Insulin, Glucagon, and Diabetes Mellitus

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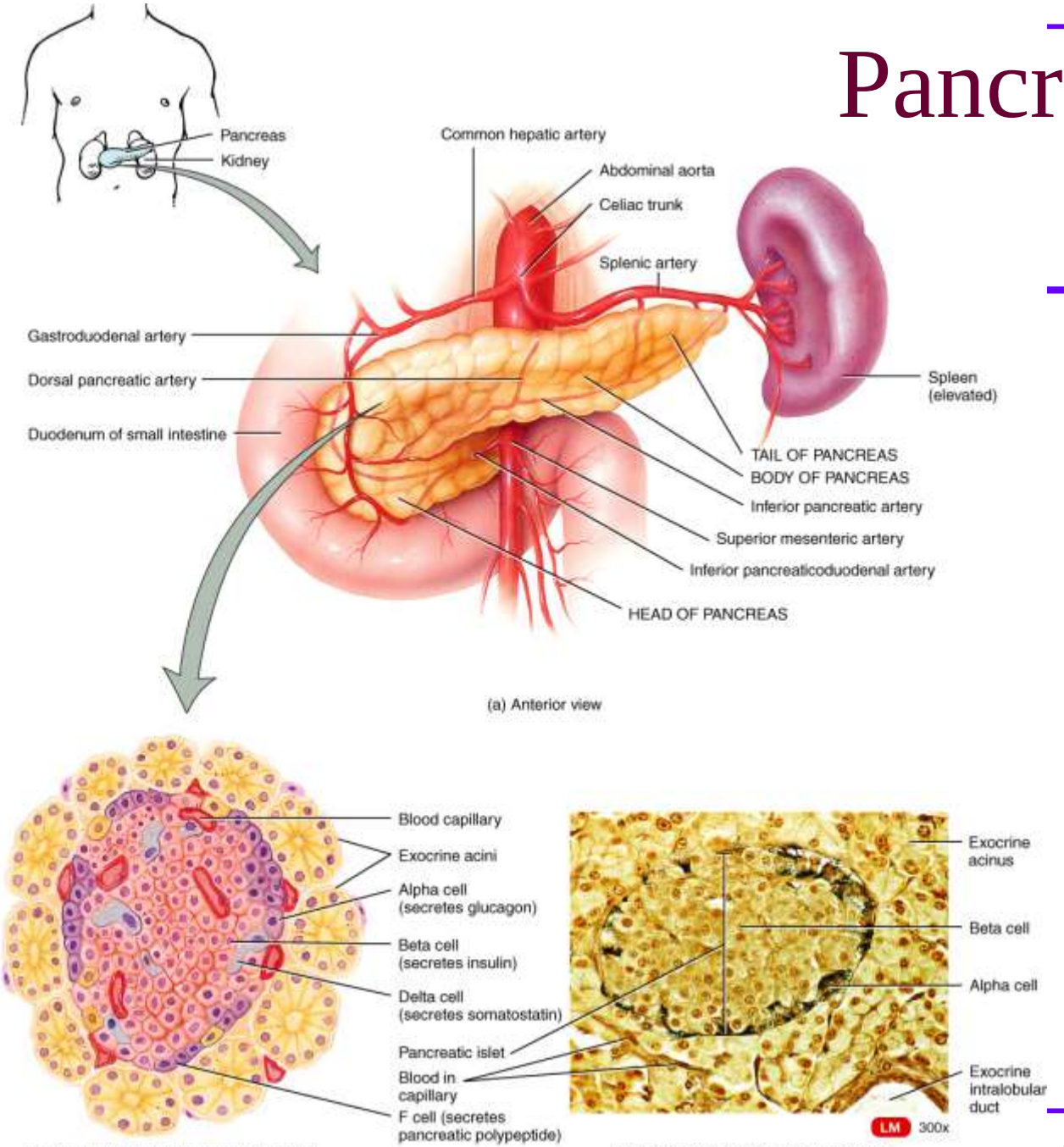
Objectives

- 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



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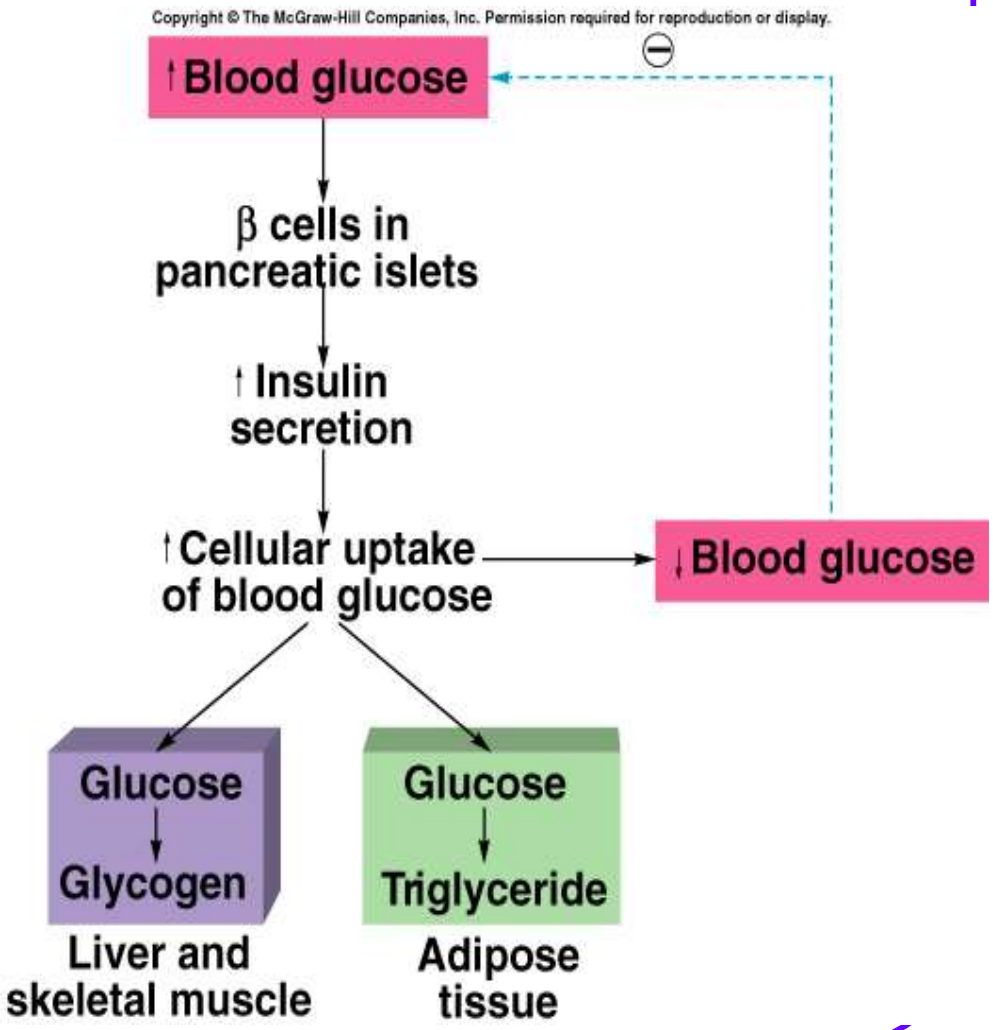
Pancreatic Islets

