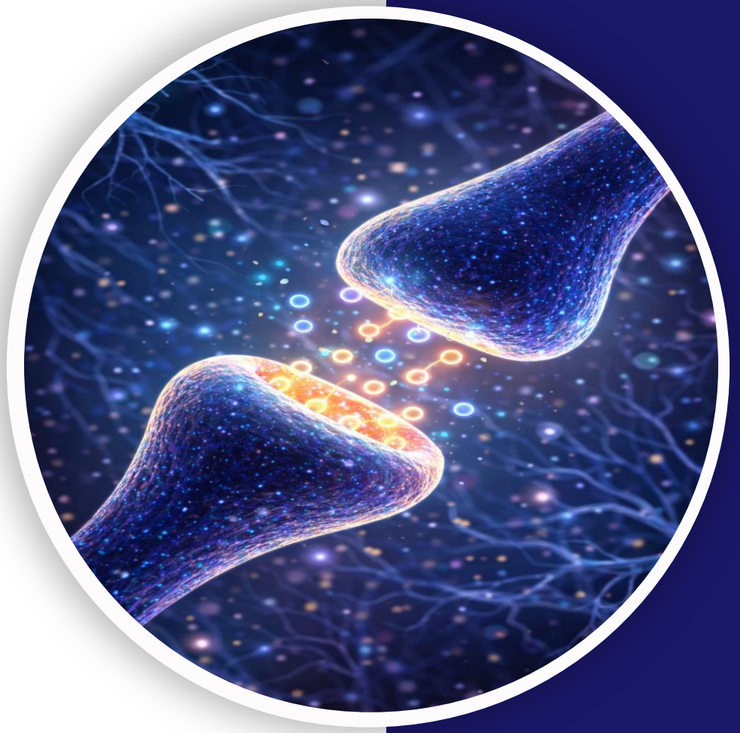
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Physiology | MID L6

Insulin,glucagon & DM

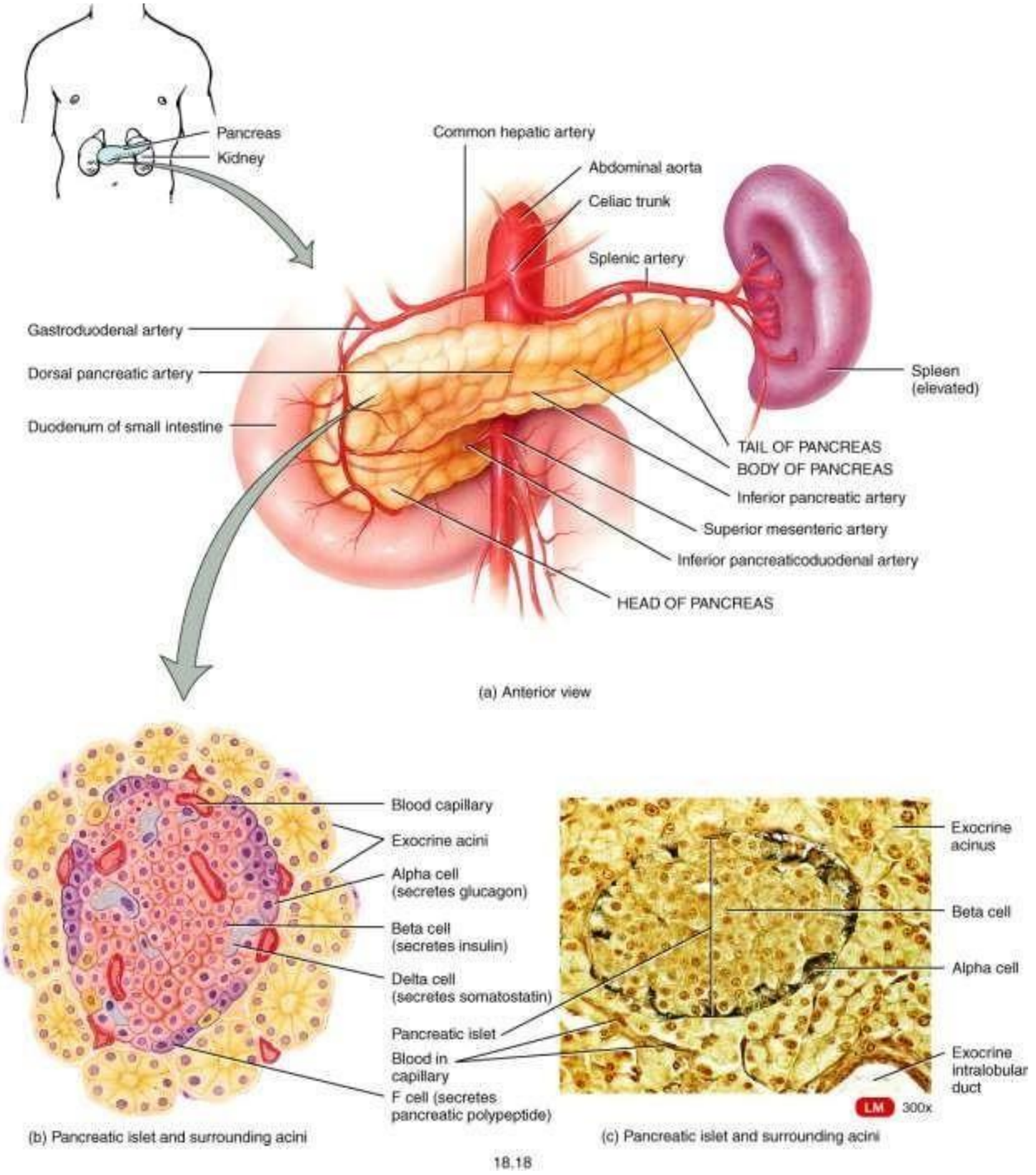


Reviewed by : Bushra Masalha
Abdallah Hindash

Objectives

- Describe structures of insulin and glucagon
- List the actions of insulin and glucagon
- Explain the mechanism of actions of insulin and glucagon
- Describe other hormone that affect glucose homeostasis

Pancreas

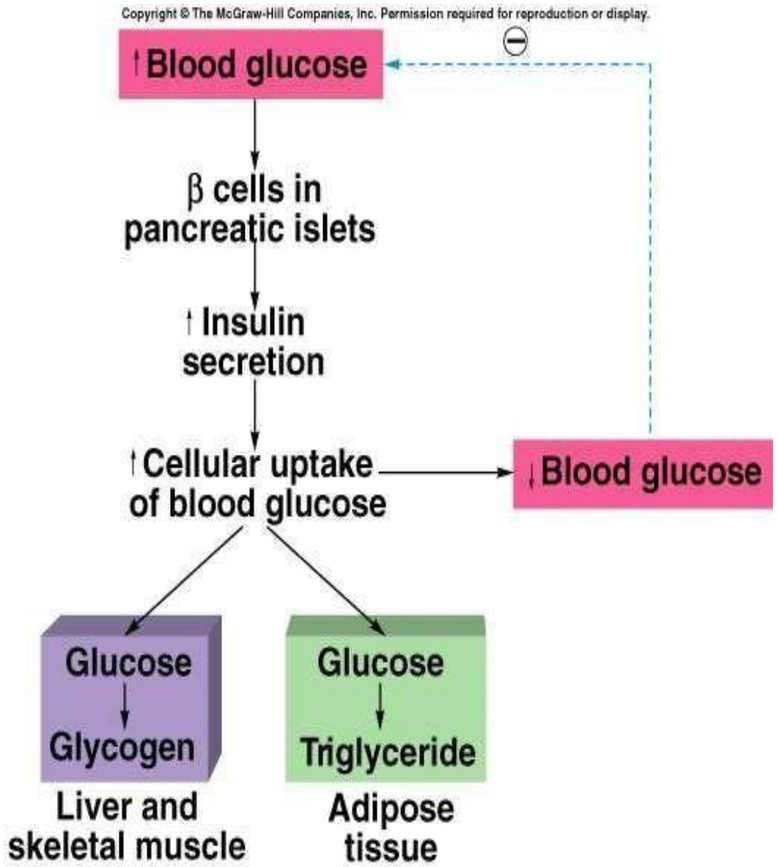

Pancreas
Kidney
Common hepatic artery
Abdominal aorta
Celiac trunk
Splenic artery
Gastroduodenal artery
Dorsal pancreatic artery
Duodenum of small intestine
Spleen (elevated)
TAIL OF PANCREAS
BODY OF PANCREAS
Inferior pancreatic artery
Superior mesenteric artery
Inferior pancreaticoduodenal artery
HEAD OF PANCREAS
(a) Anterior view
Blood capillary
Exocrine acini
Alpha cell (secretes glucagon)
Beta cell (secretes insulin)
Delta cell (secretes somatostatin)
Pancreatic islet
Blood in capillary
F cell (secretes pancreatic polypeptide)
(b) Pancreatic islet and surrounding acini
Exocrine acinus
Beta cell
Alpha cell
Exocrine intralobular duct
LM 300x
(c) Pancreatic islet and surrounding acini
18.18

Pancreatic Islets

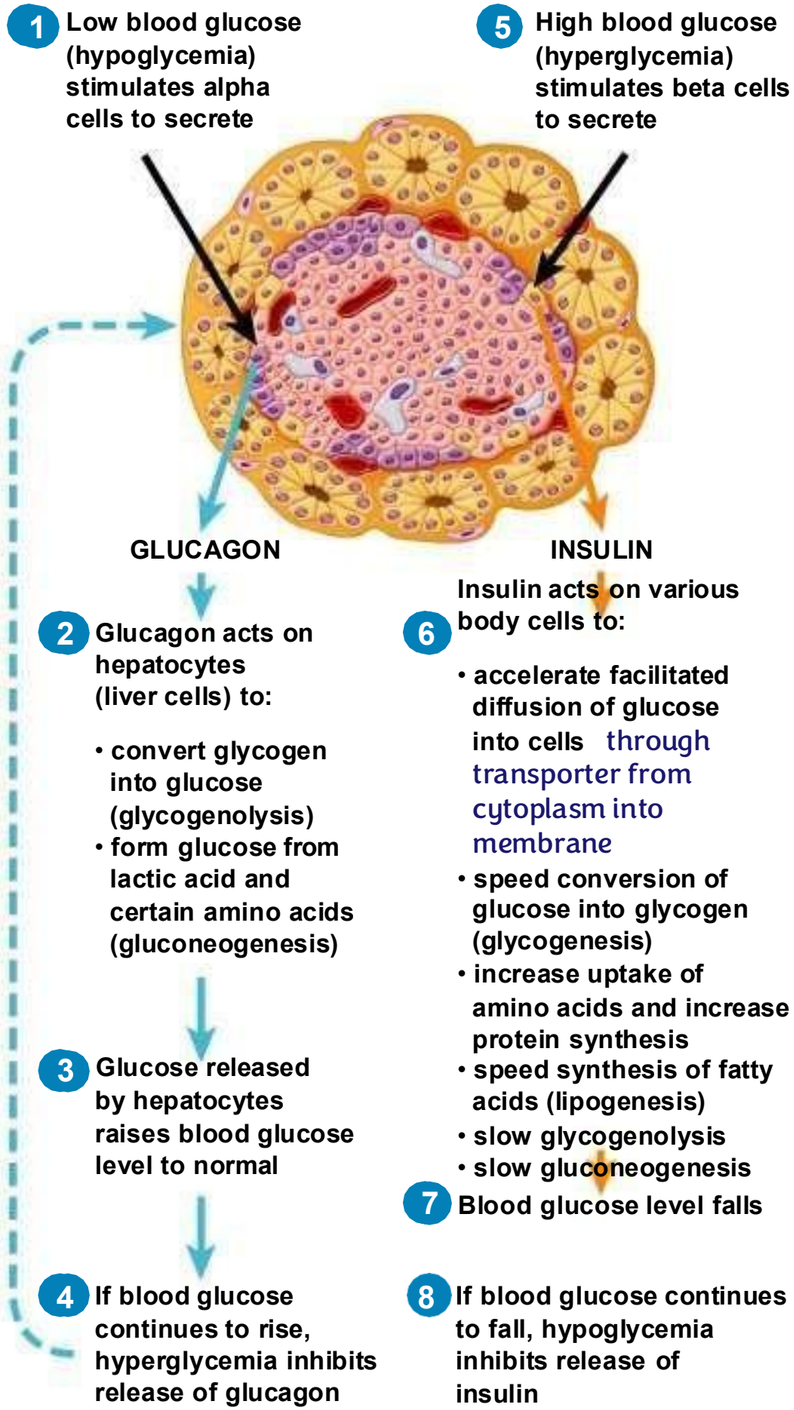
- Both exocrine and endocrine gland
- Roughly 99% of cells produce digestive enzymes
- Pancreatic islets or islets of Langerhans
  - **Alpha** or α (A) cells secrete **glucagon** – raises blood sugar
  - **Beta** or β (B) cells secrete **insulin** – lowers blood sugar
  - **Delta** or δ (D) cells secrete **somatostatin** – inhibits both insulin and glucagon ,it depends on situations
  - **F cells** secrete **pancreatic polypeptide** – inhibits somatostatin, gallbladder contraction, and secretion of pancreatic digestive enzymes

Pancreatic Islets (Islets of Langerhans)

- Alpha cells secrete glucagon.
  - Stimulus is **decrease in blood [glucose].**
  - Stimulates glycogenolysis, gluconeogenesis and lipolysis.
  - Stimulates conversion of fatty acids to ketones (ketogenesis).
- Beta cells secrete insulin.
  - Stimulus is **increase in blood [glucose] .**
  - Promotes entry of glucose into cells.
  - Converts glucose to glycogen (in liver)and fat (in adipose tissue)
  - Aids entry of amino acids into cells.



