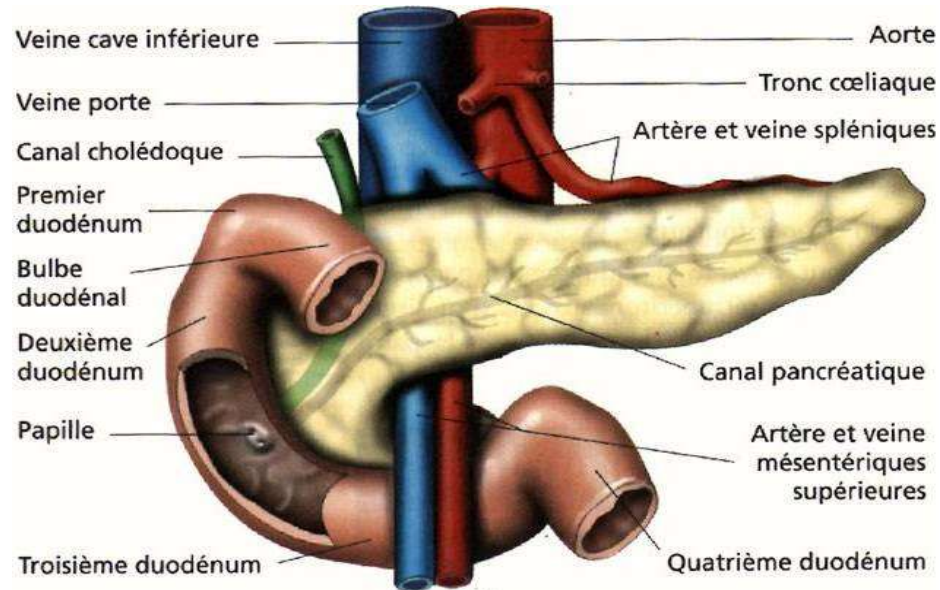


# Physiology of the pancreas and Insulin

*Dr. Ahmed Alsabih*

*Dr. Manan Alhkbani*

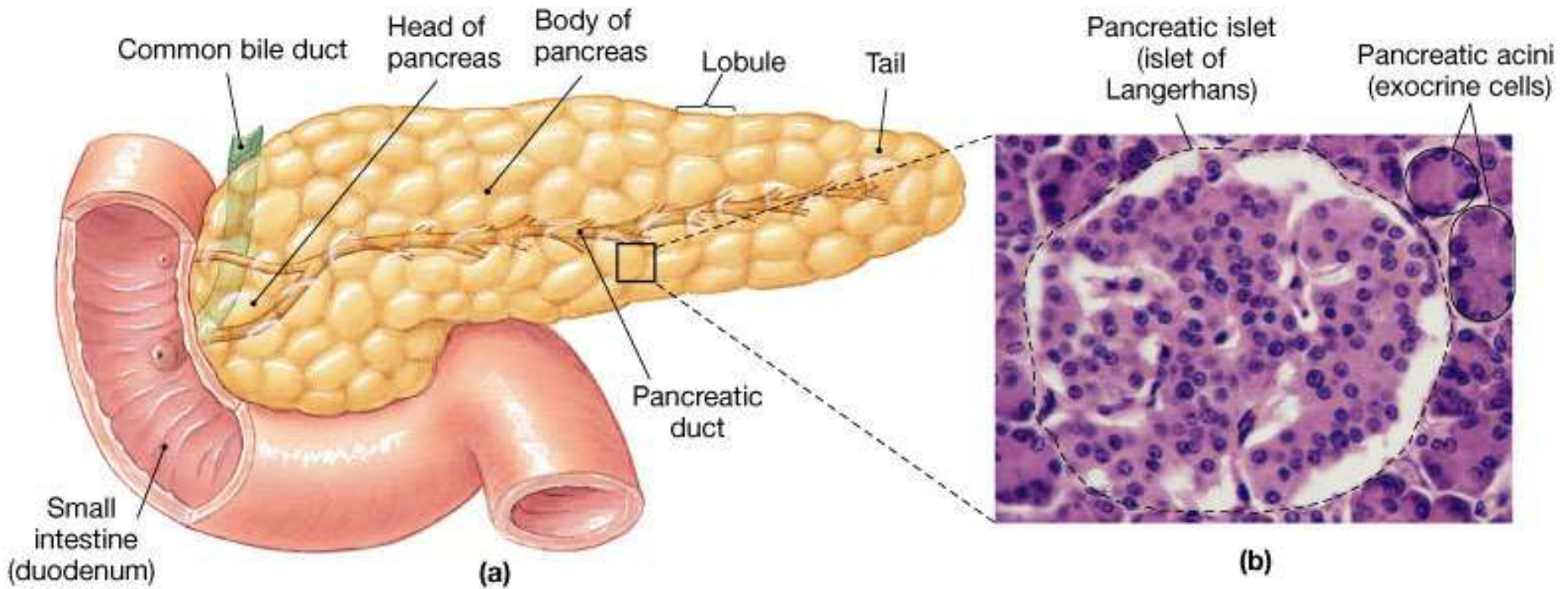


# Pancreas

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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.