- 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
  - F cells secrete pancreatic polypeptide – inhibits somatostatin, gallbladder contraction, and secretion of pancreatic digestive enzymes

Pancreatic Islets (Islets of Langerhans)

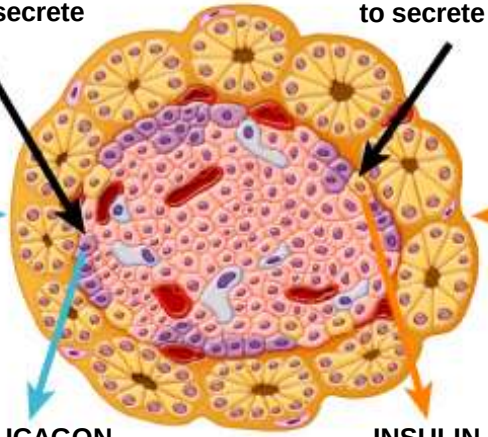
- Alpha cells secrete glucagon.
  - Stimulus is decrease in blood [glucose].
  - Stimulates glycogenolysis and lipolysis.
  - Stimulates conversion of fatty acids to ketones.
- Beta cells secrete insulin.
  - Stimulus is increase in blood [glucose].
  - Promotes entry of glucose into cells.
  - Converts glucose to glycogen and fat.
  - Aids entry of amino acids into cells.



Negative Feedback Regulation of Glucagon and Insulin

1 Low blood glucose (hypoglycemia) stimulates alpha cells to secrete

5 High blood glucose (hyperglycemia) stimulates beta cells to secrete



GLUCAGON

INSULIN

2 Glucagon acts on hepatocytes (liver cells) to:

- convert glycogen into glucose (glycogenolysis)
- form glucose from lactic acid and certain amino acids (gluconeogenesis)

3 Glucose released by hepatocytes raises blood glucose level to normal

4 If blood glucose continues to rise, hyperglycemia inhibits release of glucagon

6 Insulin acts on various body cells to:

- accelerate facilitated diffusion of glucose into cells
- speed conversion of glucose into glycogen (glycogenesis)
- increase uptake of amino acids and increase protein synthesis
- speed synthesis of fatty acids (lipogenesis)
- slow glycogenolysis
- slow gluconeogenesis