Negative Feedback Regulation of Glucagon and Insulin



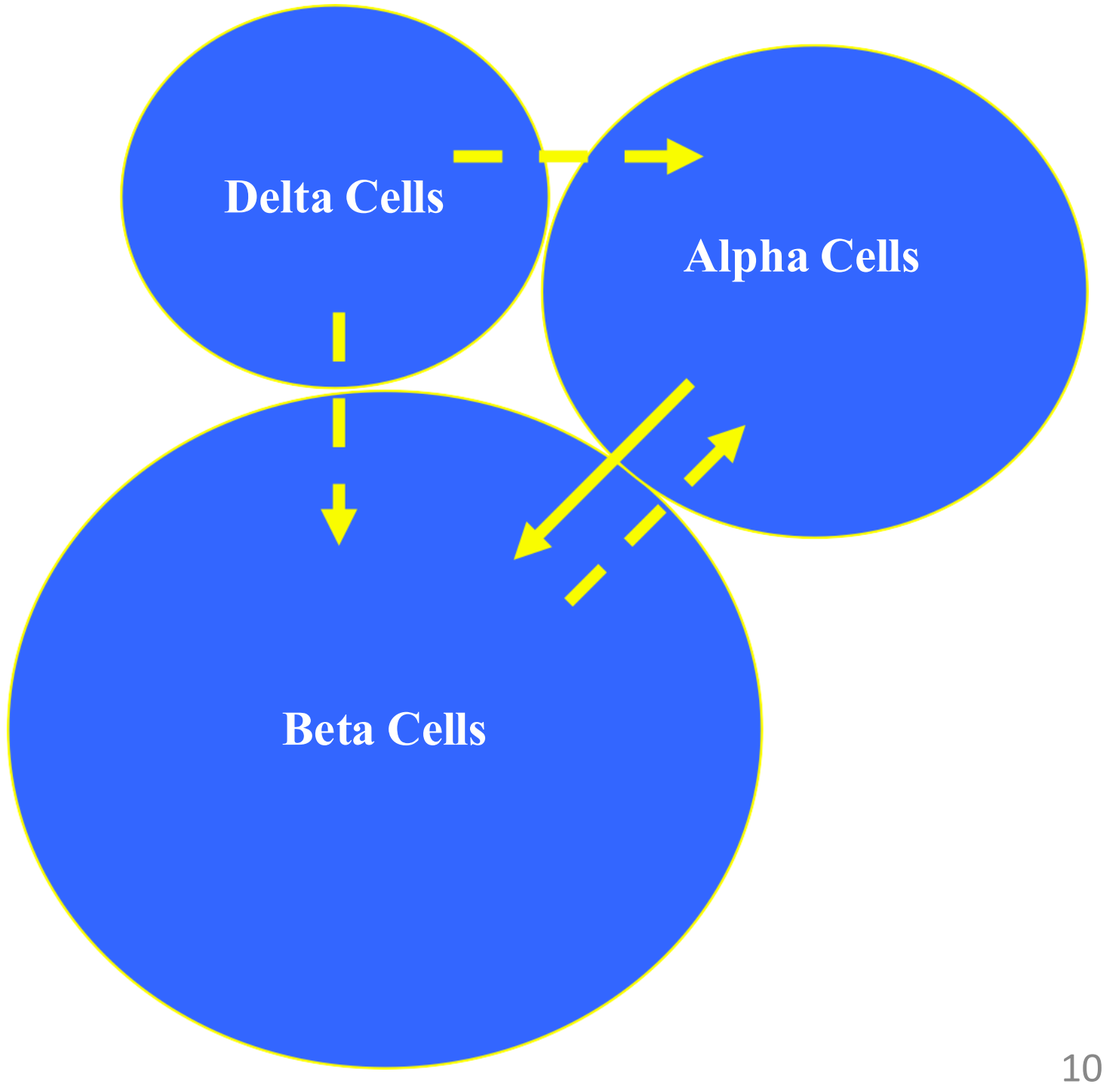
Some patients with insulin deficiency have **reduced** muscle mass because there is **insufficient insulin** to promote the **uptake of amino acids** into cells and to **stimulate protein synthesis**.

Pancreatic Hormones

- The **endocrine** part of the pancreas is responsible for secreting the following hormones:
  - Insulin
  - Glucagon
  - Somatostatin
  - Pancreatic polypeptide

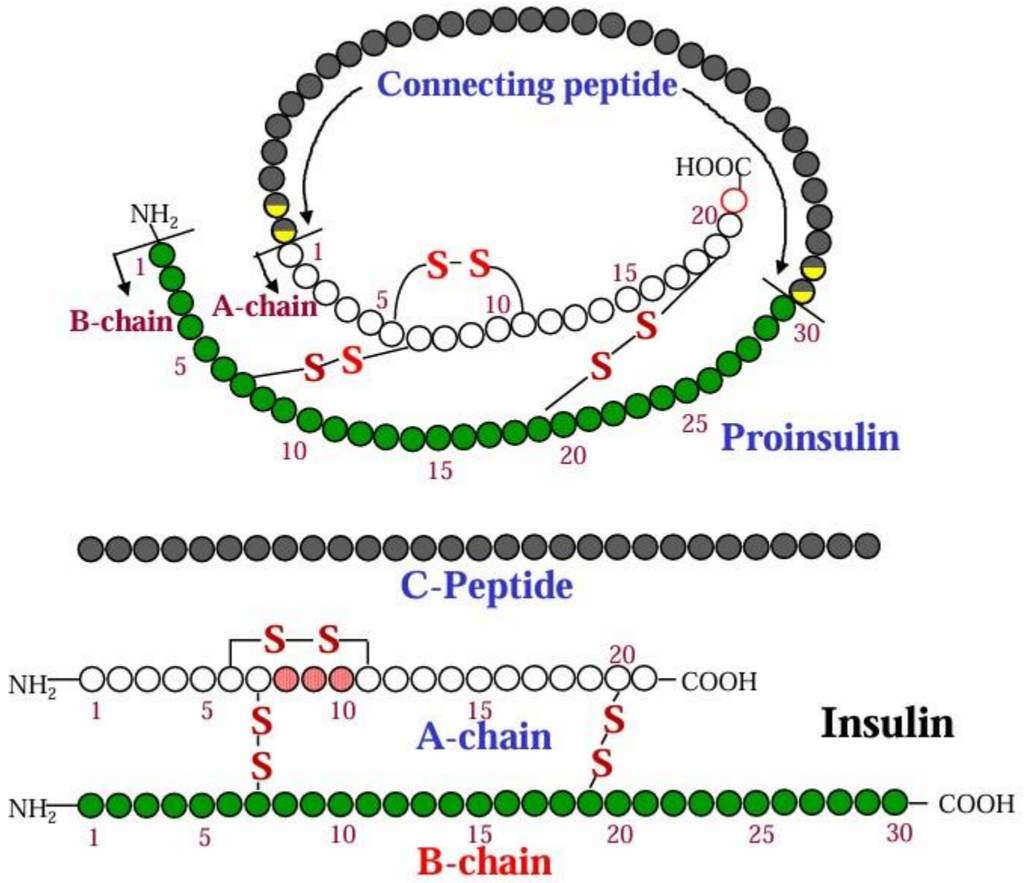
Paracrine Influence of Pancreatic Hormones

- **Delta Cells** (somatostatin–secreting)
  - **Inhibit beta cells** (yellow dashed arrow): Somatostatin **suppresses insulin secretion.**
  - **Inhibit alpha cells** (yellow dashed arrow): Somatostatin **also suppresses glucagon secretion.**
- **Beta Cells** (insulin–secreting)
  - **Inhibit alpha cells** (yellow dashed arrow): Insulin **inhibits glucagon secretion.**
- **Alpha Cells** (glucagon–secreting)
  - **Activate beta cells** (solid arrow): Glucagon **stimulates insulin secretion.**



Processing of Proinsulin

- Insulin is a peptide it form as proinsulin(large protein) break down into insulin and c– peptide has alpha(200AA) and beta subunit (30AA) they connect by disulphide bond.
- After the cleavage of the **connecting (C) peptide**, both insulin and **C-peptide** are secreted in **equal concentrations.**
- This makes it possible to assess **endogenous insulin secretion** by measuring **C-peptide levels**, since **exogenous insulin lacks C-peptide.**

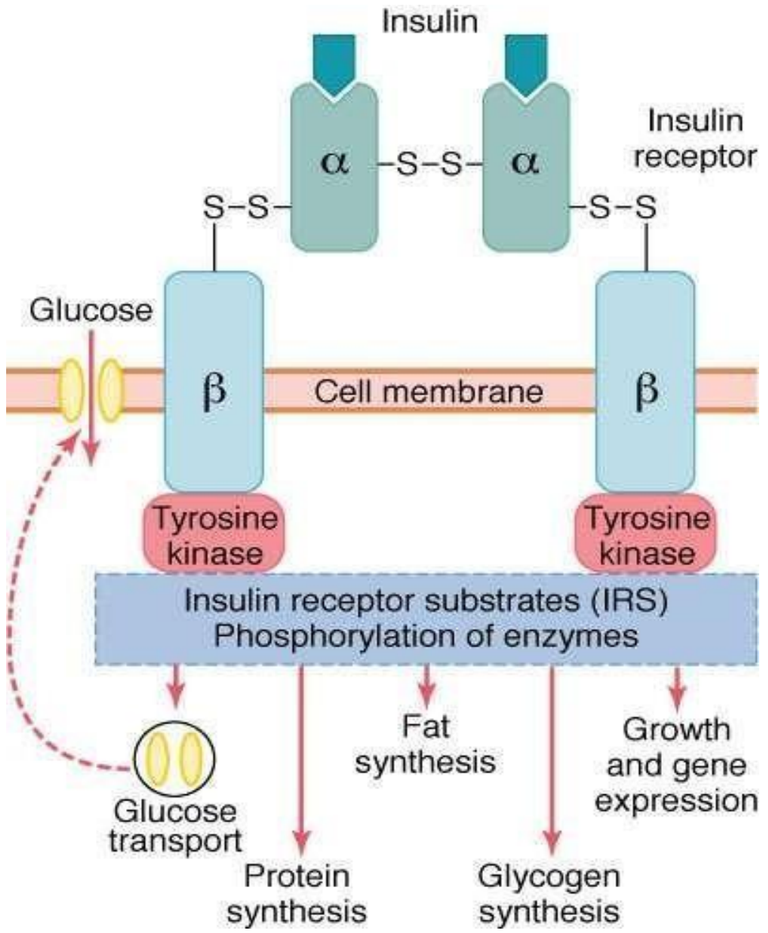


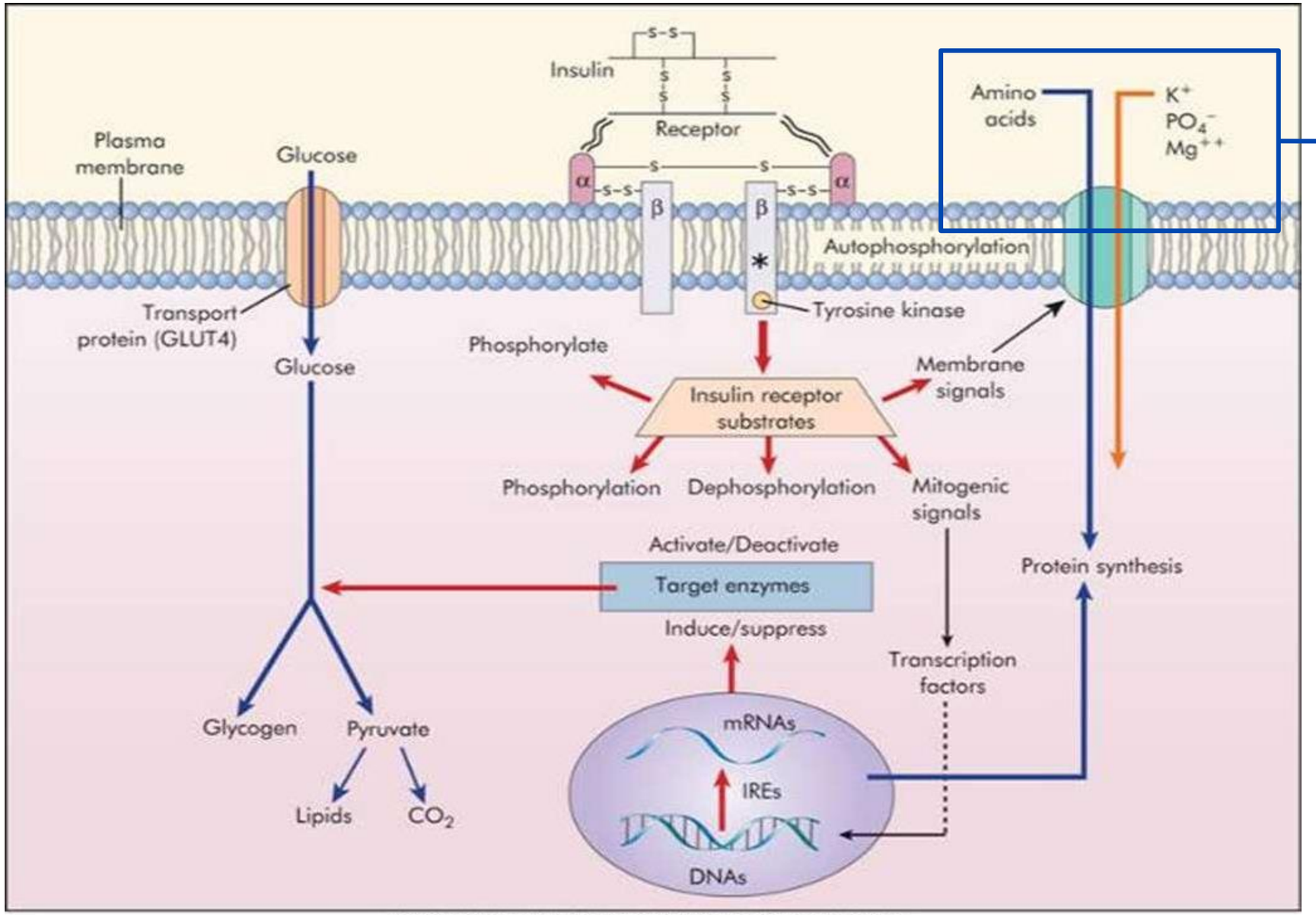
Tyrosine Kinase

- Insulin receptor consists of 2 units that dimerize when they bind with insulin.
  - Insulin binds to ligand–binding site on plasma membrane **on alpha subunit** , activating enzymatic site **bata subunit** in the cytoplasm.
- Autophosphorylation occurs **(Change activity of enzyme (activate,deactivate))**, increasing tyrosine kinase activity.
- Activates signaling molecules.
  - Stimulate glycogen, fat and protein synthesis.
  - Stimulate insertion of GLUT-4 carrier proteins.