# The Endocrine Pancreas



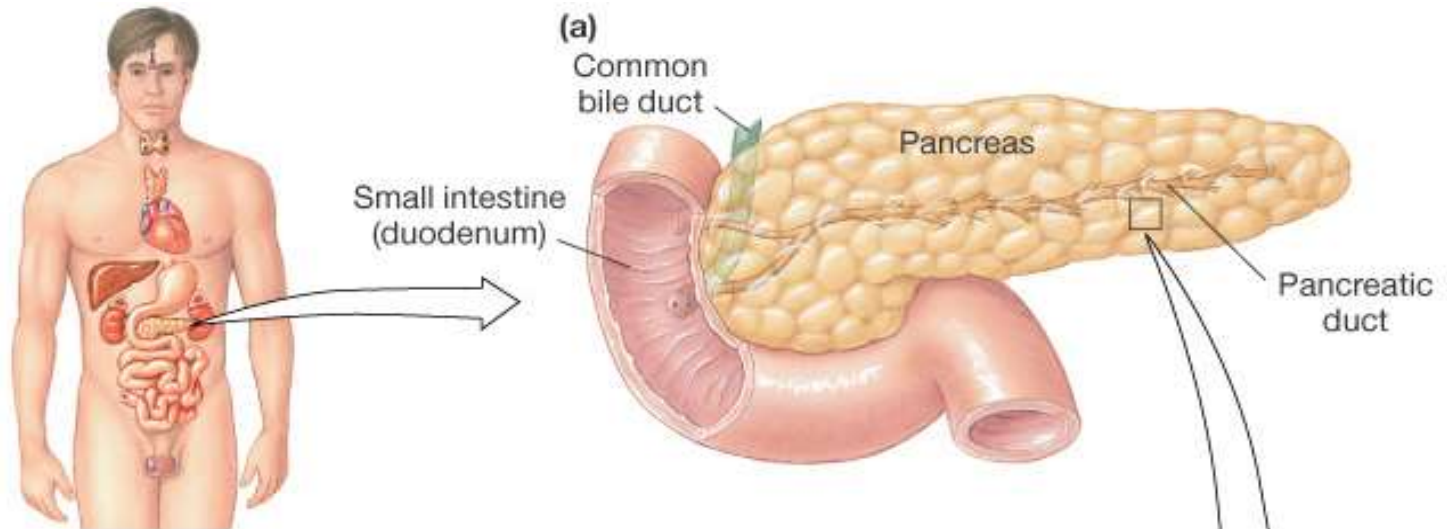
# Islets of Langerhans

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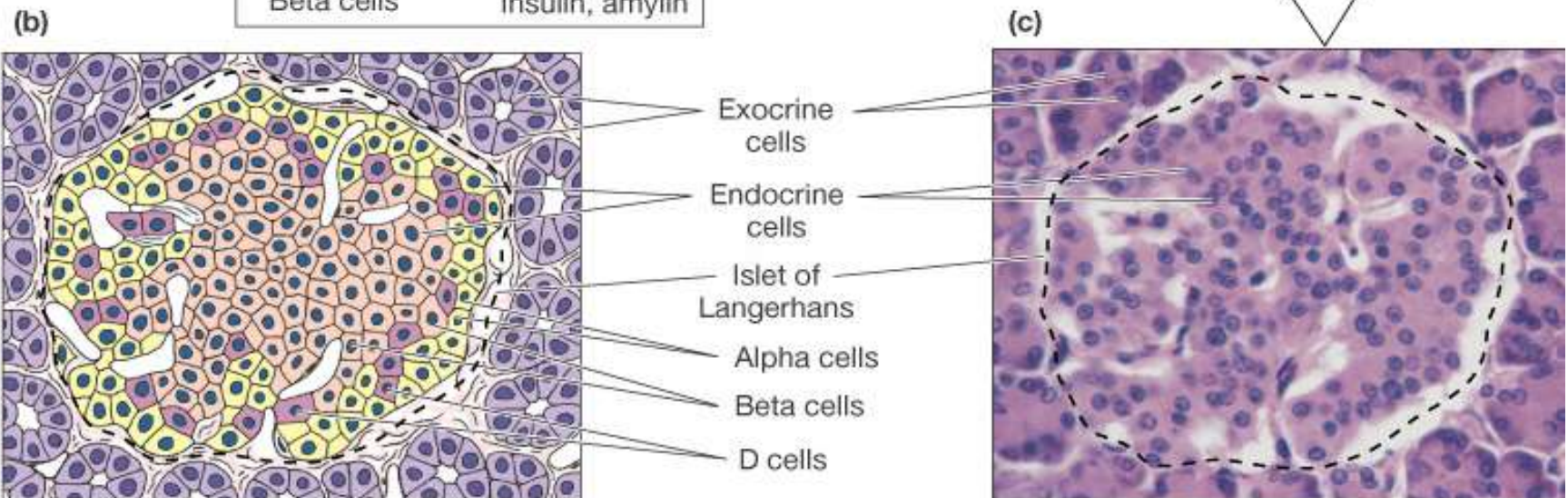
- 1-2 million islets
- **Beta ( $\beta$ )** cells produce insulin (70%)
- **Alpha ( $\alpha$ )** cells produce glucagon (20%)
- **Delta ( $\delta$ )** cells produce somatostatin (5%)
- **F cells** produce pancreatic polypeptide (5%)



# Islets of Langerhans



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



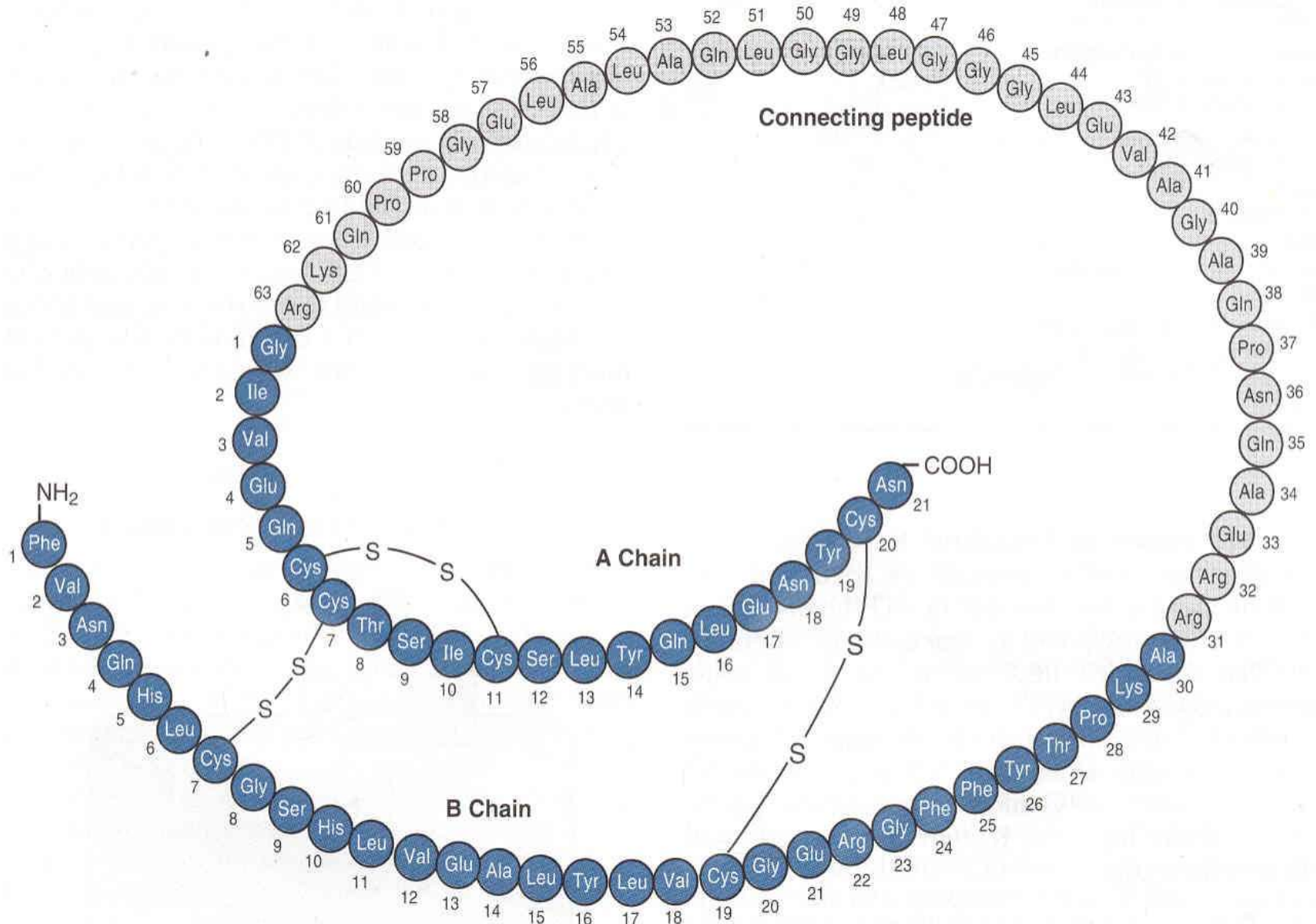
# Insulin

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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 Structure

## PROINSULIN



# Insulin Synthesis

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DNA (chromosome 11) in  $\beta$  cells



