
	Exercise

*Especially gluconeogenic amino acids (amino acids used in gluconeogenesis)

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



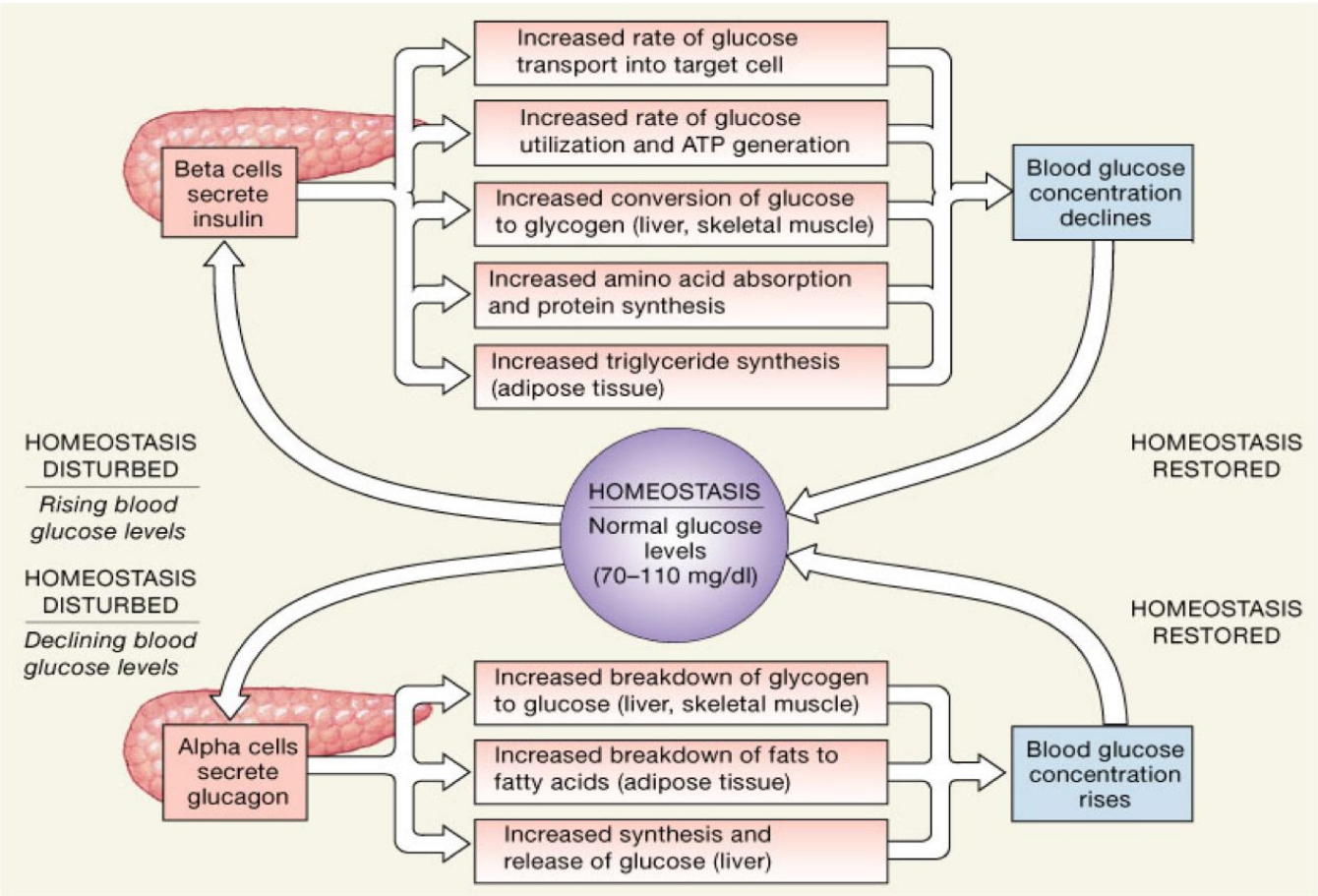
Glucagon actions

- Glycogenolysis.
- Gluconeogenesis.
- Lipid oxidation (fully to CO2 or partially to produce keto acids "ketone bodies").
- Release of glucose to the blood from liver cells.