The Insulin Receptor & Mechanisms of Insulin Action

- Insulin binds to the **α-subunits** of the insulin receptor (**outside the cell**).
- This activates the **β-subunits** (**inside the cell**), which **have tyrosine kinase activity**.
- The receptor **autophosphorylates** and phosphorylates **Insulin Receptor Substrates (IRS).**
- This triggers a signaling cascade that leads to:
  - ↑ **Glucose transporter insertion into cells (glucose uptake)**
  - ↑ **Protein synthesis**
  - ↑ **Fat synthesis**
  - ↑ **Glycogen synthesis**
  - ↑ **Growth and gene expression**





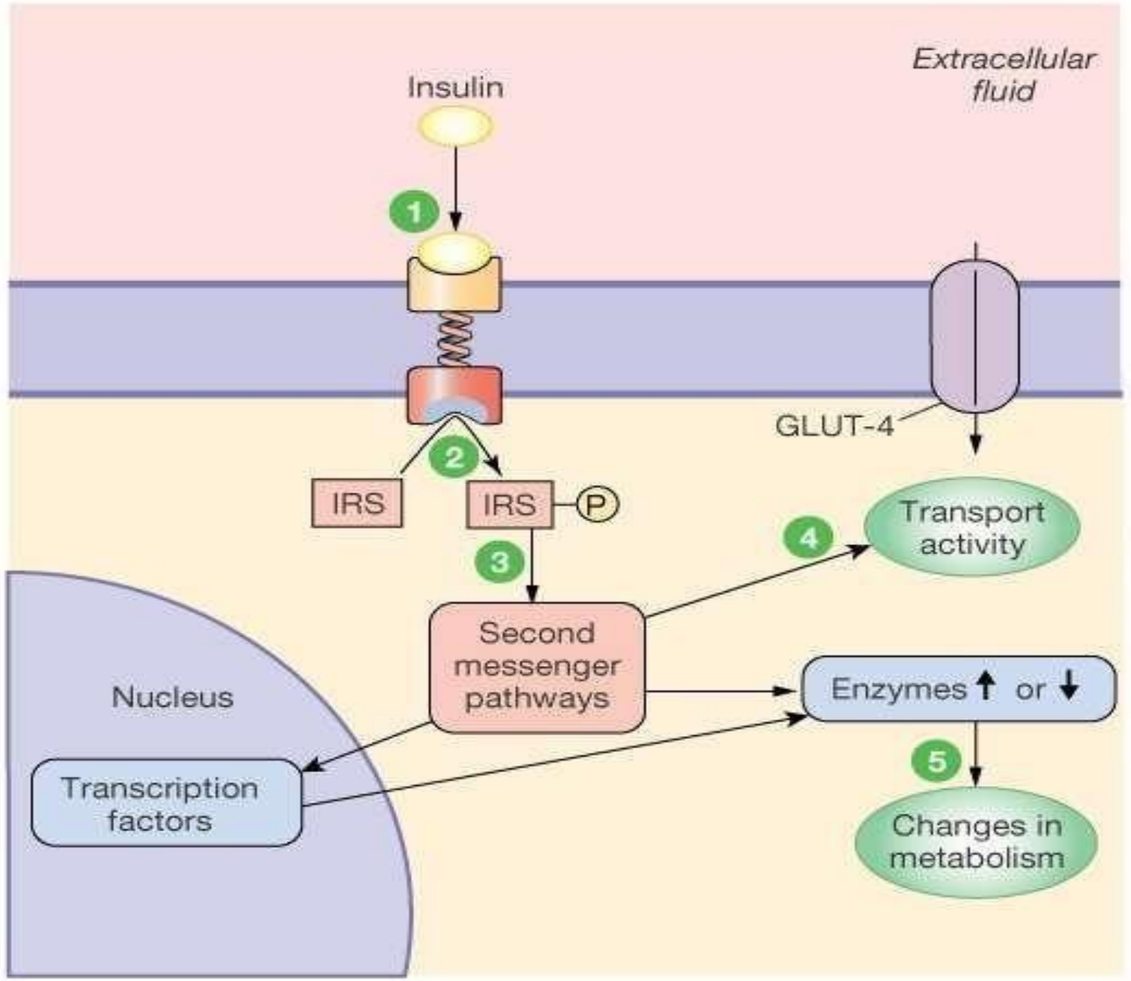
From Berne RM, Levy MN. *Principles of physiology*. ed 3, St Louis, 2000, Mosby.

In **hyperkalemia**, doctors sometimes give **insulin (along with glucose)** to **promote potassium uptake from the blood into cells.**

Explanation of the previous figure

- When **Insulin Receptor Substrates (IRS)** are phosphorylated, they trigger **intracellular signaling** that leads to:
  - ↑ **GLUT4 translocation** to the membrane, causing ↑ **glucose uptake**
- Glucose is used for:
  - ↑ **Glycogen synthesis**
  - ↑ **Pyruvate production**, which is either **used in lipid synthesis** or **converted to CO_2**
- **Activation or inhibition of target enzymes** through **phosphorylation** or **dephosphorylation**
- **Activation of transcription factors** that:
  - ↑ or ↓ **gene expression**
  - **Bind to Insulin Response Elements (IREs)** on DNA
  - ↑ **mRNA synthesis**, leading to **protein synthesis** (e.g. enzymes, receptors)
- **Amino acids** also enter the cell and are used for **protein synthesis**
- **Minerals** (e.g., K^+, PO_4^{3-}, Mg^{2+}) are transported into cells under **insulin's effect**

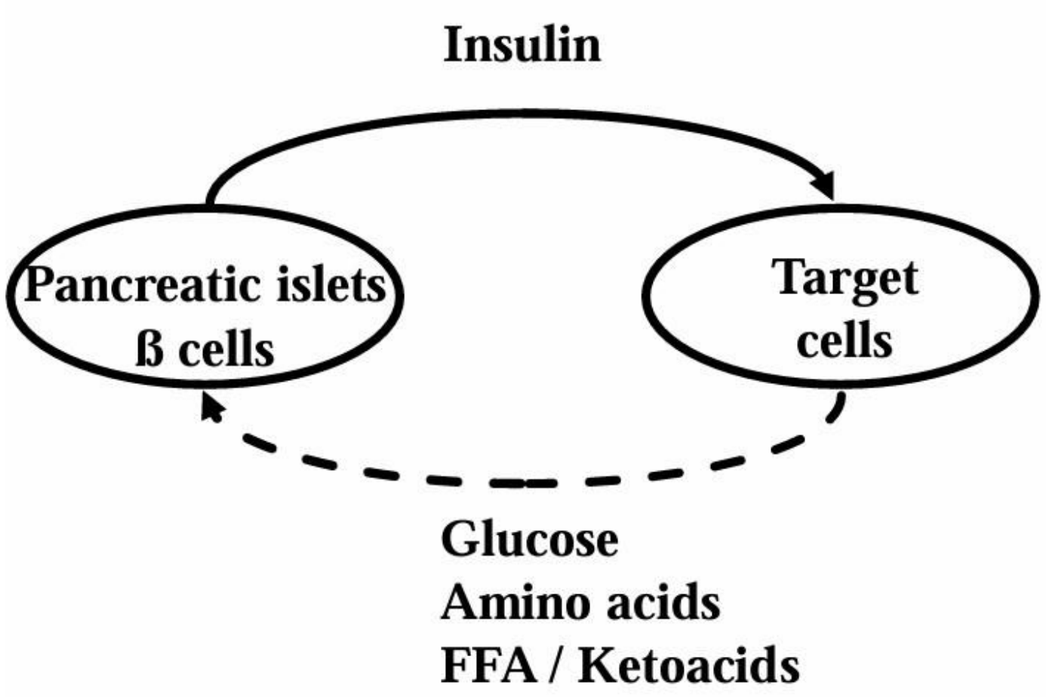
Insulin Action on Cells



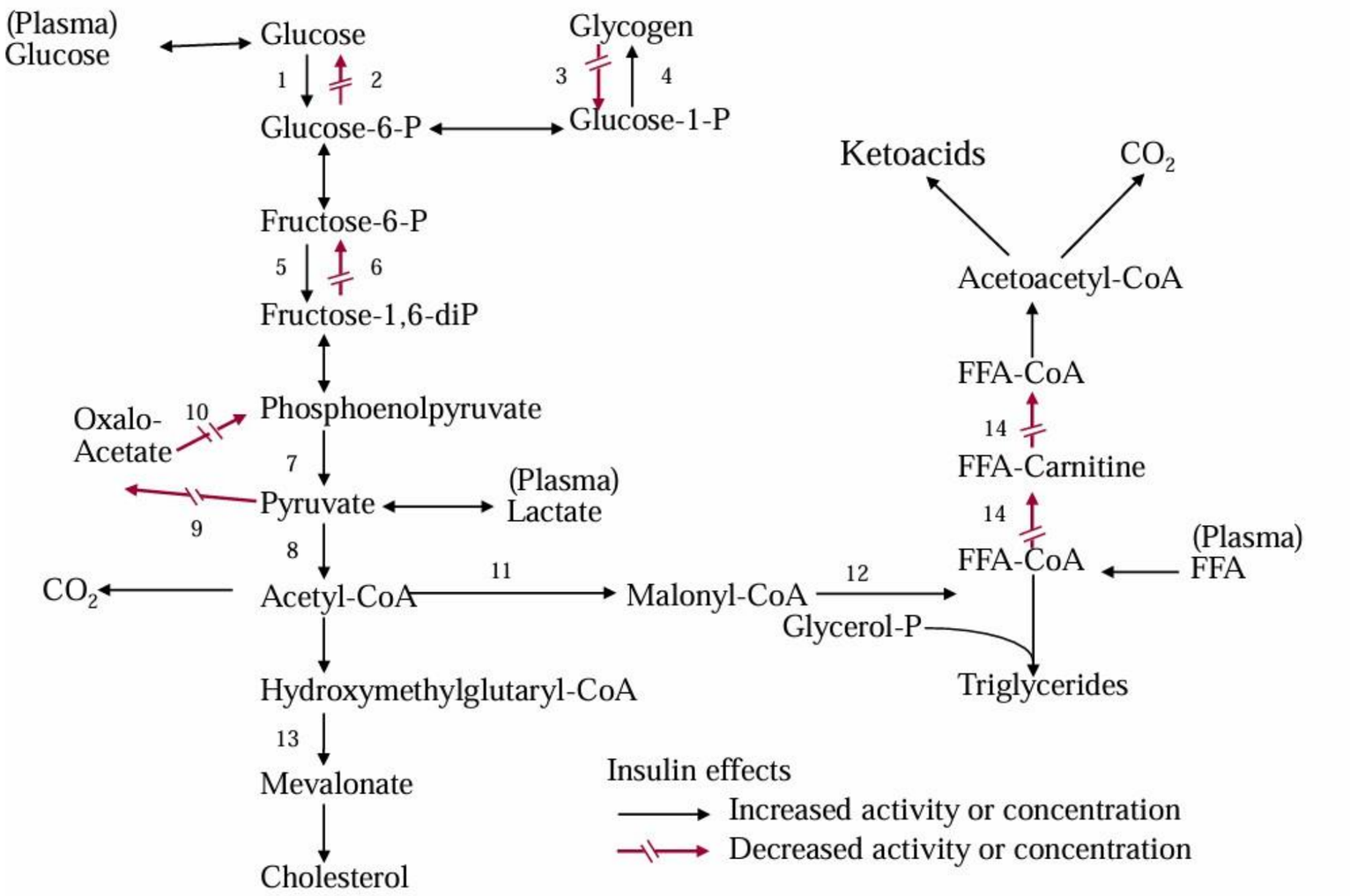
1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
3. Second messenger pathways alter protein synthesis and existing proteins.
4. Membrane transport is modified.
5. Cell metabolism is changed.