mRNA



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



proinsulin



insulin

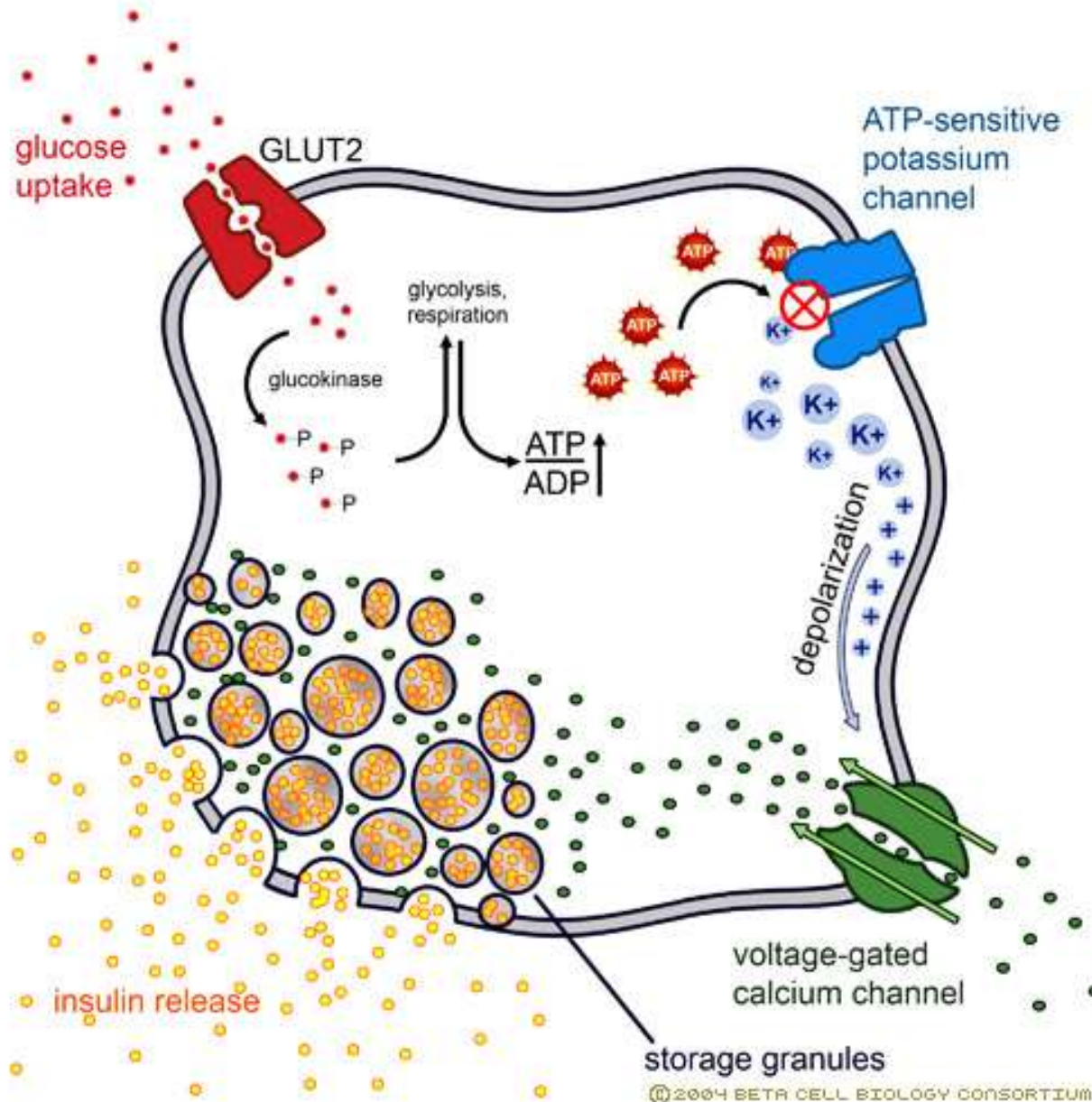


# Insulin Synthesis

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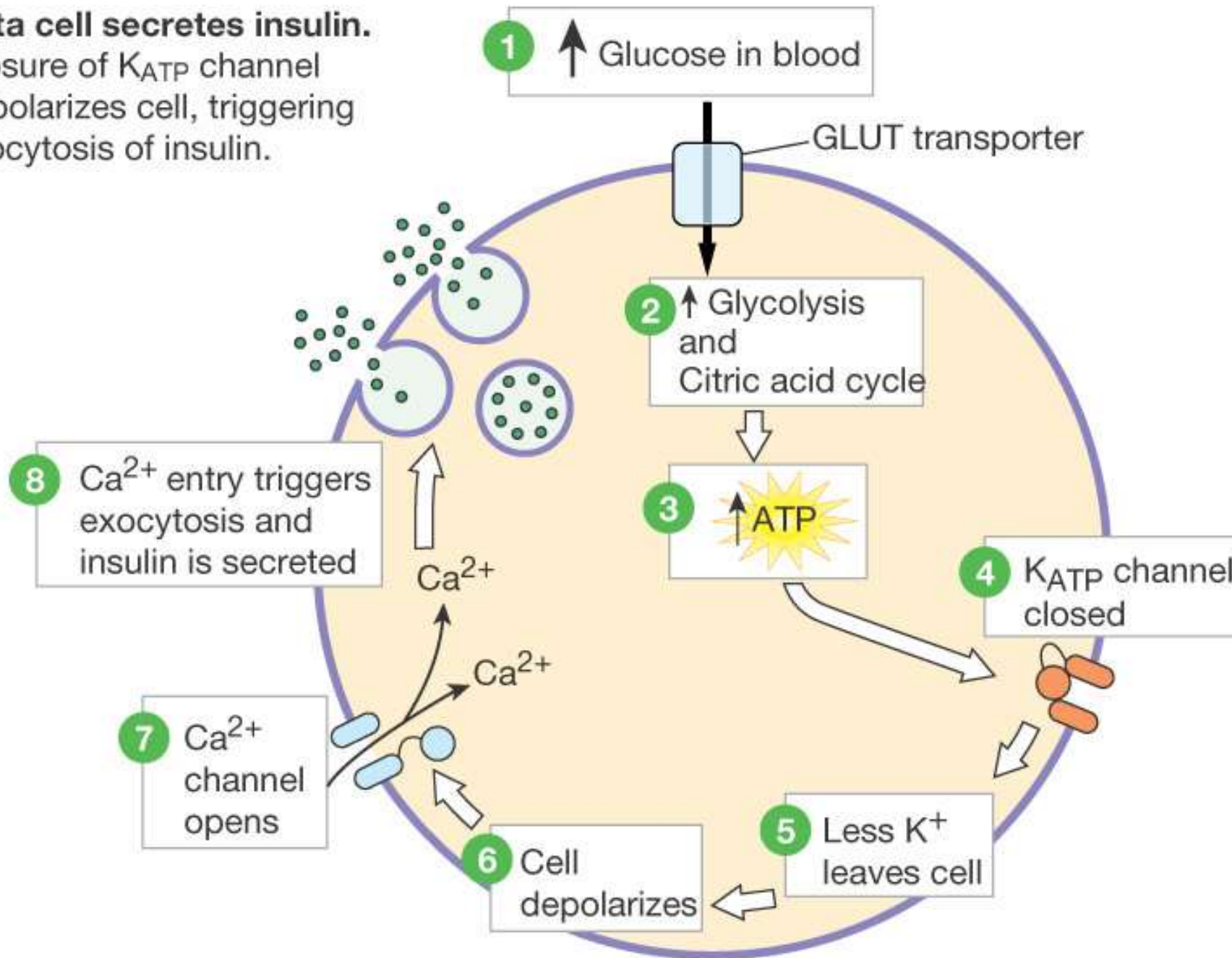
- Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
- Threshold of glucose-stimulated insulin secretion is 100 mg/dl.
- Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene

# Glucose is the primary stimulator of insulin secretion

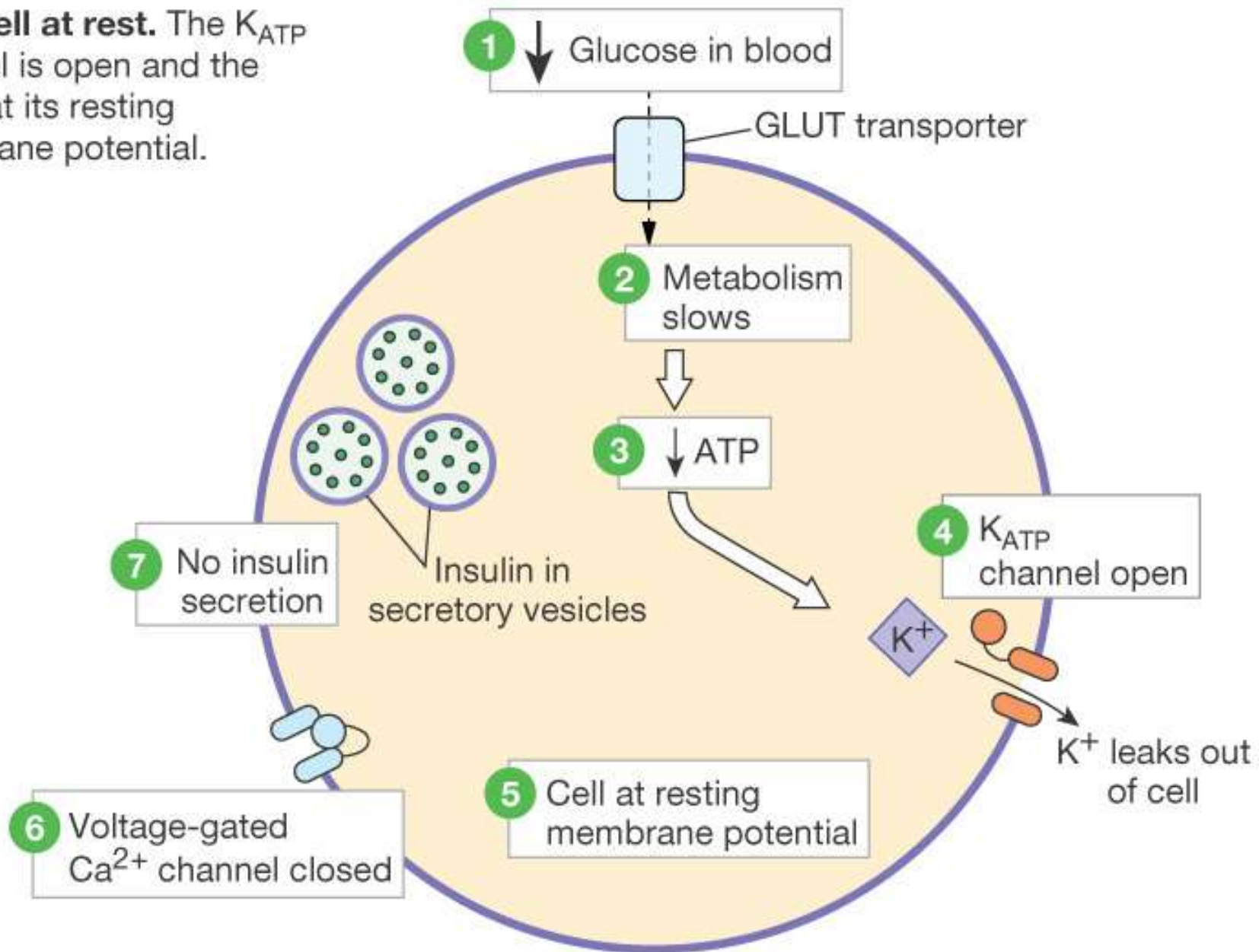


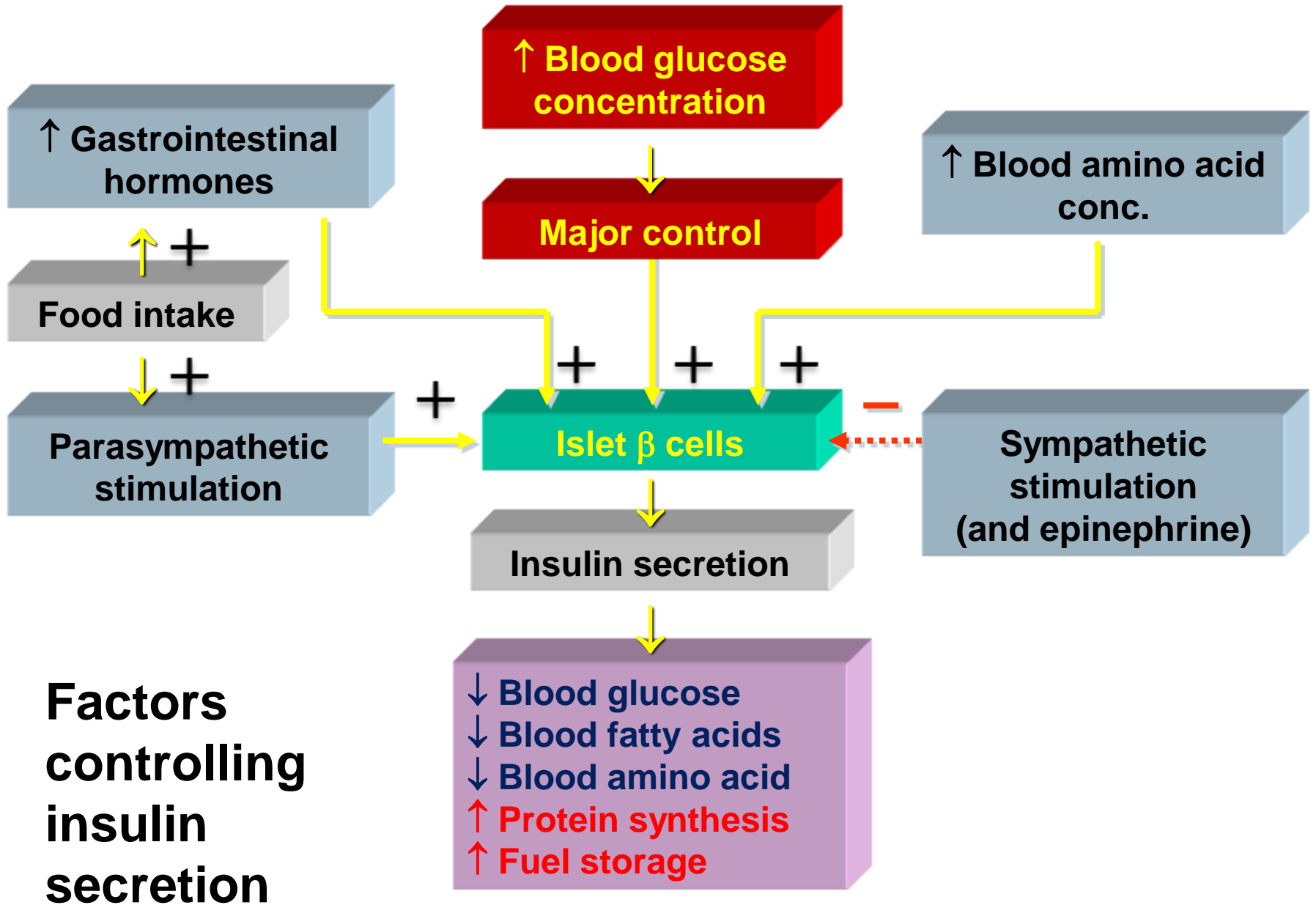
**(b) Beta cell secretes insulin.**

Closure of  $K_{ATP}$  channel depolarizes cell, triggering exocytosis of insulin.



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







# Regulation of Insulin Secretion

## Regulators of insulin secretion

### Stimulators of insulin secretion

↑ Serum glucose

↑ Serum amino acids

↑ Serum free fatty acids

↑ Serum ketone bodies

#### Hormones

Gastroinhibitory peptide (GIP)

Glucagon

Gastrin

Cholecystokinin (CCK)

Secretin

Vasoactive intestinal peptide (VIP)

Epinephrine ( $\beta$ -receptor)

Parasympathetic nervous system

### Inhibitors of insulin secretion

↓ Glucose

↓ Amino acids

↓ Free fatty acids

#### Hormones

Somatostatin

Epinephrine ( $\alpha$ -receptor)