- Most important effect on Liver.
- No effect on the muscles.
- Work in starvation.

High level of glucagon have positive inotropic effect on the heart (increase contraction)

The Regulation of Blood Glucose Concentrations



Diabetes Mellitus

Symptoms:

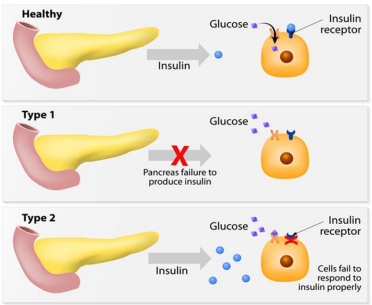
1. Hyperglycemia
2. Polyuria
3. Polydipsia
4. Polyphagia
5. Ketoacidosis (IDDM)
6. Hyperlipidemia
7. Muscle wasting
8. Electrolyte depletion

- 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)
  - **Polydipsia** (excessive thirst)
  - **Polyphagia** (excessive hunger).*

*One part of the brain called Satiety Center, needs insulin for entry of glucose. Diabetics don't have enough insulin, reduce entry of glucose to satiety center, which explains polyphagia.

That's why we feel full when eating sugars, even if it was little amount.

Type 1
Insulin dependent



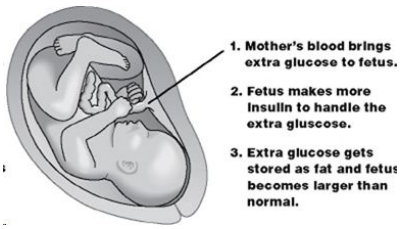
(Both lead to hyperglycemia and glycosuria)

- Affects children (juvenile onset)
- Cause: inadequate insulin secretion (by an immune-mediated selective destruction of β cells)
- Treatment: insulin injection
- β cells are destroyed while α cells are preserved:
  - No insulin :::: high glucagon -> high production of glucose and ketones by liver.
  - Increased glucose & ketones -> osmotic diuresis
  - Increased keto acids -> diabetic ketoacidosis

Type 2 (85%)
Insulin independent

- Affects adults (late onset)
- Cause: resistance of body cells to insulin
- Treatment: lifestyle modification with physical activity and/or healthy diet or OHA (Oral Hypoglycemic Agents)
- Causes defect in insulin action (resistance of body cells to insulin keeps blood glucose too high).
- Genetic and family related risk factors.
- More common in some ethnic groups.
- Chronic complications: atherosclerosis, renal failure, & blindness.
- Unhealthy foods and inactive lifestyles with sedentary behaviour increase the risk.

Gestational Diabetes



- Occurs in 2-5% of pregnancies. Associated with decreased insulin levels and/or insulin resistance.
- Resembles Type 2 Diabetes.
- Usually transient: symptoms improve following delivery.
- If untreated leads to macrosomia (high birth weight).

Long term complications of uncontrolled diabetes:

- **Microvascular disease:**
  - Hyperglycemia damages small blood vessels:
    - Diabetic retinopathy -> vision loss.
    - Diabetic neuropathy -> damage to nerves -> most common cause of amputation in Western world.
    - Diabetic nephropathy -> kidney damage -> chronic renal failure.

Glucose Tolerance Test (GTT)

- 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.
- The following results suggest different conditions:
- **Normal values:** FPG <100 mg/dl 2hr PPG < 140 mg/dL

Impaired fasting glucose	Impaired glucose tolerance	Diabetes
FPG = 100-125	2hr PPG = 140-199 mg/dL	FPG ≥ 126 mg/dl 2hr PPG levels ≥ 200 mg/dL

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
	Protein catabolism and gluconeogenesis			**Polyphagia**
	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