Metabolic Control by Insulin

- Insulin stimulates the cellular uptake of **glucose, amino acids, and free fatty acids**, and **inhibits ketone body production**.
- As the plasma concentrations of these molecules decrease, this provides **negative feedback** that reduces further insulin secretion.
- In diabetic patients, **insulin deficiency** leads to **increased lipolysis and ketogenesis**, which can result in **ketoacidosis.**



Insulin Actions on Glucose and Fatty Acid Metabolism in the Liver



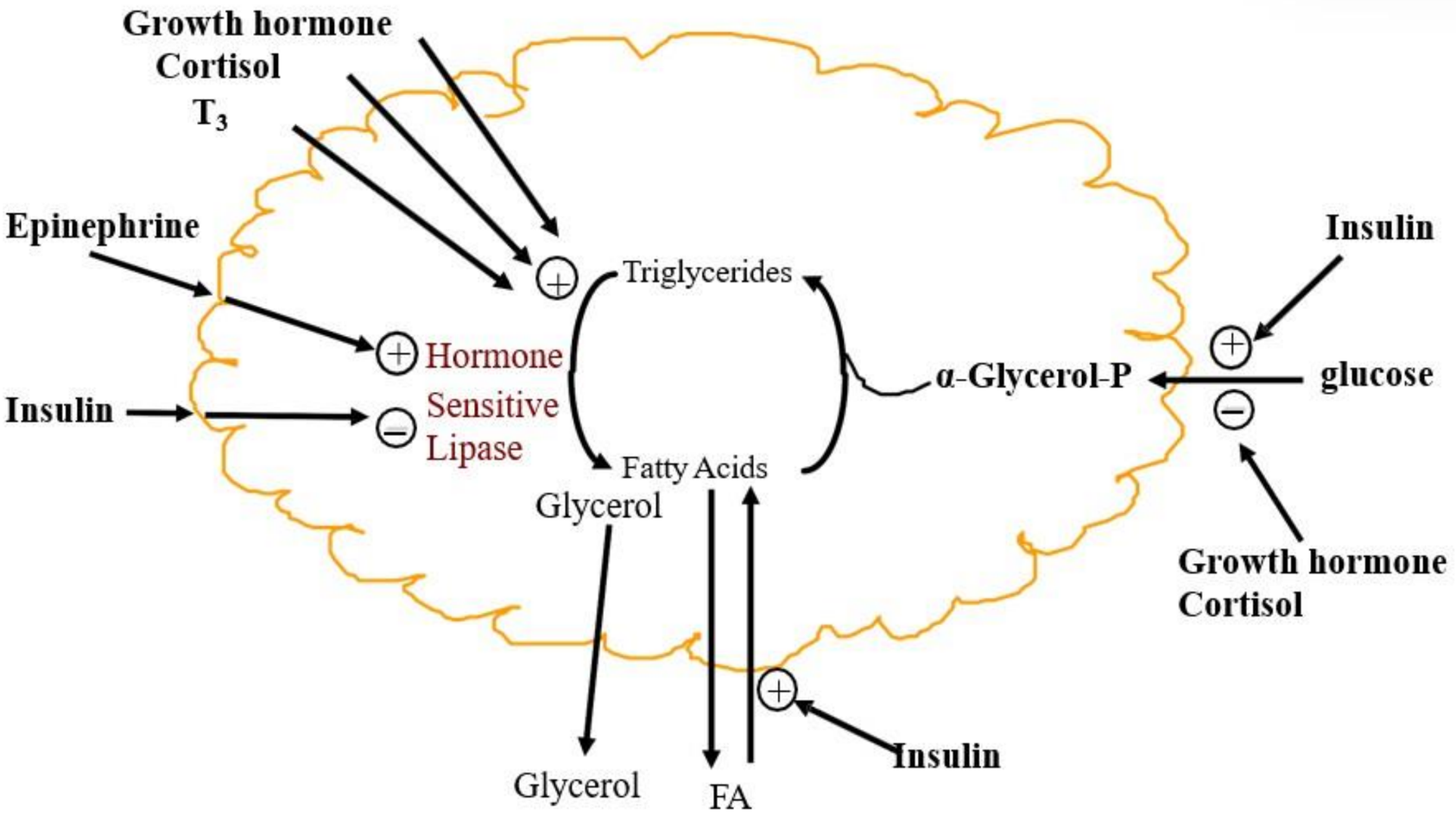
Not For Memorization

Key Enzymes Influenced by Insulin

activated or deactivated

1. Glucokinase
2. Glucose-6-phosphatase
3. Phosphorylase
4. Glycogen synthase
5. Phosphofructokinase
6. Fructose-1,6- diphosphatase
7. Pyruvate kinase
8. Pyruvate dehydrogenase
9. Pyruvate carboxylase
10. Phosphoenolpyruvate carboxykinase
11. Acetyl-CoA carboxylase
12. Fatty acid synthase
13. Hydoxy-methylglutaryl-CoA reductase
14. Carnitine acyltransferase

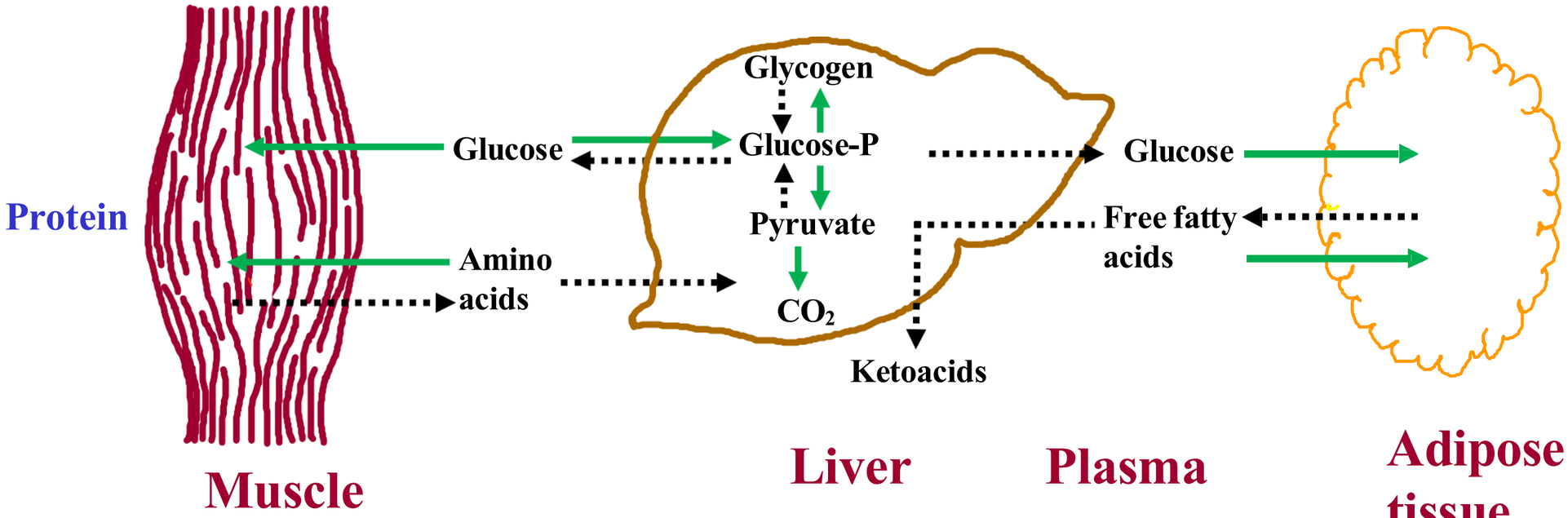
Hormonal Effects on FFA Production in Adipose Tissue



Hormonal Regulation of Triglyceride Metabolism in Adipose Tissue

- Triglycerides are stored in adipose tissue and can be broken down into **fatty acids and glycerol** by **Hormone Sensitive Lipase (HSL).**
  - **HSL is activated by**: epinephrine, growth hormone, cortisol, and T_3
  - **HSL is inhibited by**: insulin
- **Insulin promotes fat storage by**:
  - Enhancing the **uptake of fatty acids and glycerol** into adipose tissue
  - Stimulating the conversion of **glucose to α-glycerol phosphate** (via glycolysis), which is required for **triglyceride synthesis**
- **Growth hormone and cortisol**:
  - **Inhibit glucose uptake**, decreasing **α-glycerol phosphate formation**, and thereby **reducing triglyceride synthesis**
  - **Stimulate lipolysis** through **HSL activation**
- **Note:**
  - Glucose–derived **dihydroxyacetone phosphate (DHAP)** is converted to **α-glycerol phosphate**, which combines with fatty acids to form triglycerides —a process **promoted by insulin** and **inhibited by growth hormone and cortisol.**

Metabolic Effects of Insulin



↓ Glucose
↓ Free fatty acids
↓ Ketoacids
↓ Amino acids

Effects of Insulin on Different Tissues

- **In Muscle Tissue:**
  - Insulin stimulates **glucose uptake**
  - Insulin promotes **amino acid uptake**, leading to **protein synthesis**
  - Result: ↓ **plasma amino acid** levels
- **In the Liver:**
  - Insulin stimulates **glucose uptake & storage as glycogen**
  - Insulin **inhibits fatty acids breakdown**, reducing **ketoacid production**
  - **Inhibits amino acid uptake**
  - Result: ↓ **plasma glucose** and ↓ **ketoacid** levels
- **In Adipose Tissue:**
  - Insulin promotes **glucose uptake**
  - Insulin **stimulates fat storage** and **inhibits fat breakdown**
  - Result: ↓ **plasma free fatty acid** levels
- **Overall Effect of Insulin on Plasma Levels:**
  - ↓ **Glucose**
  - ↓ **Free fatty acids (because increase uptake of FFA)**
  - ↓ **Ketoacids (because the glucose is low)**
  - ↓ **Amino acids**

Insulin -- Liver

- GLUT2 transporters
- ↑ **Glucokinase** (stimulate glucose uptake into liver for glycogen synthesis)
- ↑ Glycogen
- ↓ Glucose release
  - ↓ **G6Pase**
- ↑ Glycolysis
  - ↑ acetyl CoA, ↑ FA synthesis
- ↑ Triglyceride storage & export (VLDLs)
- ↑ Protein synthesis, ↓ protein degradation

Insulin -- Adipocytes

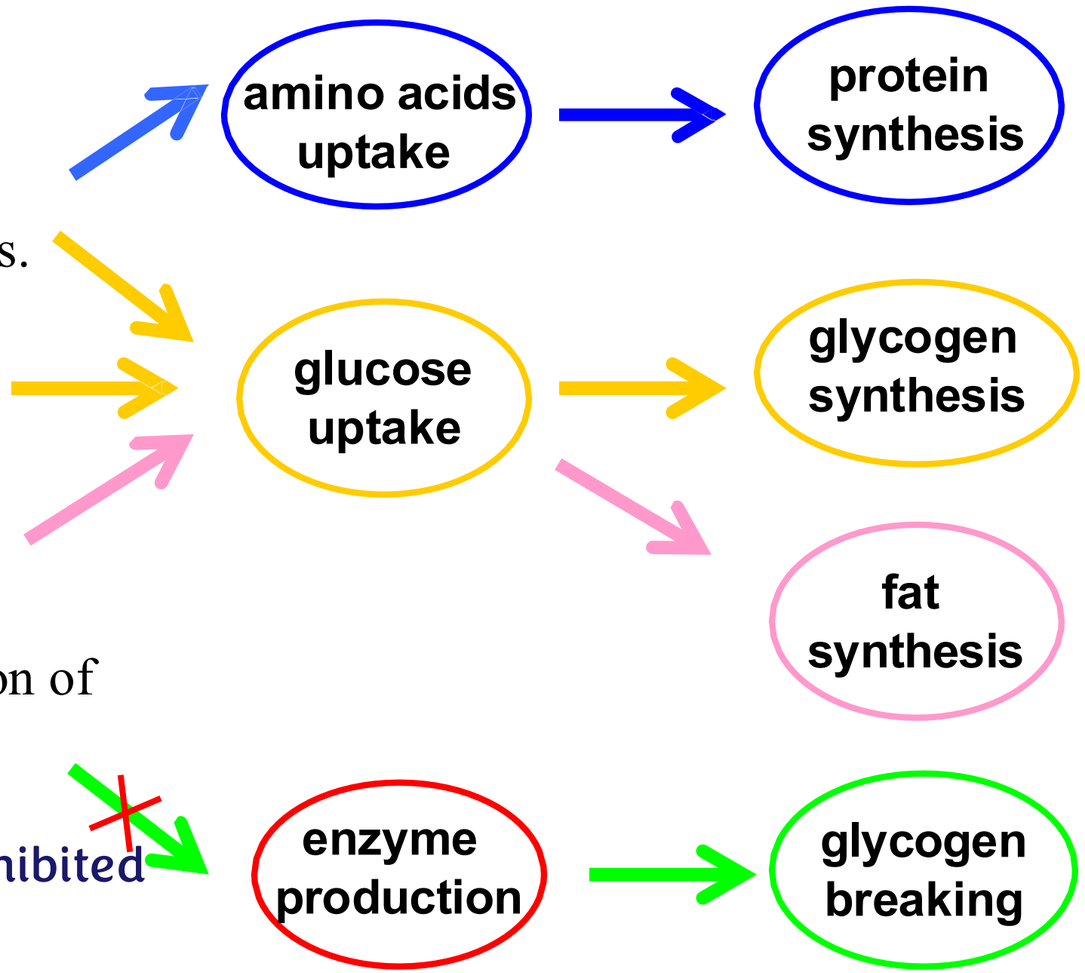
- ↑ GLUT4 transporters
- ↑ Glycolysis
  - ↑ α-glycerol phosphate
  - ↑ acetyl CoA, ↑ FA synthesis
- ↑ Triglycerides
  - ↓Hormone sensitive lipase **to prevent break down of fat**
  - ↑ Lipoprotein lipase
  - بكسرtriglycerides in chylomicrons then re enter the adipose tissue and **reform the triglycerides**

Insulin -- Muscle

- ↑ GLUT4 transporters
- ↑ Glycogen **the storage form of energy**
- ↑ Glycolysis
- ↑ Protein synthesis, ↓protein degradation
- ↑ Triglycerides (FA's from circulation