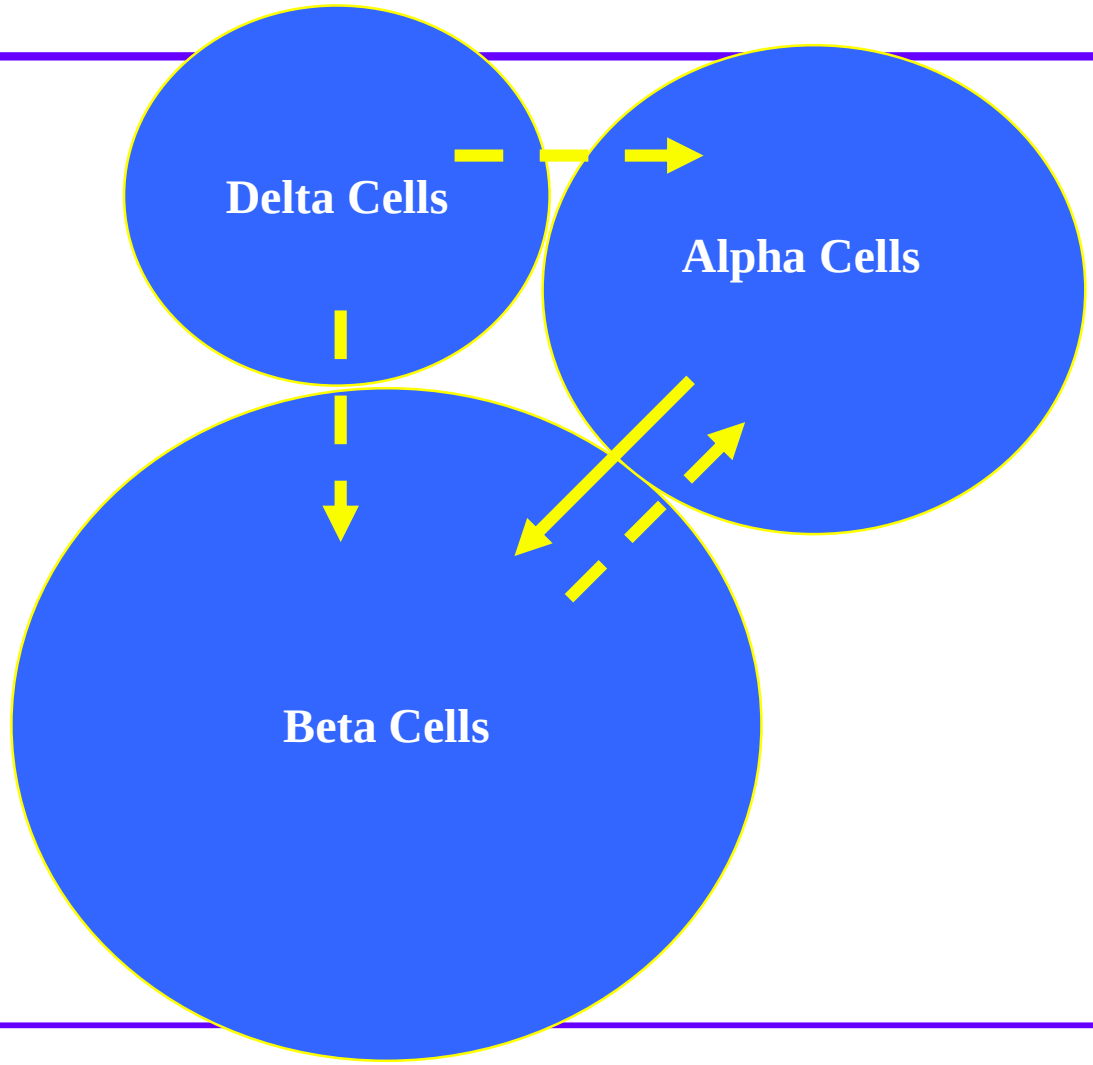
7 Blood glucose level falls

8 If blood glucose continues to fall, hypoglycemia inhibits release of insulin

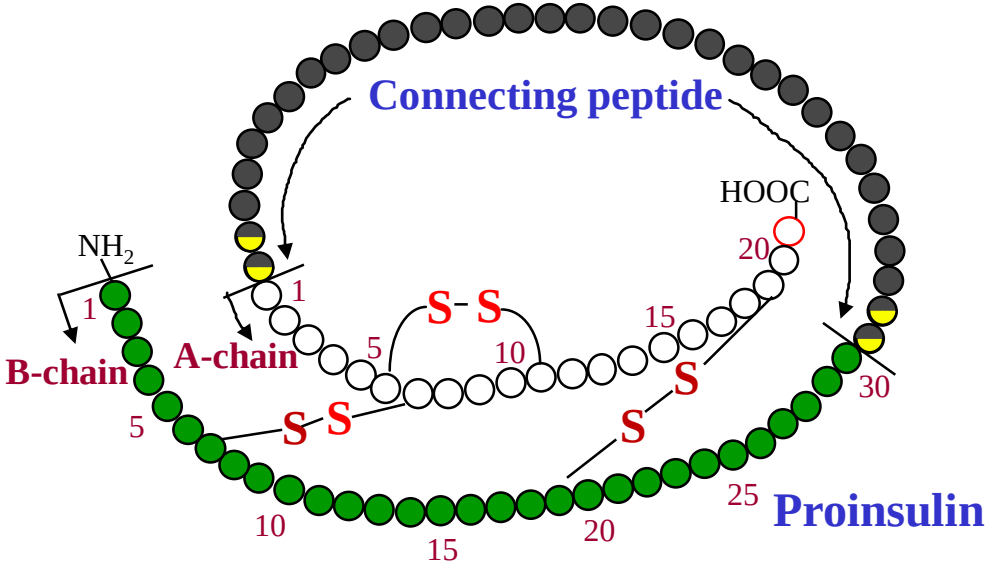
Pancreatic Hormones

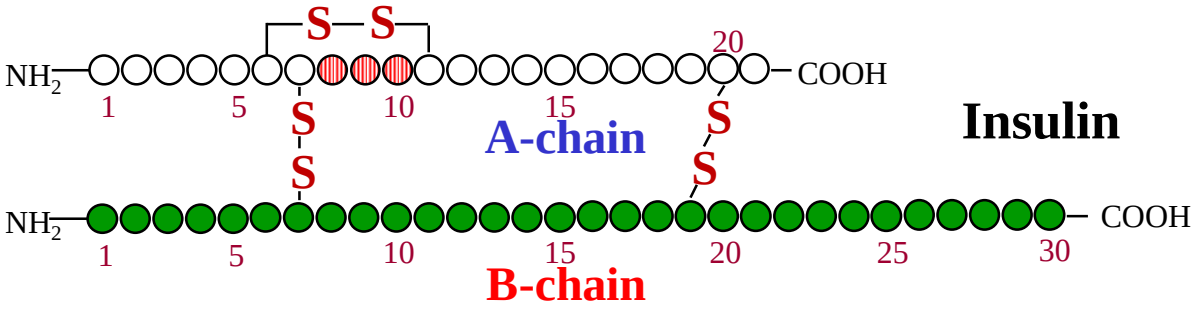