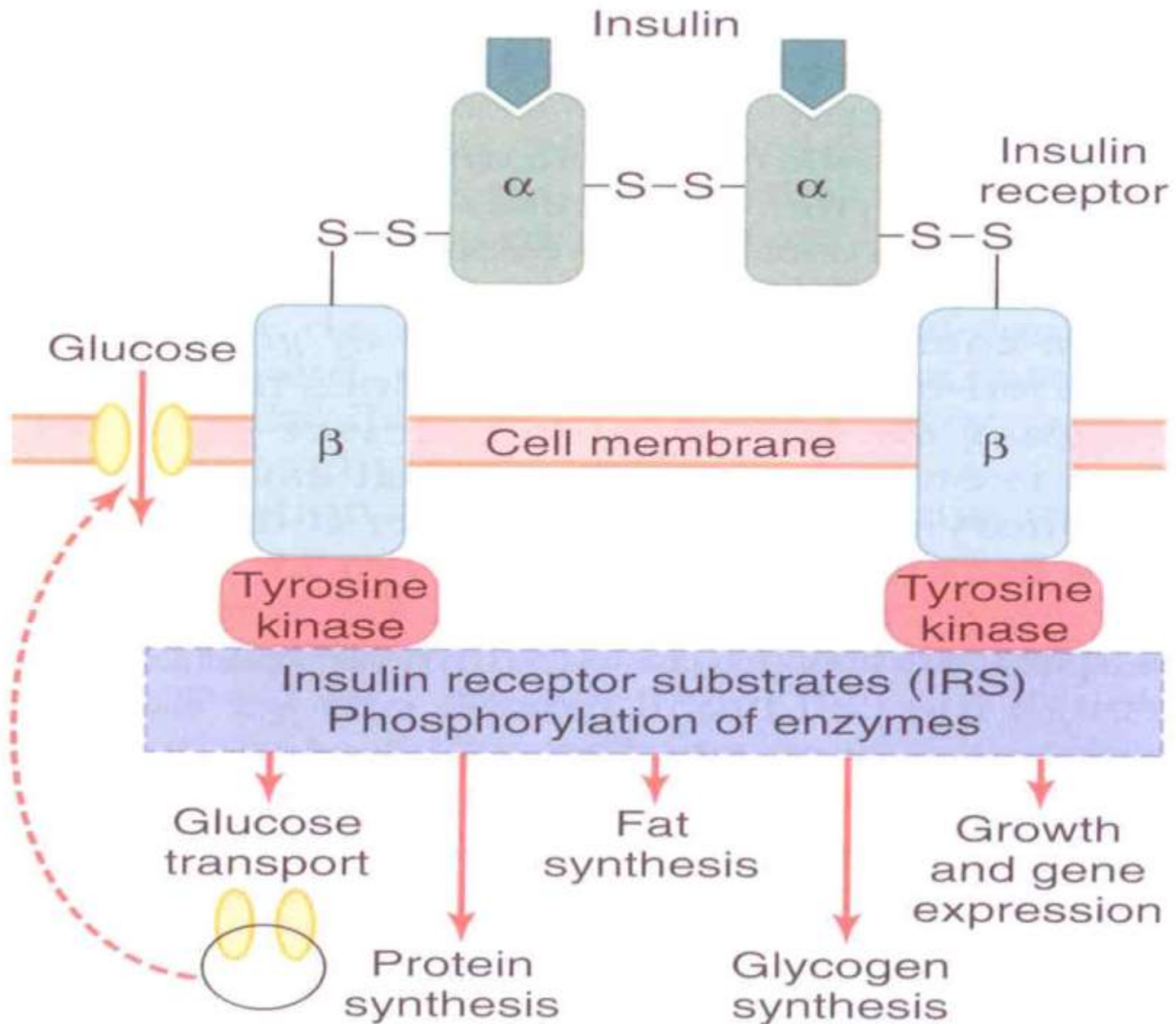
Sympathetic nervous system stimulation



# 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



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# **Actions of insulin**

# Glucose regulation and metabolism terms

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- **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** - the breakdown of glucose into pyruvate by cells for the production of ATP

- **Rapid (seconds)**
- (+) transport of glucose, amino acids, K<sup>+</sup> 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

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



# Action of insulin on Muscle:

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- (+) 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 Liver:

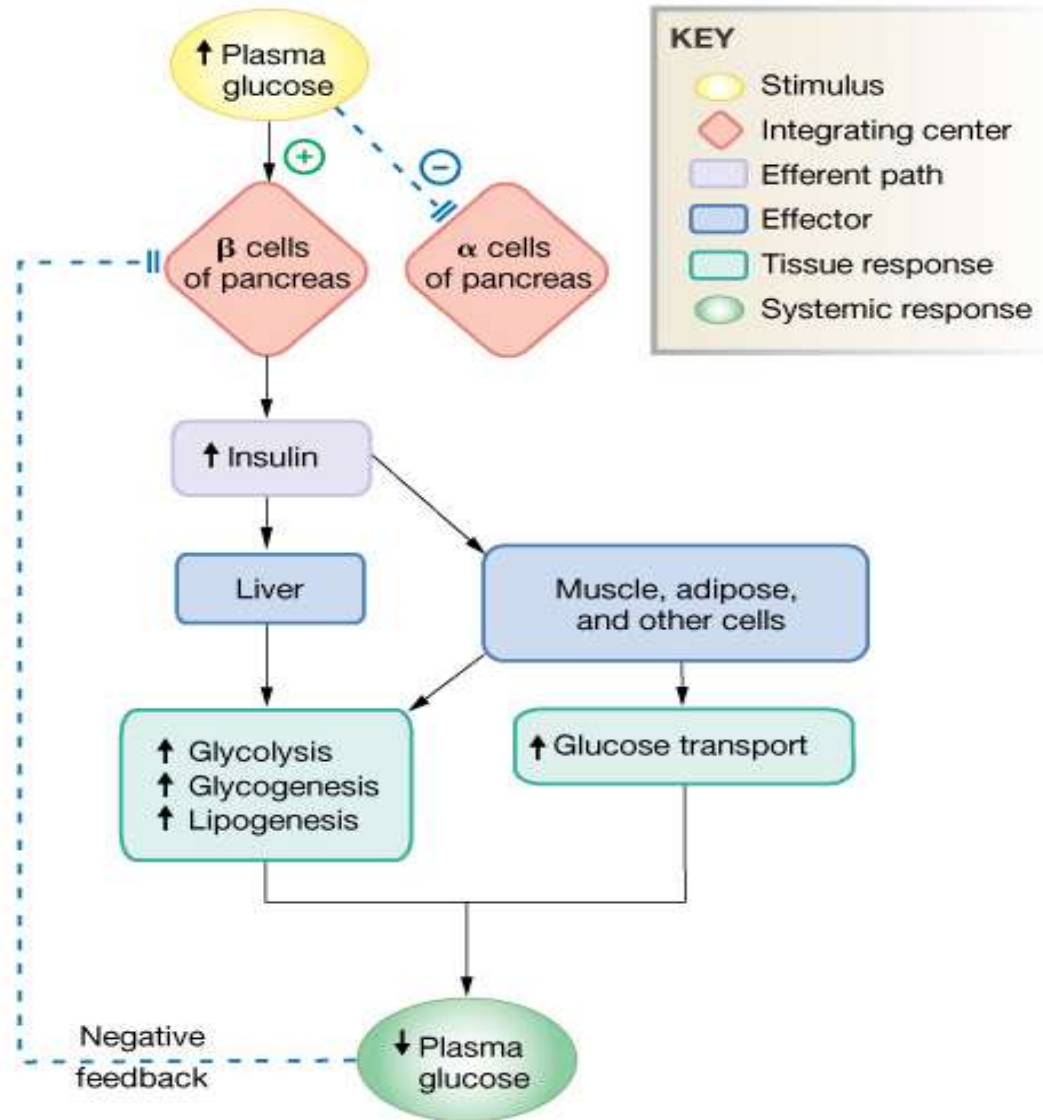
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- (-) ketogenesis
  - (+) protein synthesis
  - (+) lipid synthesis
  - (-) gluconogenesis, (+) glycogen synthesis, (+) glycolysis.
- 
- **General:**
  - (+) cell growth

# Glucose transporter systems

<u>TRANSPORTERS</u>	<u>PRESENT IN</u>
<b>GLUT-1</b>	Placenta, Blood brain barrier, RBCs, Kidneys and Colon.
<b>GLUT-2</b>	$\beta$ cells of Pancreas, Liver, Epithelial cells of small intestines and Kidneys.
<b>GLUT-3</b>	Brain, Placenta and Kidneys.
<b>GLUT-4</b>	Skeletal Muscles, Cardiac muscles and Adipose tissue.
<b>GLUT-5</b>	Jejunum and sperm.