Insulin affects many organs:

- It stimulates skeletal muscle fibers.
- It stimulates liver cells.
- It acts on fat cells

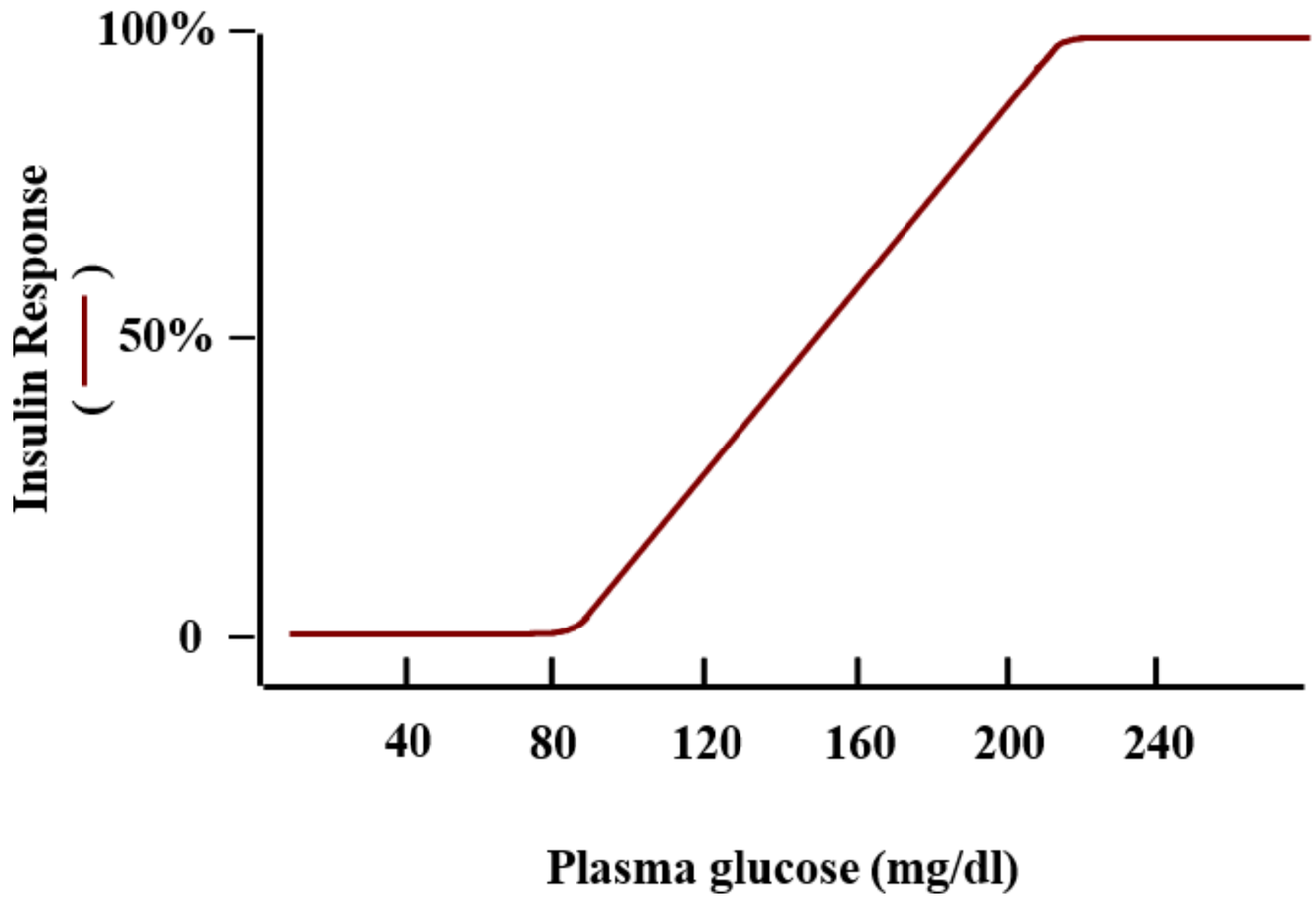


- It inhibits production of certain enzymes.
- Ex: Glycogen phosphorylase inhibited

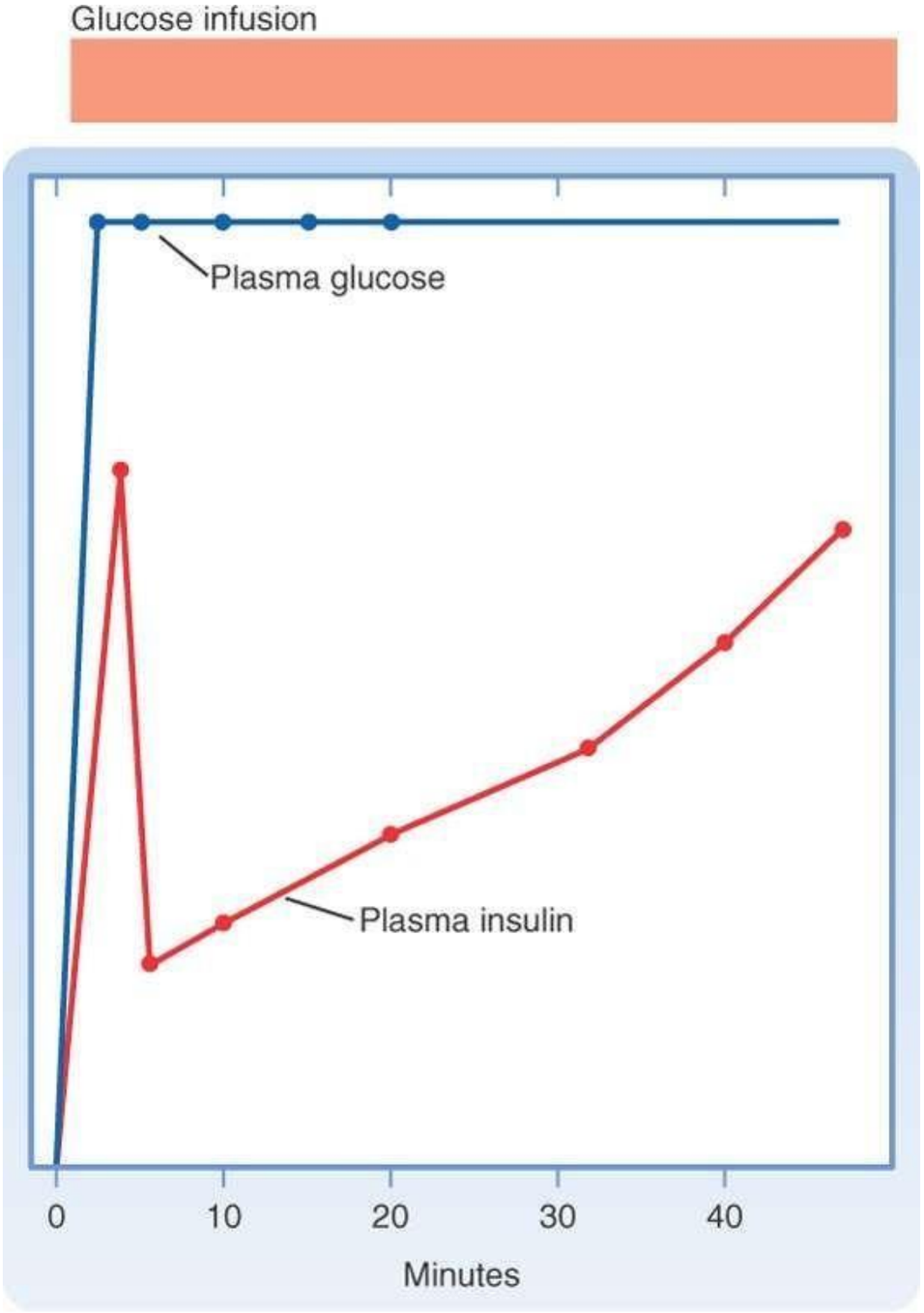
In each case, insulin triggers these effects by binding to the insulin receptor.

Blood [Glucose] & Insulin Secretion

Whenever plasma **glucose increases** (main stimulus), insulin secretion increases



- **Insulin** (red line) responds in **two distinct phases**:
  - A **sharp initial spike** (**first phase**), representing the release of **pre-stored insulin** synthesized earlier
  - Followed by a **gradual, sustained rise** (**second phase**), due to the secretion of **newly synthesized insulin**



Factors Affecting Insulin Secretion

Stimulation	Inhibition
Glucose Main Stimulus **Mannose** **Galactose** **Amino acids** **Arginine** **Lysine** **Leucine** **Alanine** **Free fatty acids** **Keto acids** **Glucagon (direct and indirect effects : hyperglycaemia-stimulate blood glucose)** **Gastro-intestinal hormones** **Glucagon-like peptide 1 (GLP-1)** **Gastric inhibitory polypeptide (GIP)** **Neural influences** **Vagal activity (acetylcholine)** **β-adrenergic stimulation** **Sulfonylurea drugs** Oral hyperglycaemic drug	**Somatostatin** **Fasting** **Exercise** **Neural influences** **Sympathetic activity-α-adrenergic stimulation** **(□norepinephrine, epinephrine)**

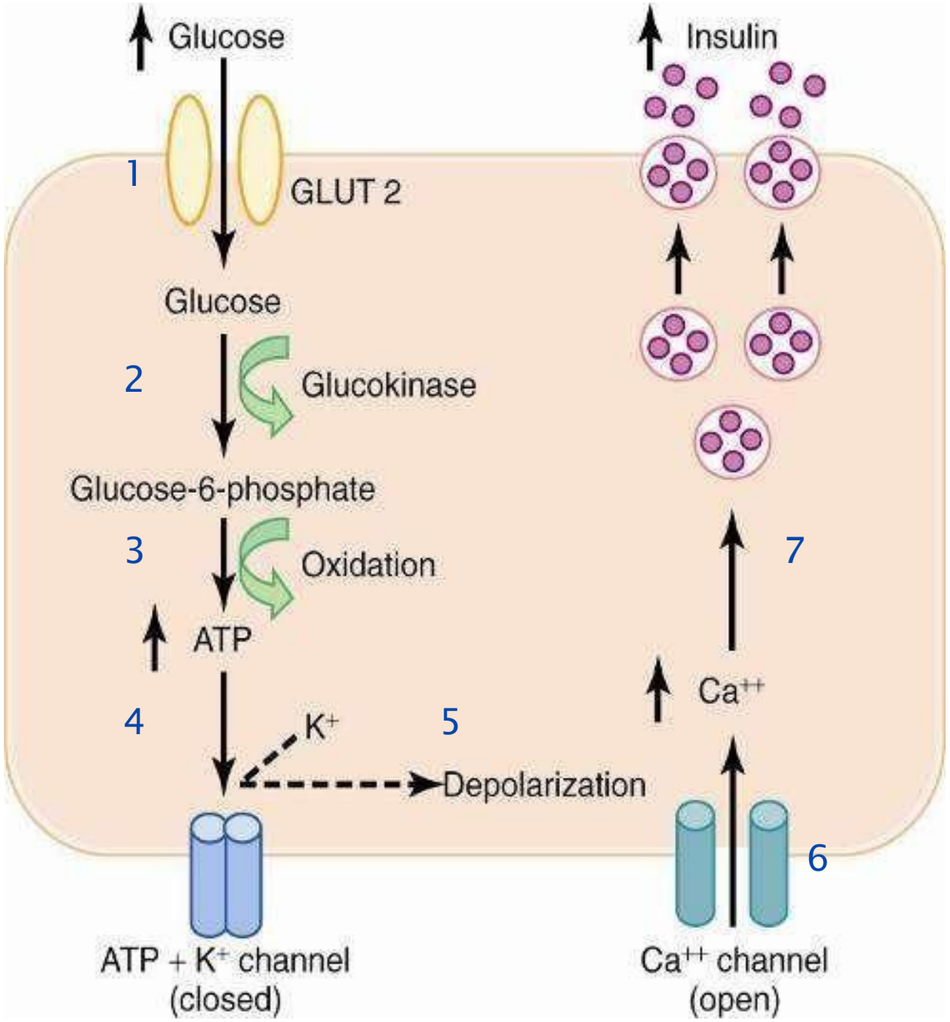
Incretin Hormones

Incretin hormones are **gastrointestinal hormones** that enhance **insulin secretion.**