	Insulin	Glucagon
Structure	• A protein hormone consisting of two amino acid chains linked by disulfide bonds. • Produced by β cells in the pancreas	• Is a potent hyperglycemic agent. • Produced by α cells in the pancreas
Factors affecting secretion	Stimulators: - ↑ Glucose, Amino acids, FFA, Ketone bodies. Hormones: - Gastrin, Glucagon, CCK, GIP, VIP, Secretin, Epinephrine (B-receptor). - Parasympathetic system Inhibitors: - ↓ Glucose, Amino acids, FFA. Hormones: - Somatostatin - Epinephrine (a-receptor) - Sympathetic system	Stimulators: - Blood glucose. - High Serum AA "arginine,alanine". - SNS stimulation. - Stress. - Exercise Inhibitors: - High blood glucose - Somatostatin. - Insulin.
Function	Anabolic effects of insulin: ↑Glucose transport in skeletal muscle and adipose tissue ↑Glycogen synthesis and storage ↑Triglycerides synthesis ↑Na+ retention (kidneys) ↑Protein synthesis (muscles) ↑Cellular uptake of K+ and amino acids Glucagon release ↓Lipolysis in adipose tissue	• 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.

Diabetes Mellitus

- Characterized by the polytriad:
  - **Polyuria** (excessive urination)
  - **Polydipsia** (excessive thirst)
  - **Polyphagia** (excessive hunger)
- Long term complication:
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy

Type 1 ;Insulin <u>dependent</u>:
- juvenile onset
- Cause: inadequate insulin secretion.
- β cells are destroyed while α cells are preserved.

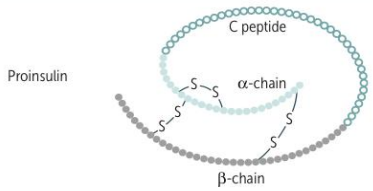
Type 2 (85%) Insulin <u>independent</u>:
- Late onset
- Cause:resistance of body cells to insulin
- Genetic and family related
- Gestational Diabetes: Occurs in pregnancies.

Summary

Insulin

SYNTHESIS

Preproinsulin (synthesized in RER) → cleavage of "presignal" → proinsulin (stored in secretory granules) → cleavage of proinsulin → exocytosis of insulin and C-peptide equally. Insulin and C-peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.



FUNCTION

Released from pancreatic β cells. Binds **in**sulin receptors (tyrosine kinase activity ❶), **in**ducing glucose uptake (carrier-mediated transport) **in**to insulin-dependent tissue ❷ and gene transcription.

Anabolic effects of insulin:

- ↑ glucose transport in skeletal muscle and adipose tissue
- ↑ glycogen synthesis and storage
- ↑ triglyceride synthesis
- ↑ Na^+ retention (kidneys)
- ↑ protein synthesis (muscles)
- ↑ cellular uptake of K^+ and amino acids
- ↓ glucagon release
- ↓ lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-dependent glucose transporters:

- GLUT4: adipose tissue, striated muscle (exercise can also ↑ GLUT4 expression)

Insulin-independent transporters:

- GLUT1: RBCs, brain, cornea, placenta
- GLUT2 (**bi**directional): β islet cells, liver, kidney, small intestine (think **2**-way street)
- GLUT3: brain, placenta
- GLUT5 (**F**ructose): spermatocytes, GI tract
- SGLT1/SGLT2 (Na^+-glucose cotransporters): kidney, small intestine

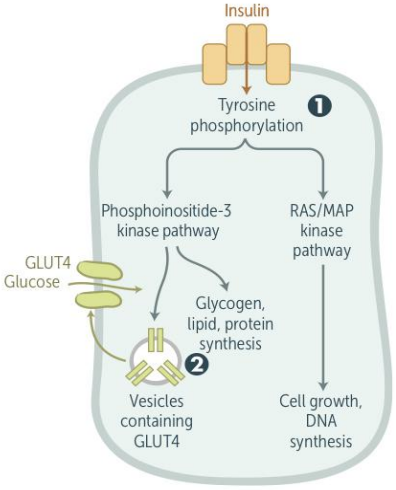
Brain utilizes glucose for metabolism but ketone bodies during starvation. RBCs utilize glucose, as they lack mitochondria for aerobic metabolism.