# 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

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



# SYNTHESIS

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DNA in  $\alpha$  cells (chromosome 2)



mRNA



Preproglucagon



proglucagon



glucagon

# Factors Affecting Glucagon Secretion:

## *Effects on Glucagon Secretion*

### **Stimuli for Glucagon Secretion**

↓ Blood glucose

↑ Serum amino acids (arginine, alanine)

Sympathetic nervous system stimulation

Stress

Exercise

### **Inhibitors of Glucagon Secretion**

Somatostatin

Insulin

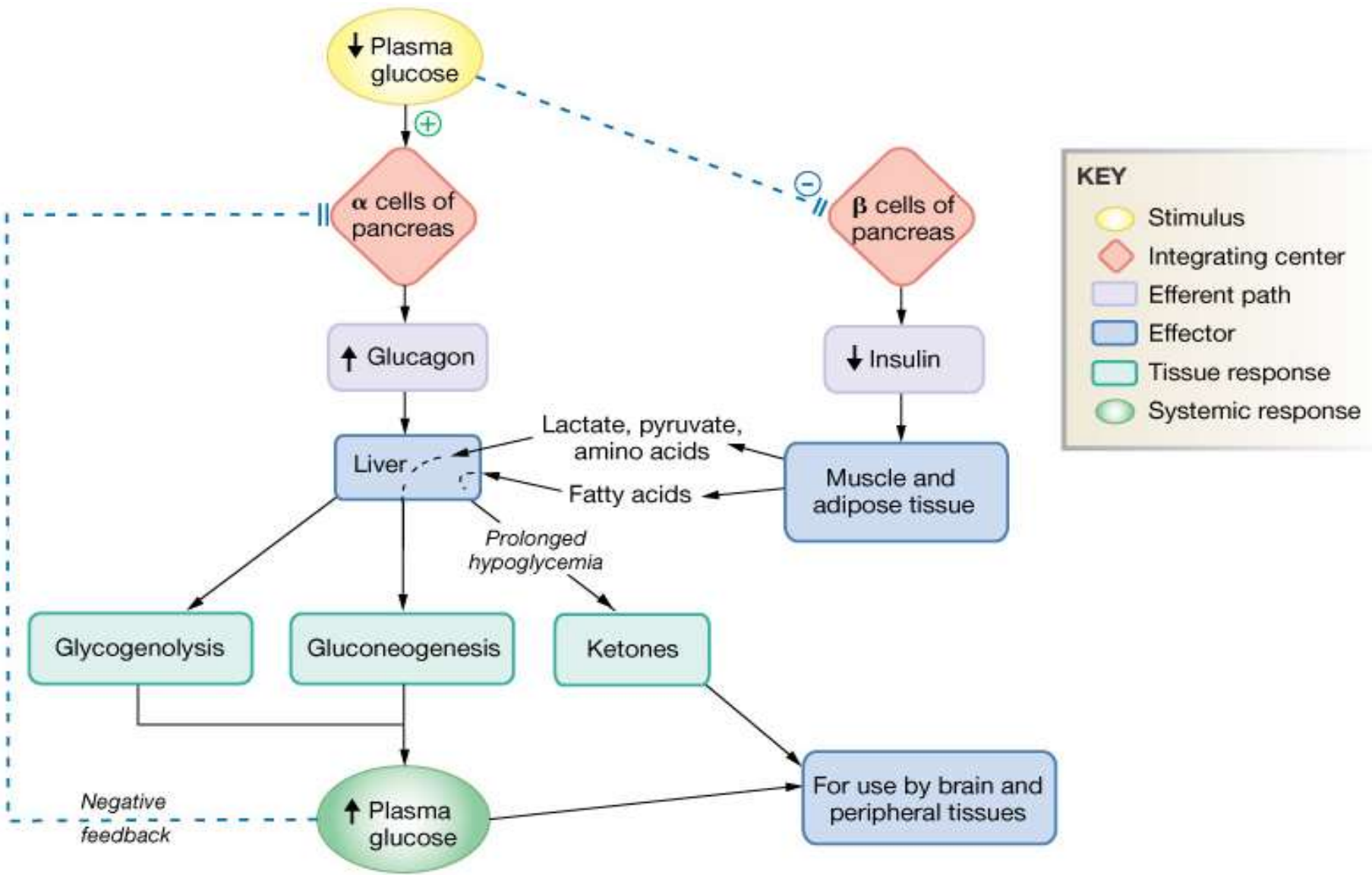
↑ Blood glucose

# Glucagon Actions

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- Its major target is **liver**:
  - **Glycogenolysis**
  - **Gluconeogenesis**
  - **Lipid oxidation** (fully to CO<sub>2</sub> or partially to produce keto acids “**ketone bodies**”).
  - Release of glucose to the blood from liver cells

# Glucagon Action on Cells:

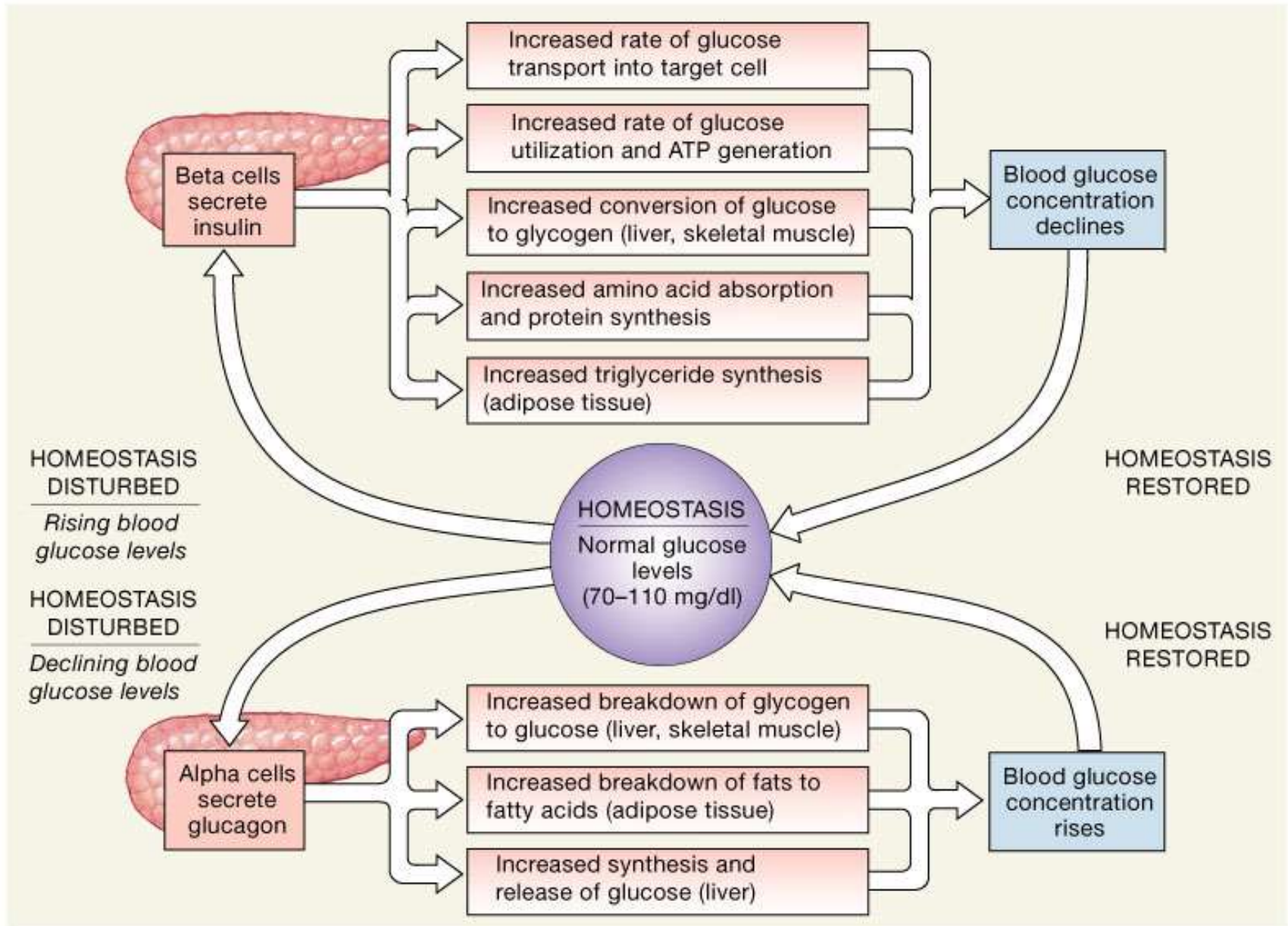


**Table 22-5: Glucagon**

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



# The Regulation of Blood Glucose Concentrations



# 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** (excessive urination)
  - **Polydypsia** (excessive thirst)
  - **Polyphagia** (excessive hunger).