- **Intestine derived hormones**

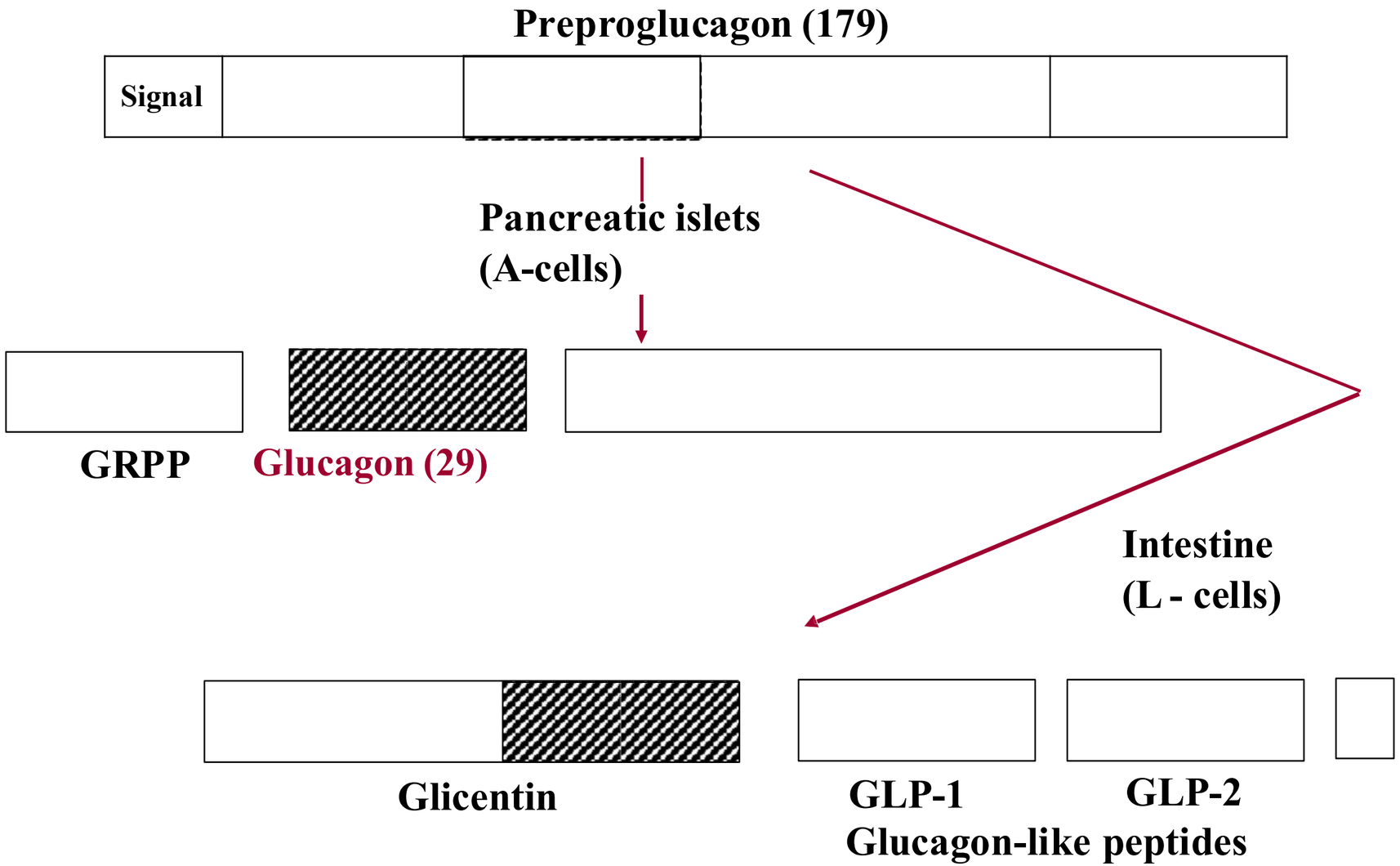
  - GLP-1, GIP
  - short $T_{1/2}$; because they are peptides; not protein bound.
  - secreted in response to GI glucose & fat
- **Simulate insulin secretion (glucose dependent)**
- **Inhibit glucagon secretion**
- **Slow gastric emptying**

Mechanism of Glucose Stimulated Insulin Secretion



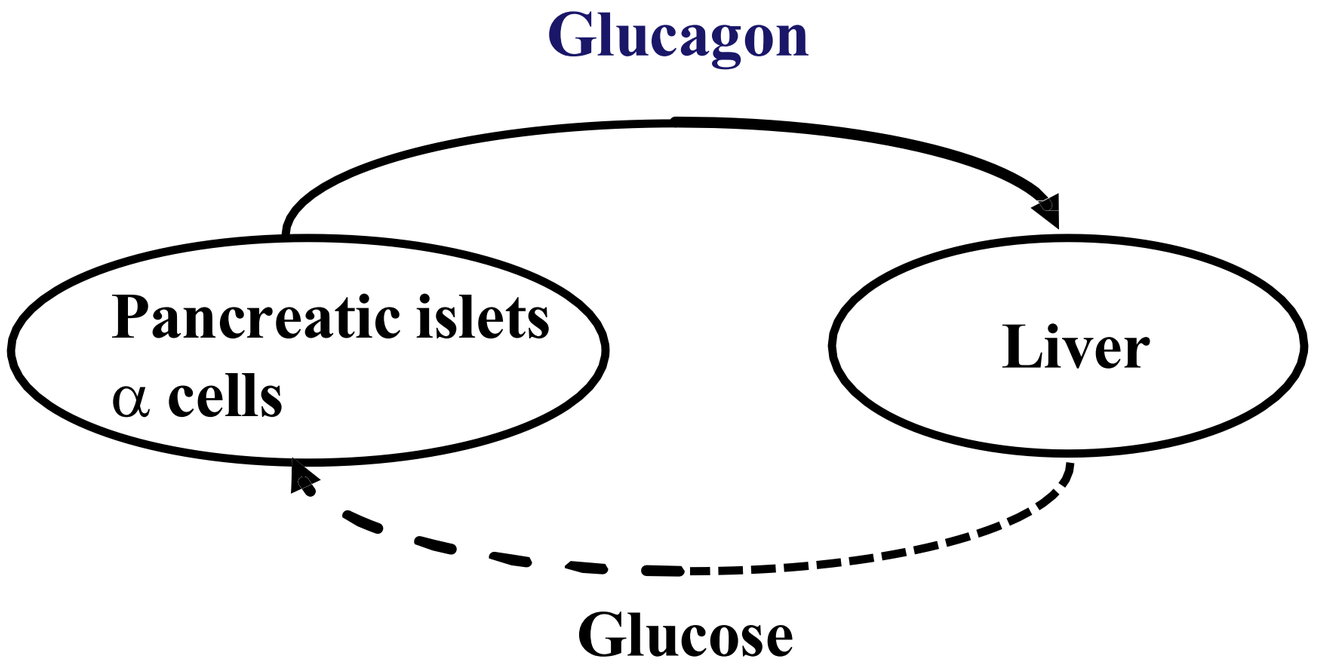
1. **GLUT2** facilitates the **entry of glucose** into pancreatic β-cells
2. **Glucokinase** converts glucose into **glucose-6-phosphate (G6P)**
3. **G6P is oxidized** to produce **ATP**
4. A high **ATP/ADP ratio** causes **ATP-sensitive K^+ channels to close**
5. This leads to **membrane depolarization**
6. Voltage–gated **Ca^{2+} channels open**
7. The **influx of Ca^{2+}** triggers the **exocytosis of insulin-containing granules**

Processing of Preproglucagon

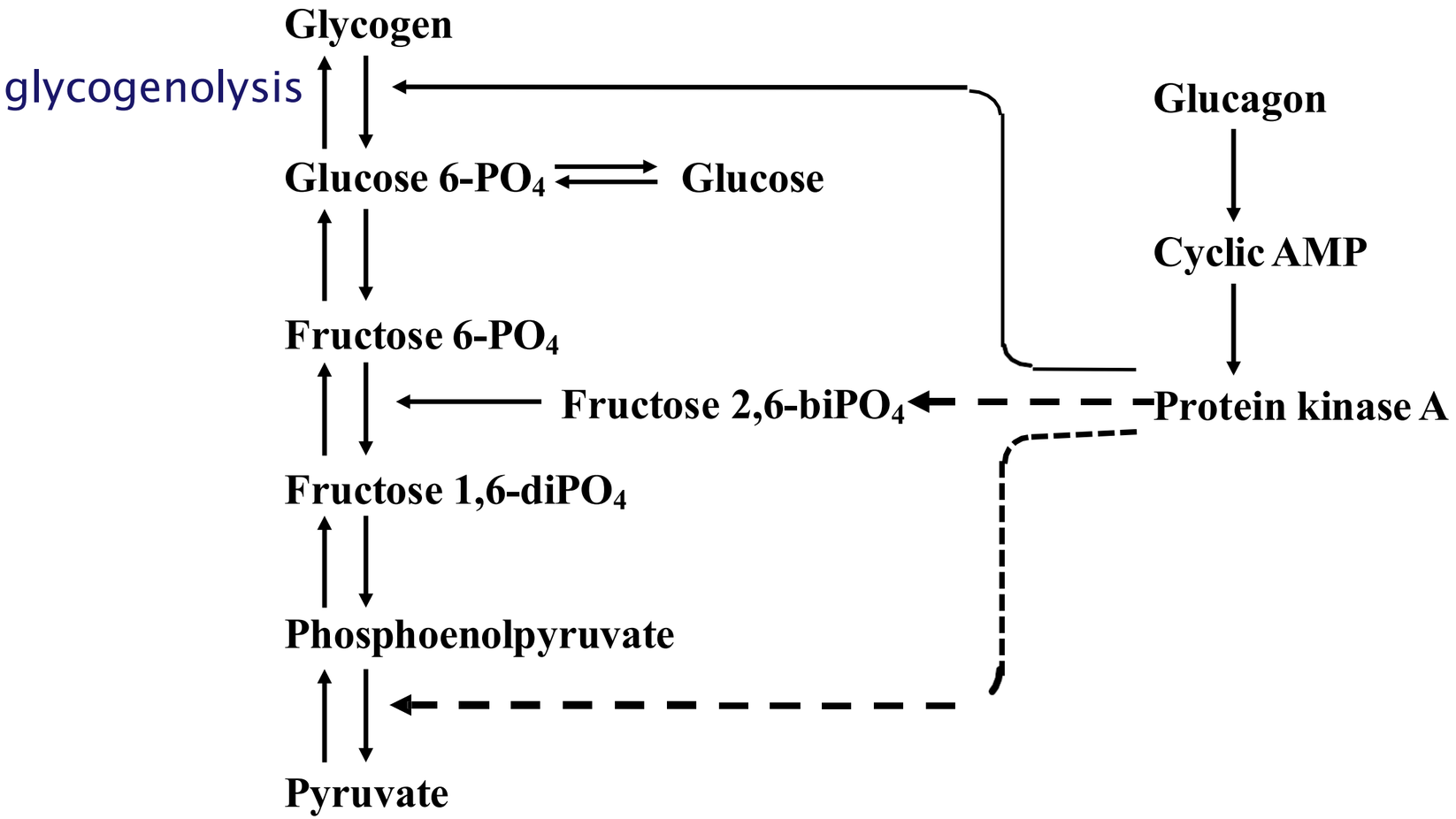


Metabolic Control by Glucagon

Glucagon is a hormone that **increases blood glucose levels** when **blood glucose levels decrease.**



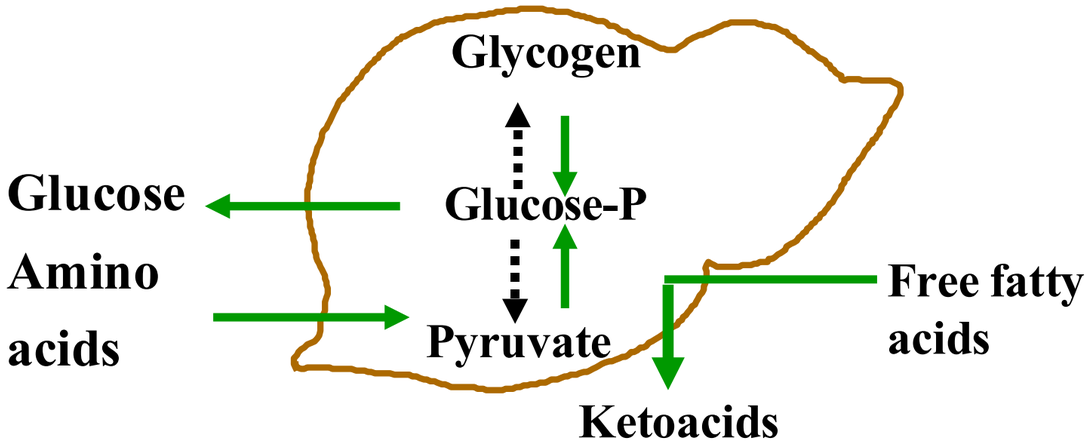
Effects of Glucagon on Glucose Output by Liver