- Insulin
- Glucagon
- Somatostatin

Paracrine Influence of Pancreatic Hormones



Processing of Proinsulin

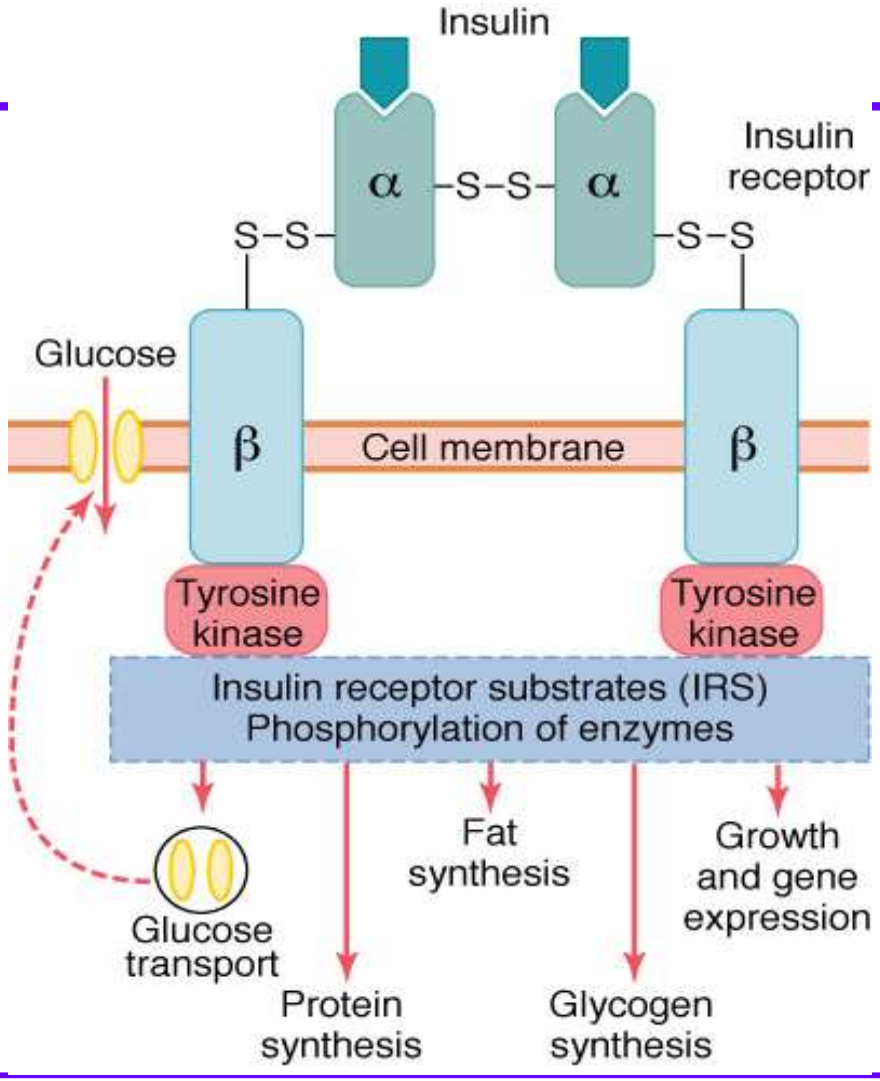


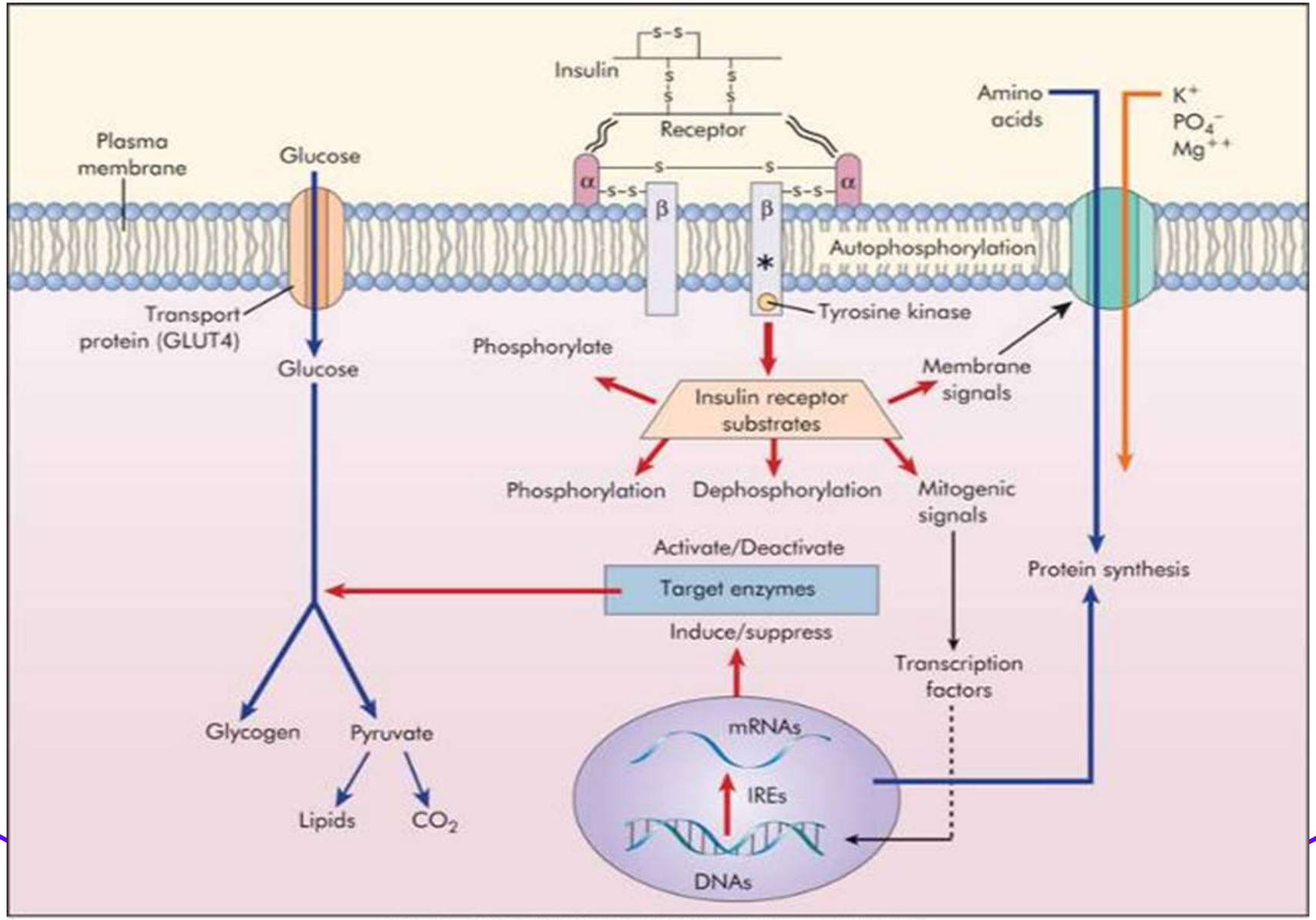


Tyrosine Kinase

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