# Symptoms of Diabetes Mellitus

## *Symptoms of Diabetes Mellitus*

Hyperglycemia

Polyuria

Polydipsia

Polyphagia

Ketoacidosis (IDDM)

Hyperlipidemia

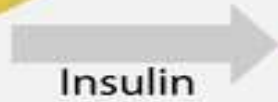
Muscle wasting

Electrolyte depletion



# DIABETES MELLITUS

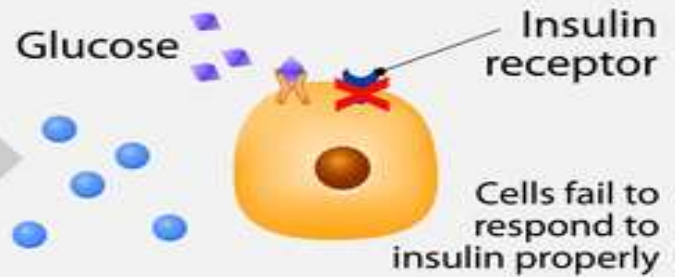
**Healthy**



**Type 1**



**Type 2**



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- **Type I Diabetes** (autoimmune attack)

  - Juvenile onset

  - Hyposecretion of insulin

  - Insulin dependent

- **Type II Diabetes** (about 85% )

  - Late onset, genetic and family related risk factors.

  - Resistance of body cells to insulin

- **Gestational Diabetes** (during pregnancy)

# Types of Diabetes

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## **Type 1** Diabetes

Affects children

**Cause:** inadequate insulin secretion

**Treatment :** insulin injection

## **Type 2** diabetes

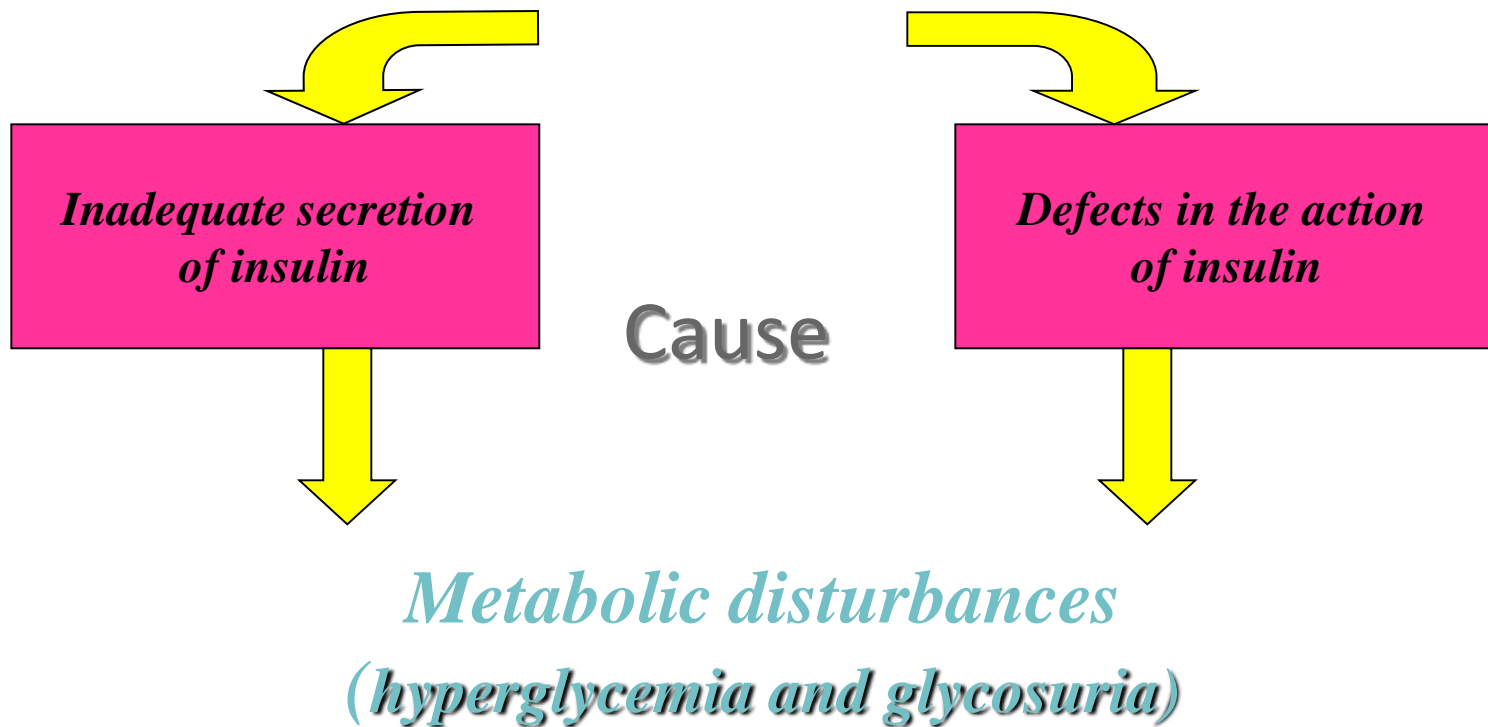
Affects adults

**Cause** defect in insulin action

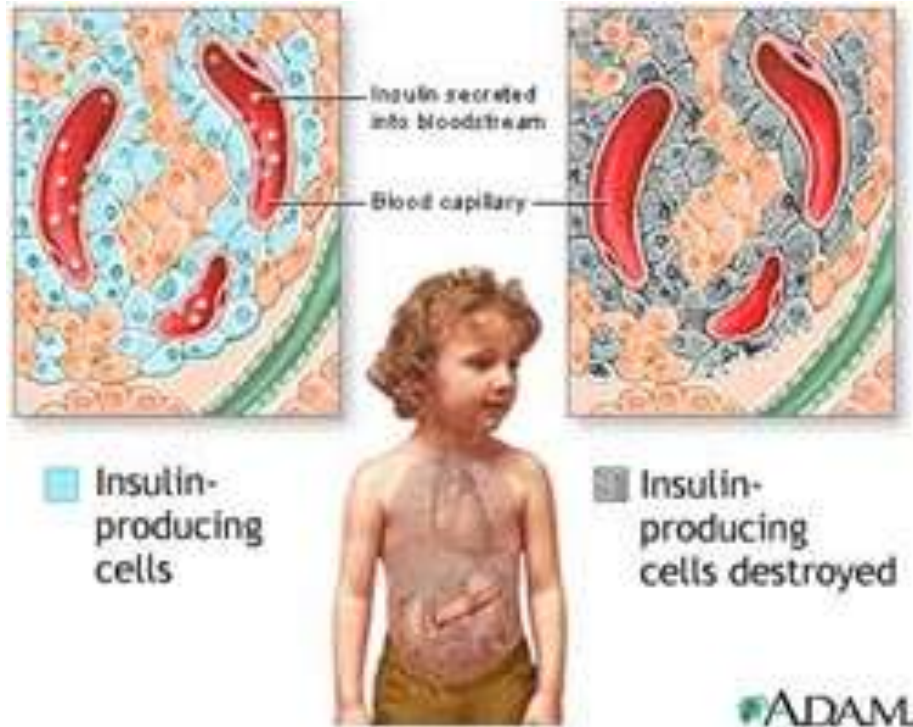
**Treatment :**

diet or OHA (Oral Hypoglycaemic Agents)