Glucagon works via a **G-protein-coupled receptor**

Metabolic Effects of Glucagon

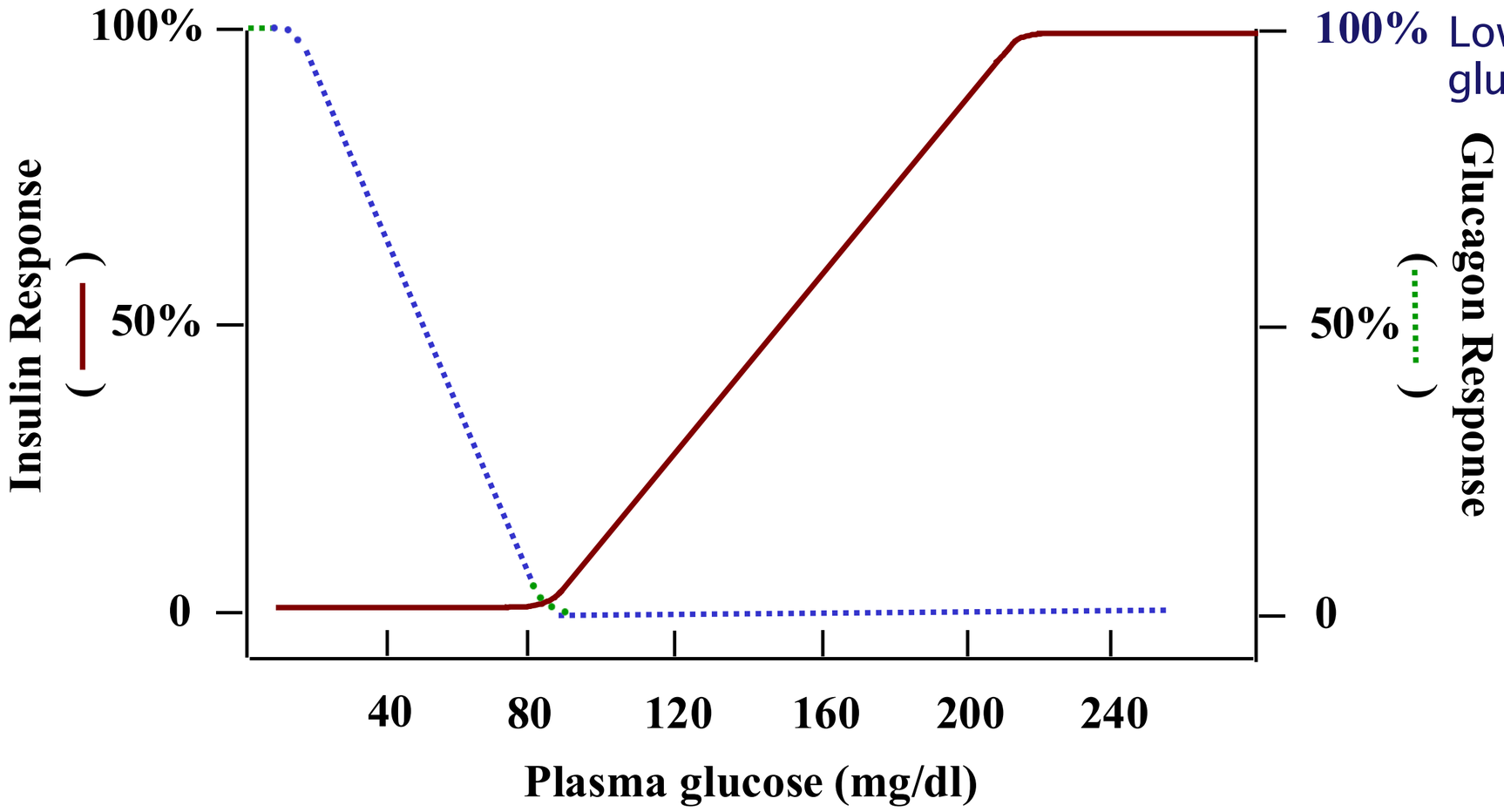
Glucagon increases hepatic amino acid uptake, providing substrates for **gluconeogenesis.**



Blood [Glucose] & Secretion of Insulin & Glucagon

High glucose → high insulin secretion

Low glucose → high glucagon secretion



Factors Affecting Glucagon Secretion

Stimulation	Inhibition
Hypoglycemia Amino acids Arginine Alanine Gastrointestinal hormones Cholecystokinin (CCK) Gastrin Fasting Exercise Neural influences Vagal activity-acetylcholine Sympathetic activity- β-adrenergic stimulation (norepinephrine, epinephrine)	• Glucose • Somatostatin • Insulin (direct effect) Gastrointestinal hormones • Secretin • Glucagon-like peptide-1 (GLP-1) • Free fatty acids • Ketoacids • Neural influences • α-adrenergic stimulation

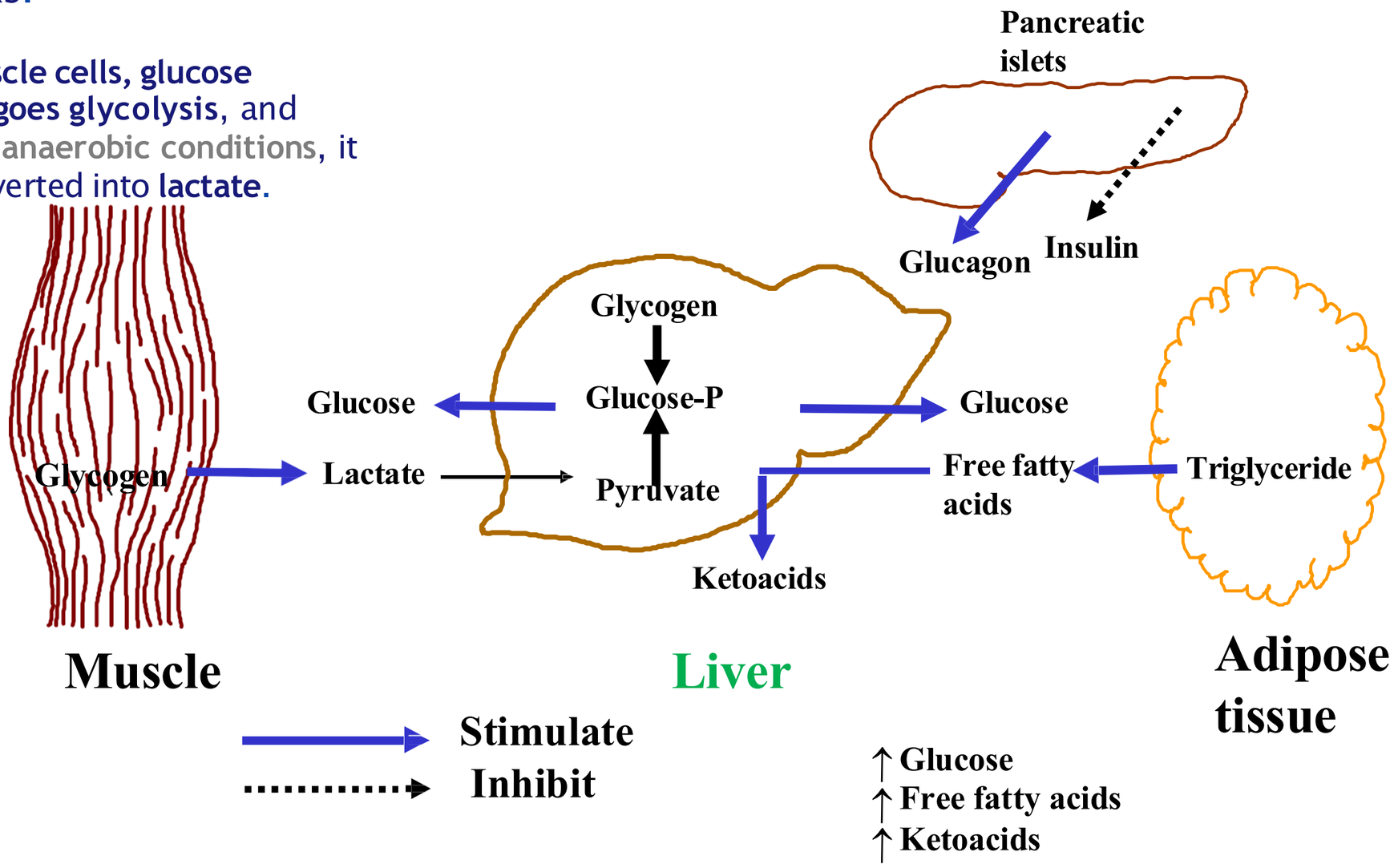
Fuel Metabolism in Anabolic & Catabolic States

State	Hormones	Fuel Source	Process
Anabolism	↑ Insulin ↓ Glucagon	Diet	Glycogen Synthesis Triglyceride Synthesis Protein Synthesis
Catabolism	↓ Insulin ↑ Glucagon	Storage Depots	Glycogenolysis Lipolysis Proteolysis Ketogenesis

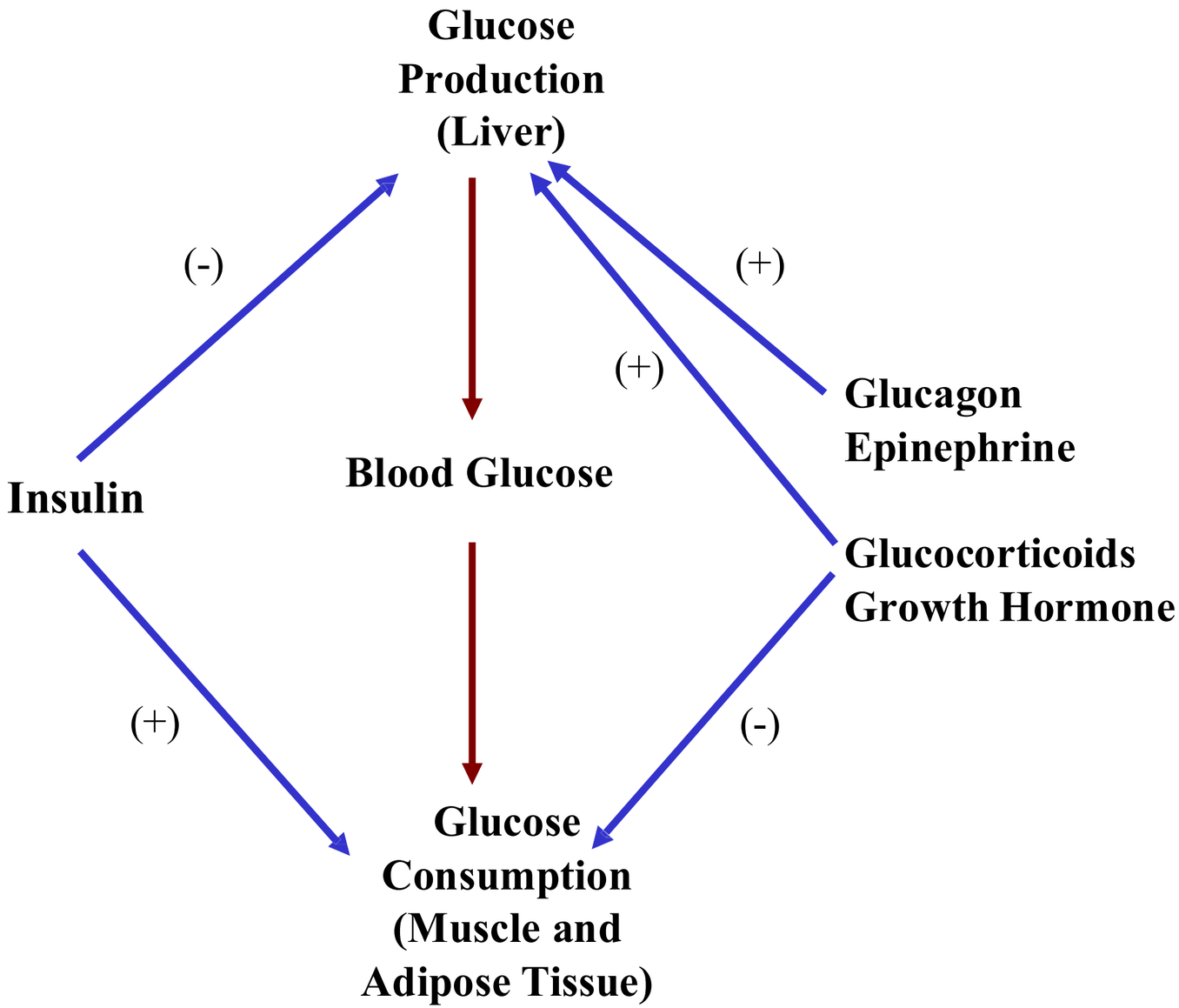
Metabolic Effects of Epinephrine

Epinephrine binds to GPCRs.

In muscle cells, glucose undergoes glycolysis, and under **anaerobic conditions**, it is converted into **lactate**.



Hormonal Interactions in the Maintenance of Blood [Glucose]



Hormonal Interactions in the Maintenance of Blood [Glucose]

- **Glucocorticoids** and **Growth Hormone decrease glucose uptake** by **muscle and adipose tissue**
- **Insulin**, in contrast, **increases glucose uptake** in these tissues
- **Glucagon** stimulates **glycogenolysis** (glycogen breakdown)
- **Insulin** stimulates **glycogenesis** (glycogen formation)
- **Glucocorticoids:**
  - **Cortisol** is a **steroid hormone** whose receptor is **intracellular** (in the cytoplasm).
  - It works through a **different mechanism than glucagon** (not via G–protein or cAMP).
  - **Cortisol increases blood glucose** mainly by promoting **glycogen breakdown.** Do your own research
  - It also supports **protein catabolism** and **lipolysis** to supply substrates for glucose production.
- **Hormones Secreted by the Adrenal Cortex:**
  - **Glucocorticoids** (e.g., cortisol): regulate **blood sugar**, **metabolism**, and **immune response**
  - **Mineralocorticoids** (e.g., aldosterone): regulate **blood pressure** by controlling **sodium and water balance**
  - **Androgens**: small amounts of **sex hormones** (e.g., testosterone)

Responses to Decreasing Plasma [Glucose]

Plasma glucose concentration (mg/dl)	Hormonal responses	CNS responses
90		
80-85	↓ Insulin	
65-70	↑Glucagon	↓Brain glucose uptake
65-70	↑ Epinephrine	
65-70	↑Cortisol + GH	
50-55		Symptoms
45-50		↓Cognition
30-35		Coma
20-25		Convulsions
10-15		Permanent brain damage