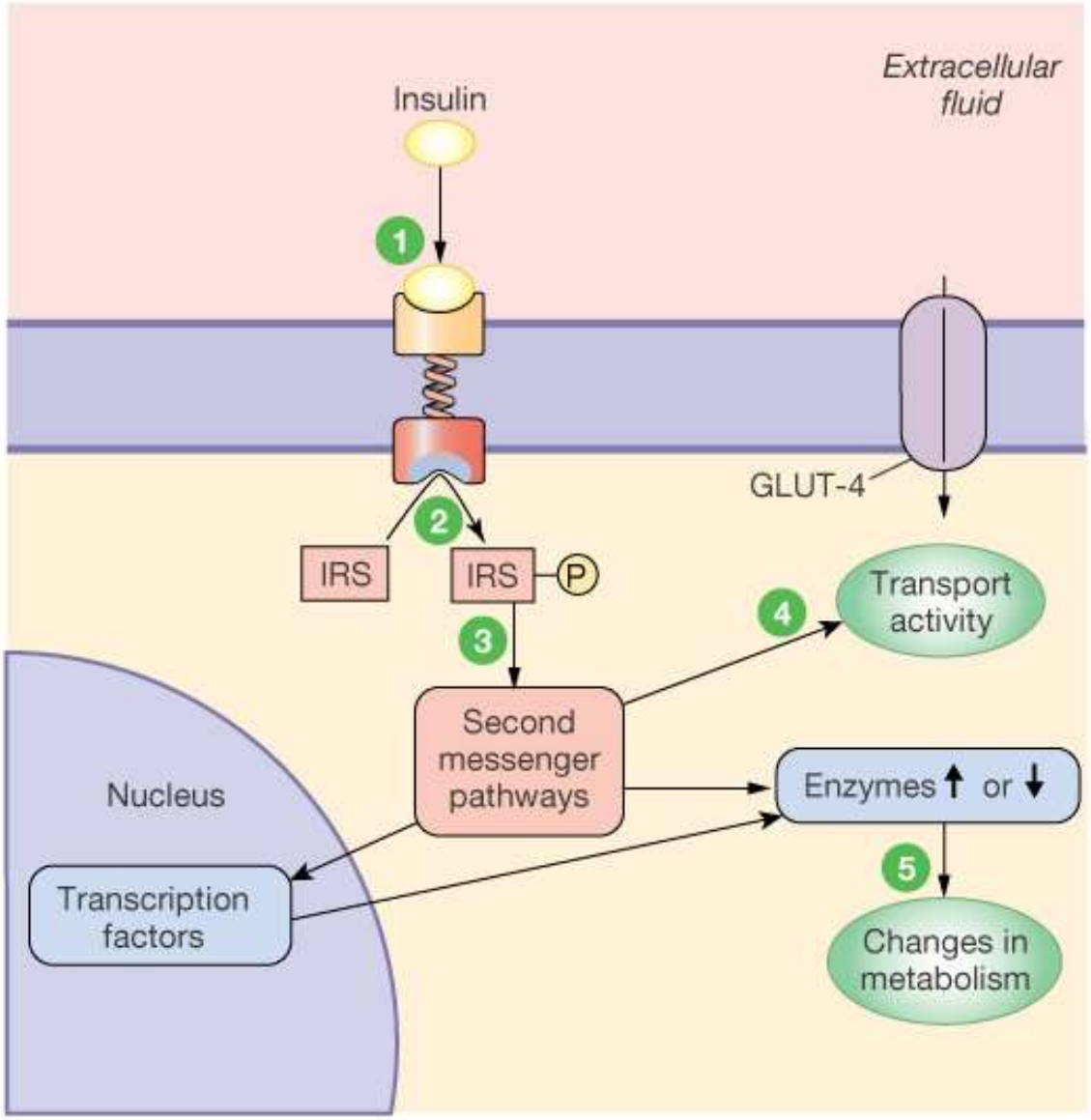
The Insulin Receptor & Mechanisms of Insulin Action





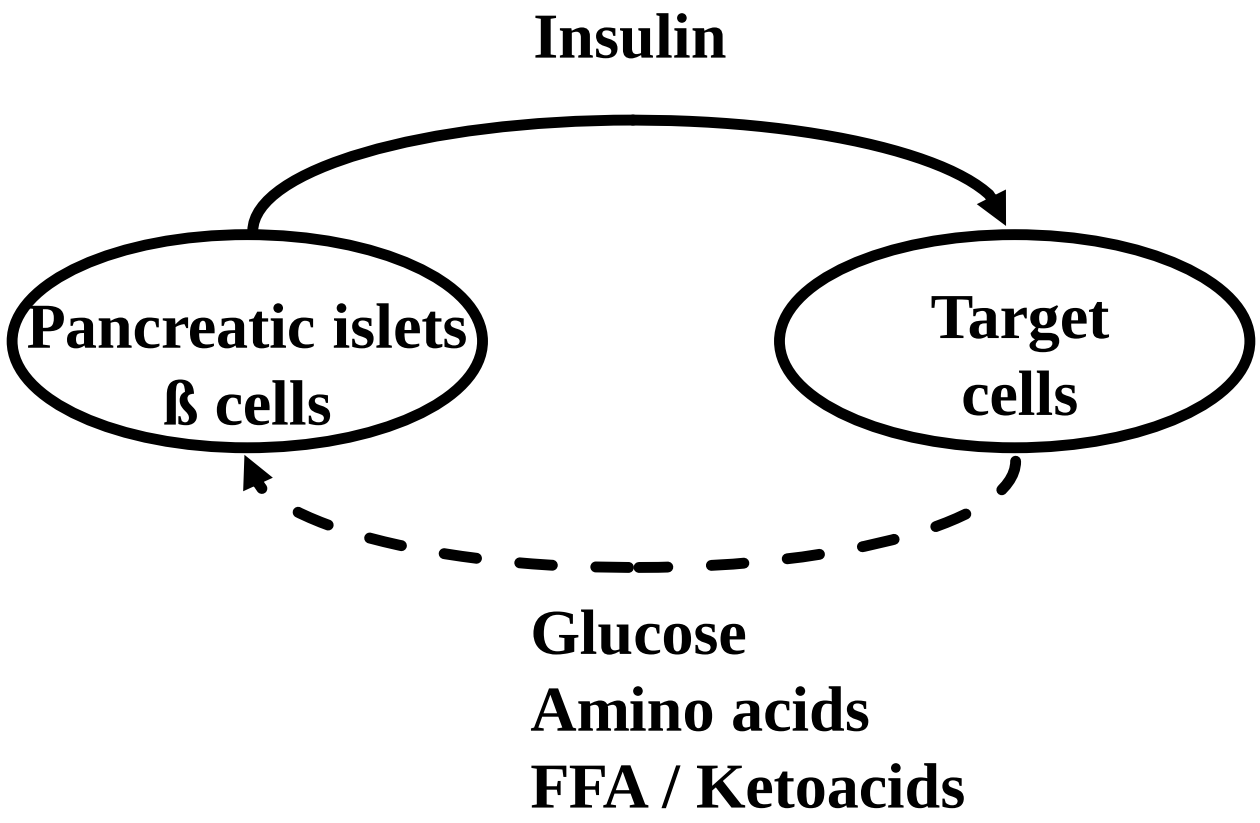
From Berne RM, Levy MN: *Principles of physiology*, ed 3, St Louis, 2000, Mosby.