BRICK LIPS (insulin-independent glucose uptake): **B**rain, **R**BCs, **I**ntestine, **C**ornea, **K**idney, **L**iver, **I**slet (β) cells, **P**lacenta, **S**permatocytes

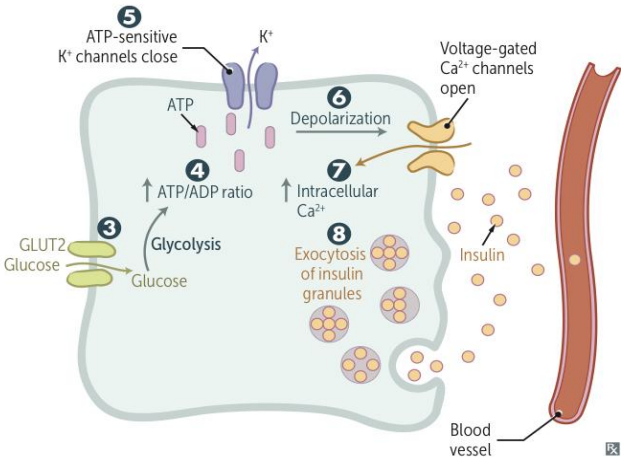
REGULATION

Glucose is the major regulator of insulin release. ↑ insulin response with oral vs IV glucose due to incretins (eg, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and ↑ β cell sensitivity to glucose. Release ↓ by α_2, ↑ by β_2 (**2** = regulates **insulin**)

Glucose enters β cells ❸ → ↑ ATP generated from glucose metabolism ❹ closes K^+ channels (target of sulfonylureas) ❺ and depolarizes β cell membrane ❻. Voltage-gated Ca^{2+} channels open → Ca^{2+} influx ❼ and stimulation of insulin exocytosis ❽.



Insulin-dependent glucose uptake



Insulin secretion by pancreatic β cells

Glucagon

SOURCE	Made by α cells of pancreas.
FUNCTION	Promotes glycogenolysis, gluconeogenesis, lipolysis, and ketone production. Elevates blood sugar levels to maintain homeostasis when concentration of bloodstream glucose falls too low (ie, fasting state).
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, and somatostatin.

MCQs

1 - Insulin is associated with:
A)lipolysis
B)proteolysis
C)glycogenolysis
D)growth

2 - which one of the following is insulin stimulator?
A)increase glucose
B)increase fatty acids
C)increase amino acids
D)All of the above

3 - What is the organ that has insulin receptors but glucose uptake isn't insulin dependent?
A)skeletal muscles
B)liver
C)exercising muscle
D)B+C

4 - Which substances are most likely to produce the greatest increase in insulin secretion?
A) Amino acids
B) Amino acids and glucose
C) Amino acids and somatostatin
D) Glucose and somatostatin

5 - The major target of Glucagon actions is:
A)Liver
B)skeletal muscle
C)adipocytes
D)cardiac muscle

6 - Which finding is most likely to occur in a patient who has uncontrolled type 1 DM?
A)Decreased plasma osmolality
B) Increased plasma volume
C)Increased plasma pH
D) Increased release of glucose from the liver
E) Decreased rate of lipolysis

7 - What does not increase when insulin binds to its receptor?
A)Fat synthesis in adipose tissue
B)Protein synthesis in muscle
C)Glycogen synthesis
D)Gluconeogenesis in the liver
E)Intracellular tyrosine kinase activity

8 - A patient has inadequate insulin Secretion, diagnosed with diabetes & treated with insulin injection. Which type of diabetes does the patient have?
A)DM1
B)DM2
C)Adrenal diabetes
D)Diabetes insipidus

9 - The DNA of alpha cells and beta cells located on chromosome:
A)Alpha:2, Beta:2
B)Alpha:11, Beta:11
C)Alpha:2, Beta:11
D)Alpha:11, Beta:2

Answers
1. D
2. D
3. D
4. B
5. A
6. D
7. D
8. A
9. C