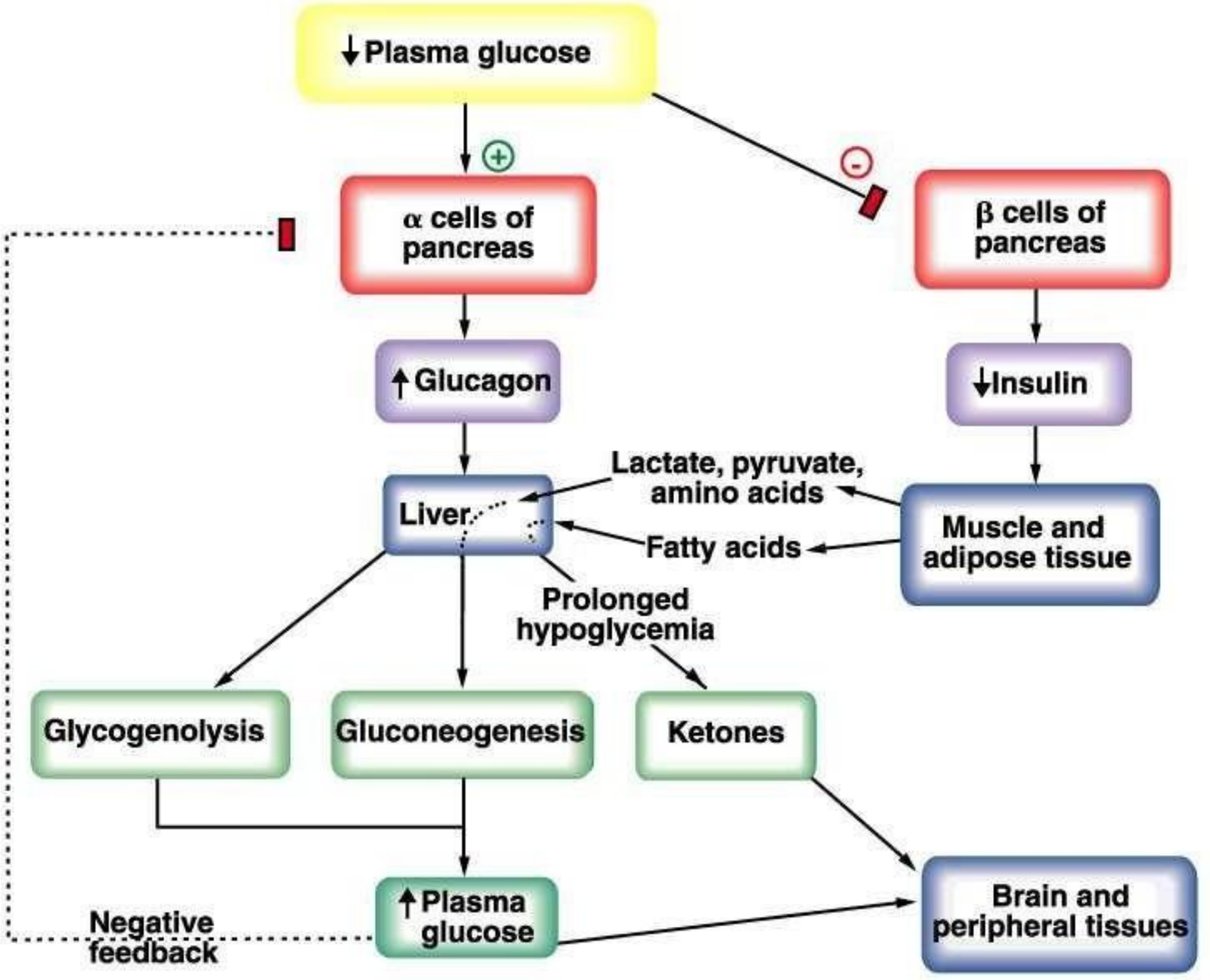
Glucose uptake in the brain is insulin-independent

Plasma Levels of Hormones During Fasting

Sampling time	Glucose mg/dl	Insulin µU/ml, (pM/L)	Glucagon pg/ml, (pM/L)	Cortisol ng/ml	Growth hormone ng/ml	T3, ng/ml	I/G
Postprandial	150	50 (300)	100 (29)		1.9	1.2	10.5
Postabsorptive	90	15 (90)	100 (29)	120		1.15	2.6
Day 1	80	11 (66)	120 (34)	120	5.4	1.15	1.7
Day 3	70	8 (48)	150 (43)	110		0.70	1.1
Day 5	70	7 (42)	150 (43)	110	6.1	0.60	1.0

Not for memorization

Postprandial: after a meal


↓Plasma glucose
α cells of pancreas
β cells of pancreas
↑Glucagon
↓Insulin
Lactate, pyruvate, amino acids
Liver
Fatty acids
Muscle and adipose tissue
Prolonged hypoglycemia
Glycogenolysis
Gluconeogenesis
Ketones
↑Plasma glucose
Negative feedback
Brain and peripheral tissues

- This test is used to evaluate **glucose handling** and diagnose **diabetes mellitus.**
- The patient's **fasting blood glucose** level is measured first.
- The patient then consumes **75 grams of glucose** (oral glucose load).
- **Blood glucose levels are monitored over the next 2 hours.**
- A graph is plotted to show how glucose levels change over time.
- **Interpretation of Results:**
  - **Normal:** Blood glucose rises after ingestion but **returns to normal** (<140 mg/dL) within 2 hours.
  - **Diabetes:** Blood glucose starts high, rises further, and remains high ≥200 mg/dL at 2 hours. It may take more than 5 hours for blood glucose levels to decrease.
  - **Prediabetes (Impaired Glucose Tolerance):** Blood glucose is **140-199 mg/dL at 2 hours**.

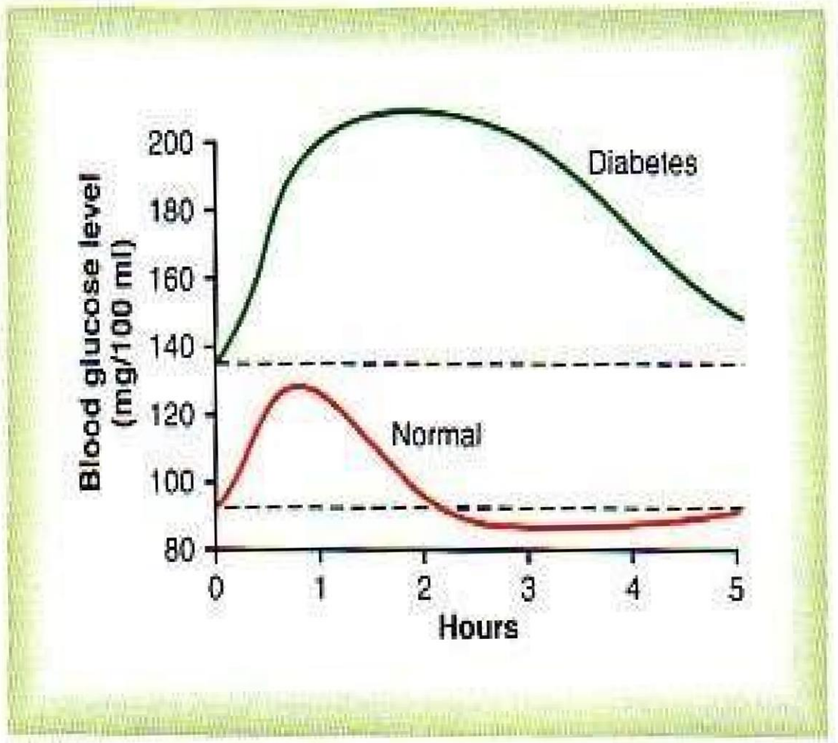


Figure 78–12

Glucose tolerance curve in a normal person and in a person with diabetes.

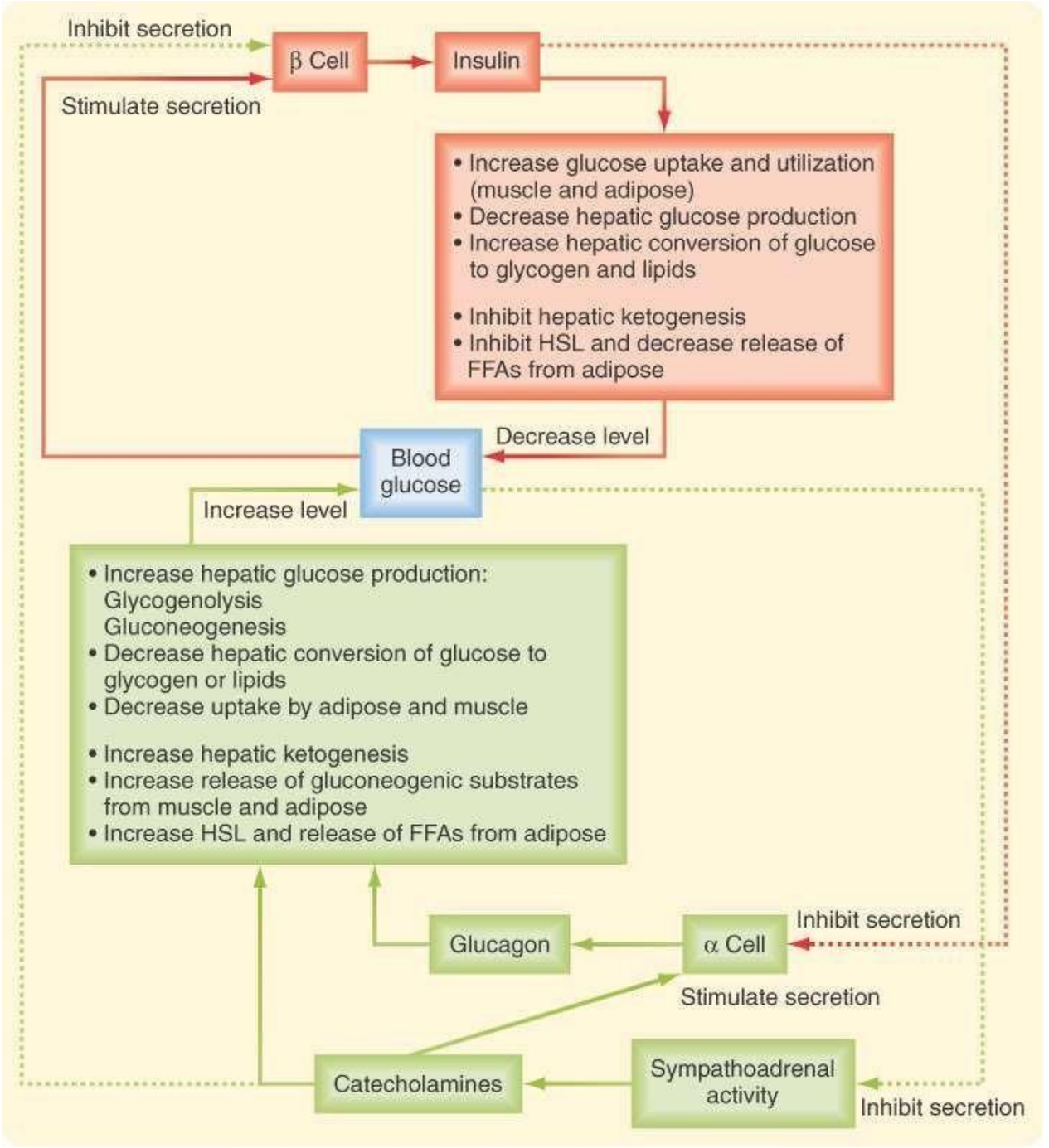
Comparison of Type I and Type II Diabetes

Formerly known as juvenile diabetes

CHARACTERISTIC	TYPE I DIABETES	TYPE II DIABETES
Level of Insulin Secretion	None or almost none	May be normal or exceed normal
Typical Age of Onset	Childhood	Adulthood
Percentage of Diabetics	10–20%	80–90%
Basic Defect	Autoimmune destruction of β cells	Reduced sensitivity of insulin's target cells
Treatment	Insulin injections; dietary management; exercise	Dietary control and weight reduction; exercise; sometimes oral hypoglycemic drugs

Type 1diabetes does not require a family history.

Type 2 diabetes has a strong genetic basis and often runs in families.



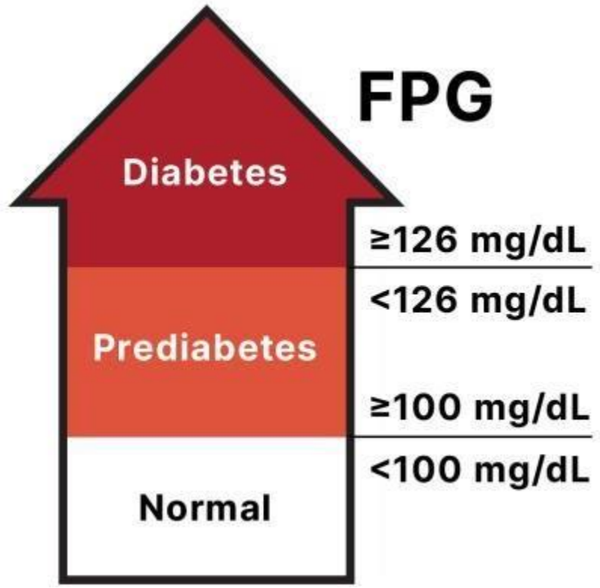
Glucose Homeostasis & Diabetes

	Normal glucose tolerance	Impaired glucose tolerance (prediabetes)	Diabetes
• FPG	<110	110-125	≥126
• 2-h PG (OGTT)	<140	140-199	≥200

FPG (Fasting Blood Glucose)
OGTT (Oral Glucose Tolerance Test)

This is an **extra** and updated table provided by the ADA, because the previous table is outdated.

	Normal Glucose Tolerance	Pre-Diabetes	Diabetes
Fasting Blood Glucose (mg/dL)	<100	100 to <126	≧126
2-hour Blood Glucose (mg/dL) during OGTT	<140	140 to <200	≧200
HbA1c (%)	<5.7	5.7 to <6.5	≧6.5



Consequences of Insulin Deficiency- Diabetes Mellitus

- **Metabolic**
  - Increased blood glucose concentration
  - Increased blood FFA and ketoacid concentration - fat depletion
  - Increased blood amino acid concentration - protein depletion
- **Fluid and Electrolyte**
  - Metabolic acidosis - diabetic ketoacidosis
  - Glycosuria and osmotic diuresis
  - Increased osmolality
  - Hyperphagia
  - Polydipsea
  - Hypovolemia and hypotension
  - Coma and death

Physiology Quiz 6

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			