Insulin Action on Cells:

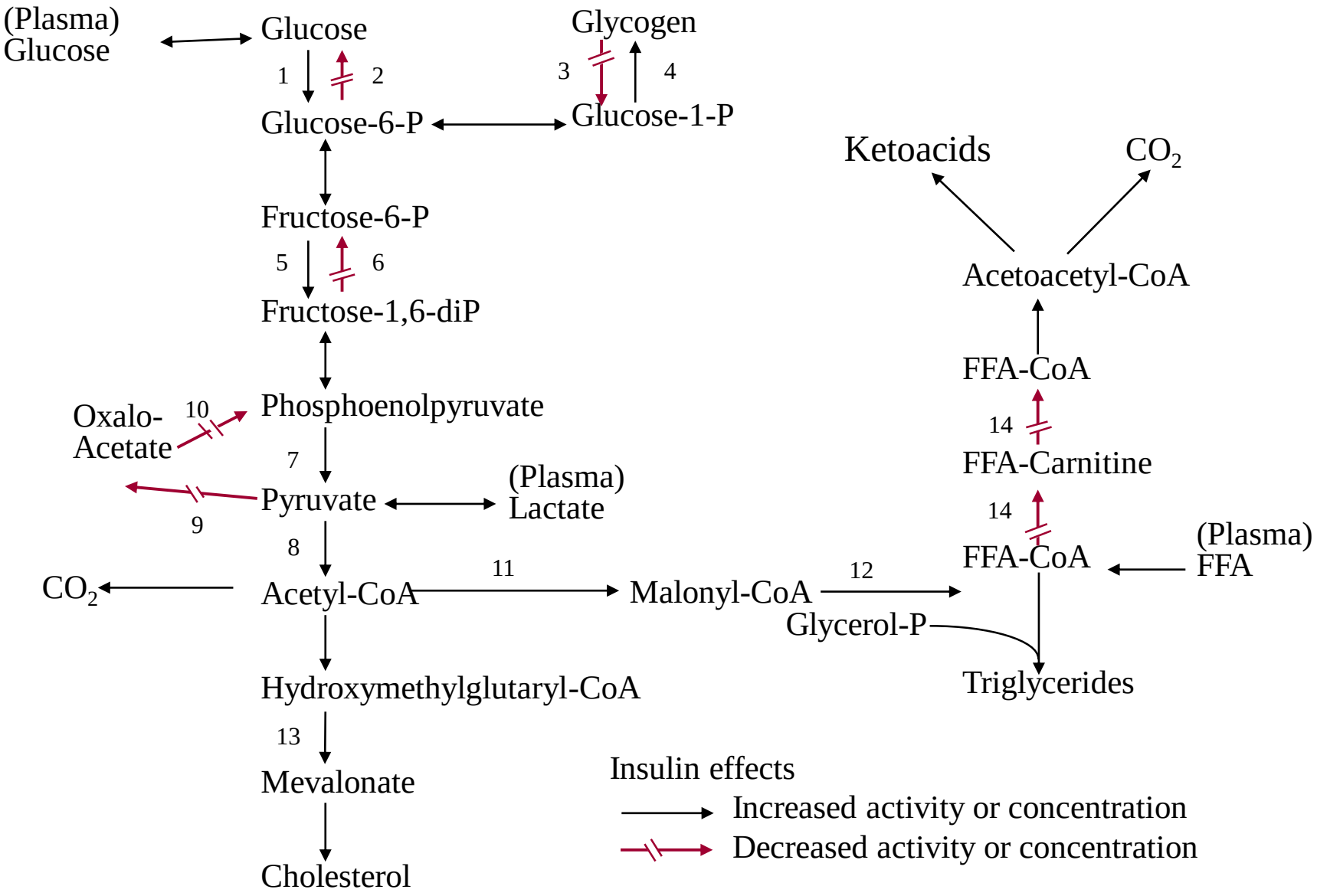


1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
3. Second messenger pathways alter protein synthesis and existing proteins.
4. Membrane transport is modified.
5. Cell metabolism is changed.