# ***Diabetes Mellitus***



# Type 1 diabetes



# Diabetes Mellitus Type I

- Caused by an immune-mediated selective destruction of  $\beta$  cells
- $\beta$  cells are destroyed while  $\alpha$  cells are preserved:  
No insulin :::: high glucagon  $\longrightarrow$  high production of glucose and ketones by liver  
glucose & ketones  $\uparrow$   $\longrightarrow$  osmotic diuresis  
keto acids  $\uparrow$   $\longrightarrow$  diabetic ketoacidosis

# Diabetes Mellitus Type II

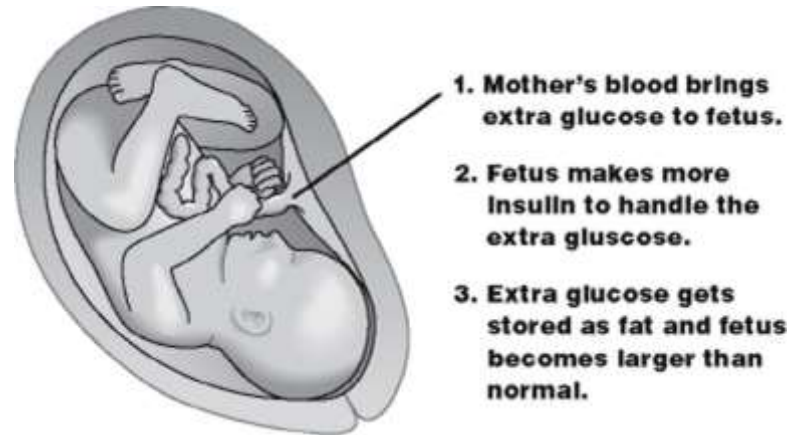
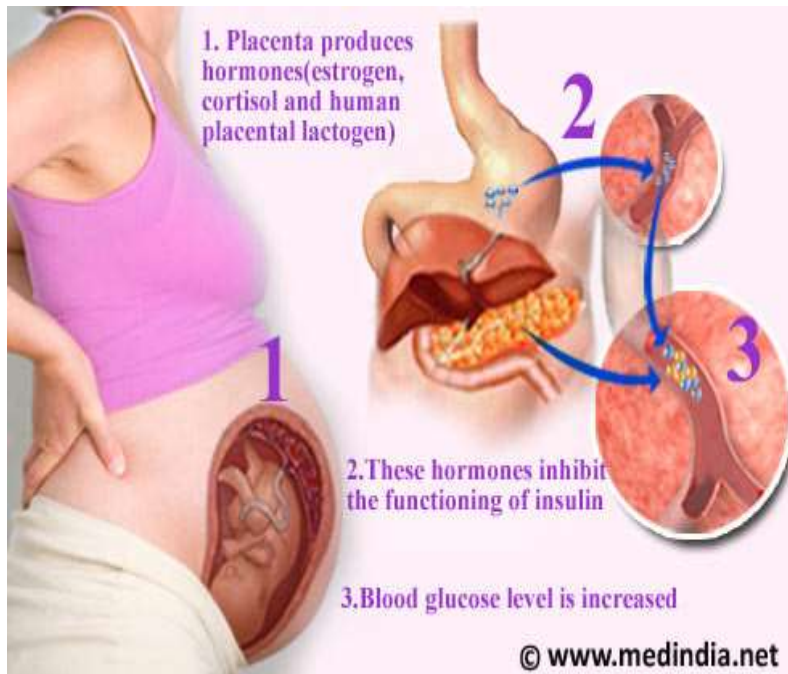
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- Late onset, genetic and family related risk factors.
- More common in some ethnic groups.
- Unhealthy foods and inactive lifestyles with sedentary behaviour.
- Resistance of body cells to insulin keeps blood glucose too high
- manage by lifestyle modification with physical activity and/or healthy diet
- Chronic complications: atherosclerosis, renal failure & blindness.





# Gestational Diabetes (during pregnancy)



- 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 → macrosomia (high birth weight)

# Long Term Complications of Uncontrolled Diabetes

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- **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*

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- 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



Oral glucose tolerance test

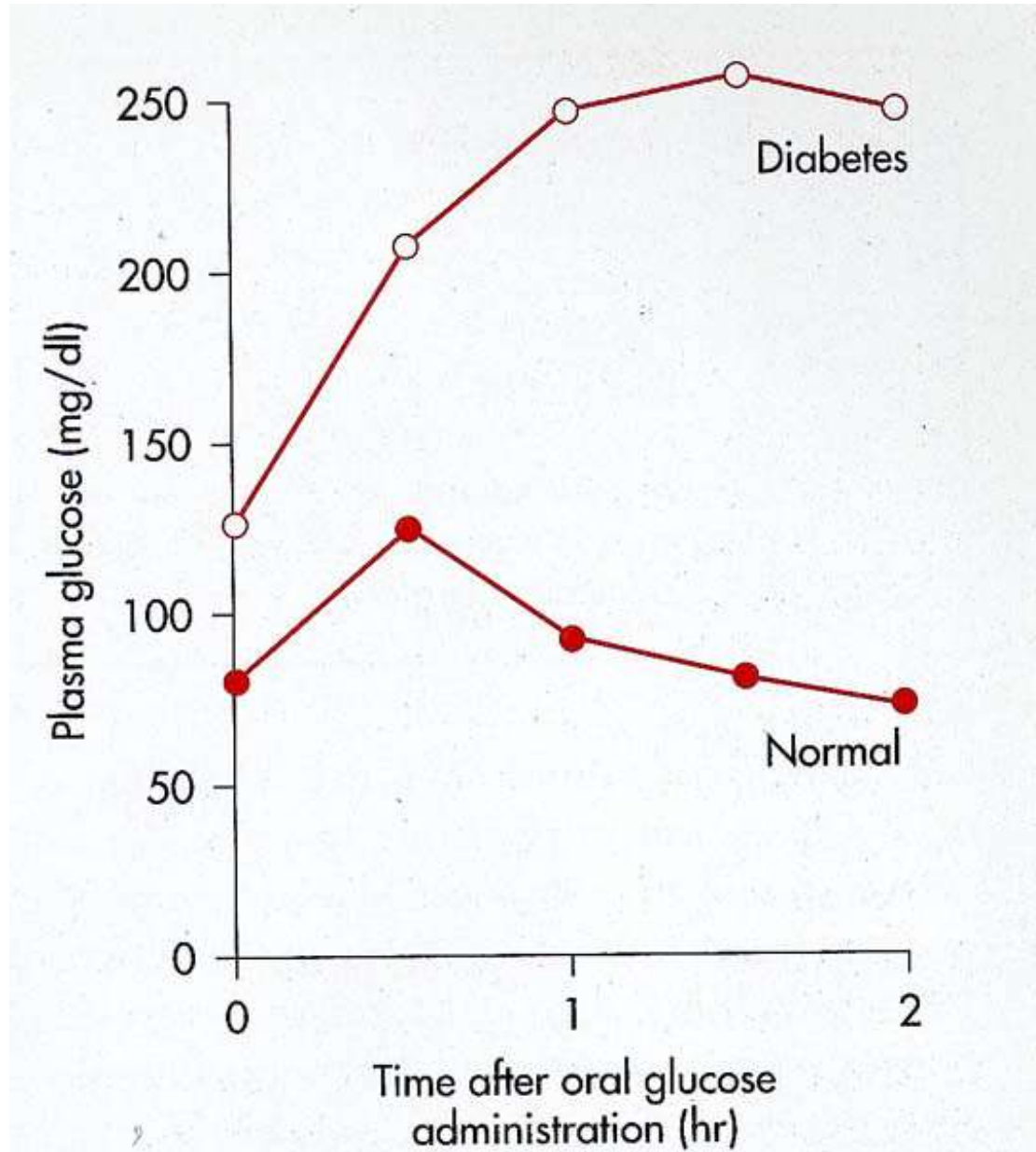
# *Glucose Tolerance Test (GTT)*

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- 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.










# GTT



# *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
- **Diabetes**
- FPG  $\geq$  126 mg/dl
- 2hr PPG levels  $\geq$  200 mg/dL

# Diabetes Mellitus (DM)

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