Metabolic Control by Insulin



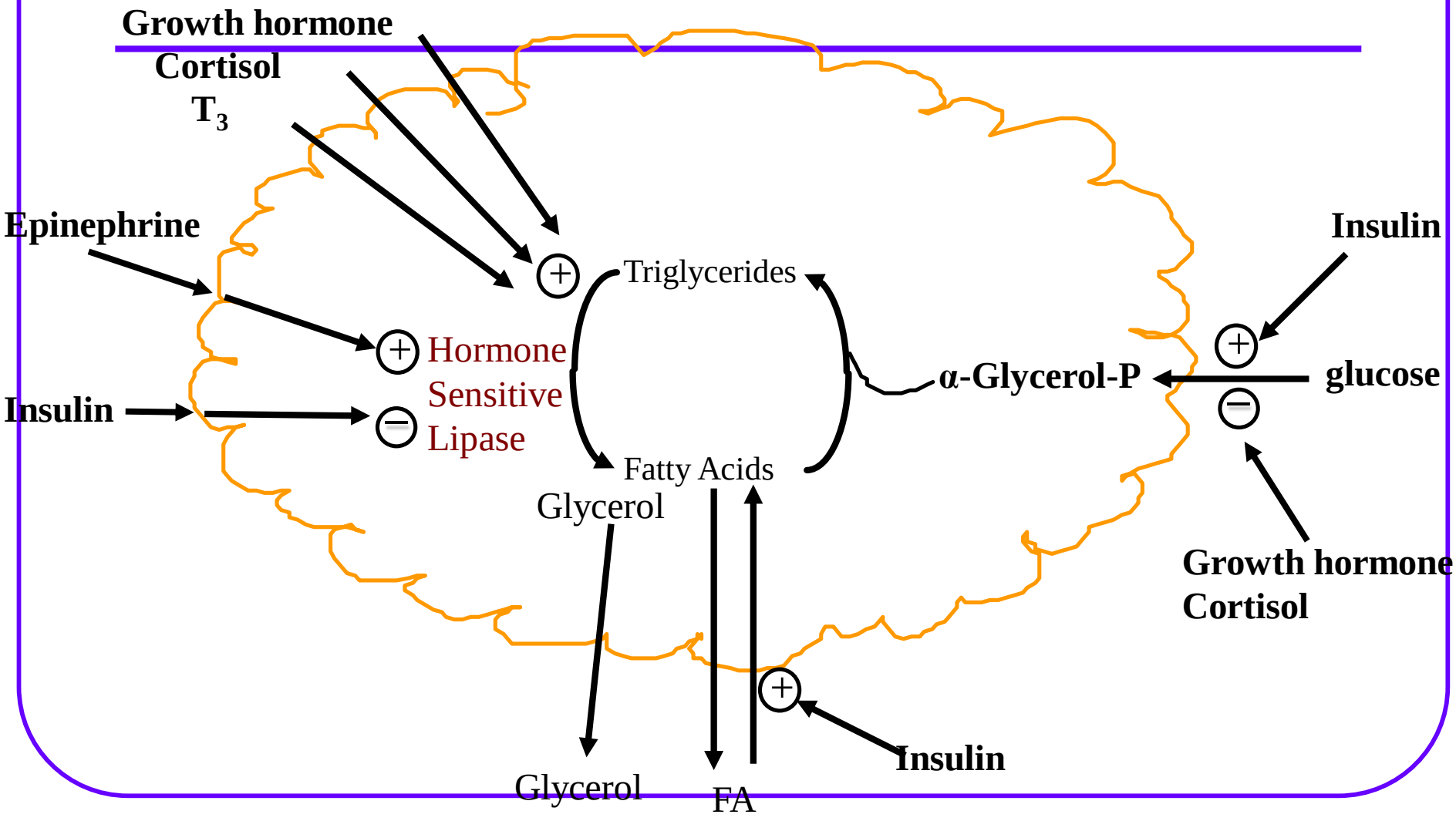
Insulin Actions on Glucose and Fatty Acid Metabolism in the Liver



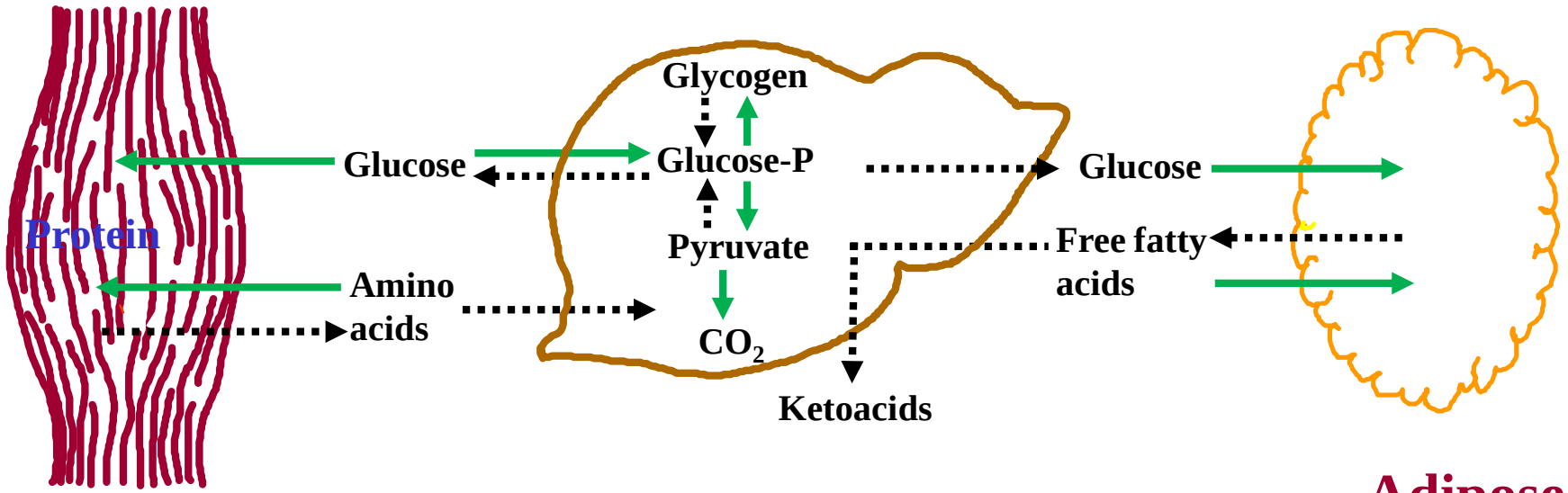
Key Enzymes Influenced by Insulin

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



Metabolic Effects of Insulin



Stimulate

Inhibit

↓ Glucose

↓ Free fatty acids

↓ Ketoacids

↓ Amino acids

Insulin -- Liver

- GLUT2 transporters
  - ↑ Glucokinase
- ↑ 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
  - ↑ Lipoprotein lipase

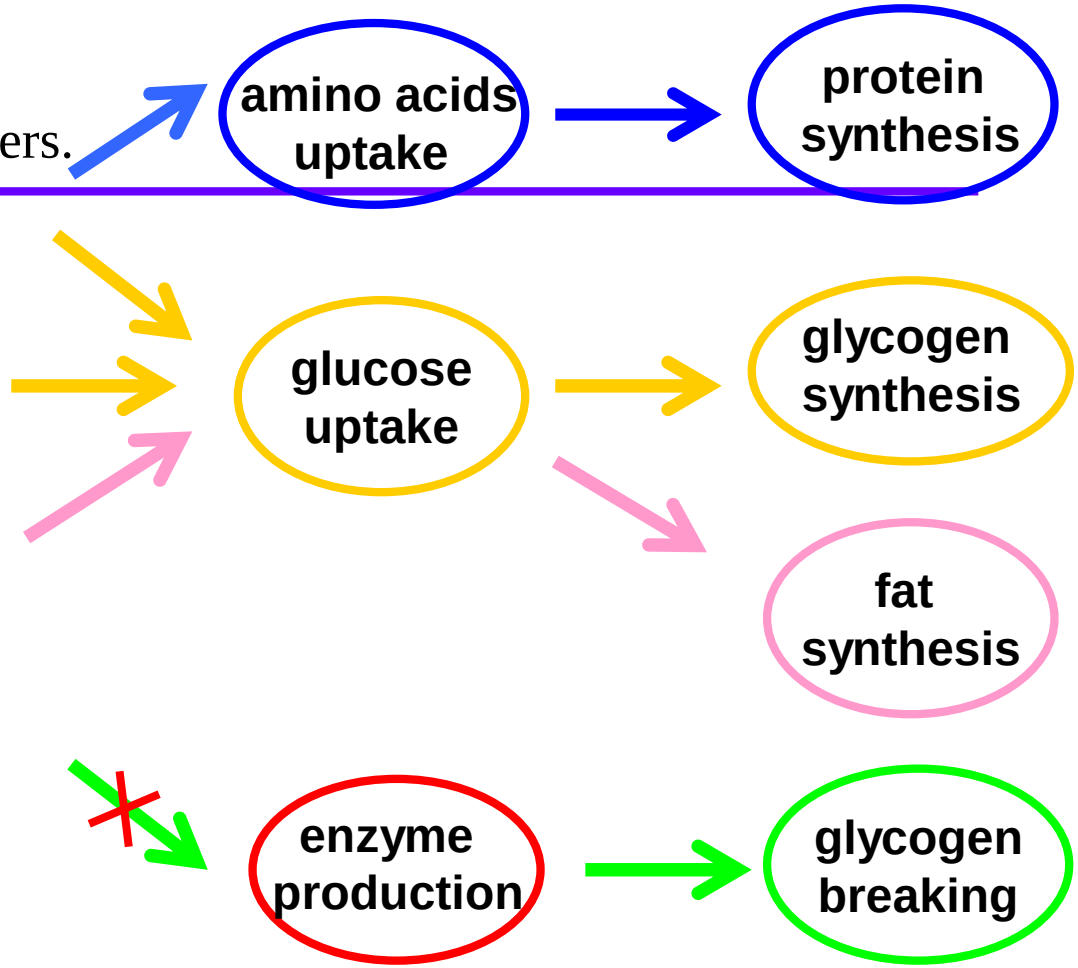
Insulin -- Muscle

- ↑ GLUT4 transporters
- ↑ Glycogen
- ↑ Glycolysis
- ↑ Protein synthesis, ↓ protein degradation
- ↑ Triglycerides (FA's from circulation)

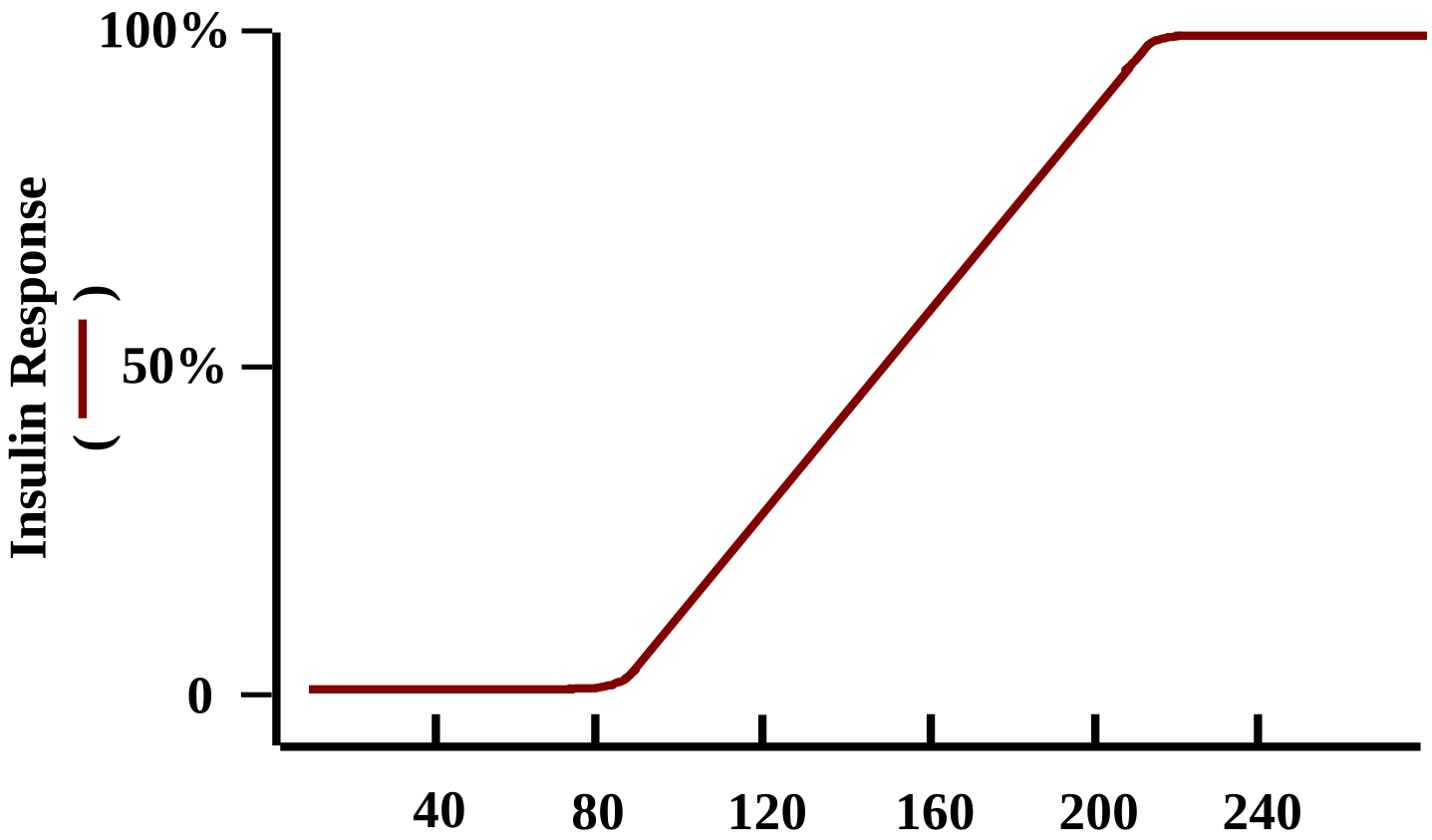
Insulin affects many organs:

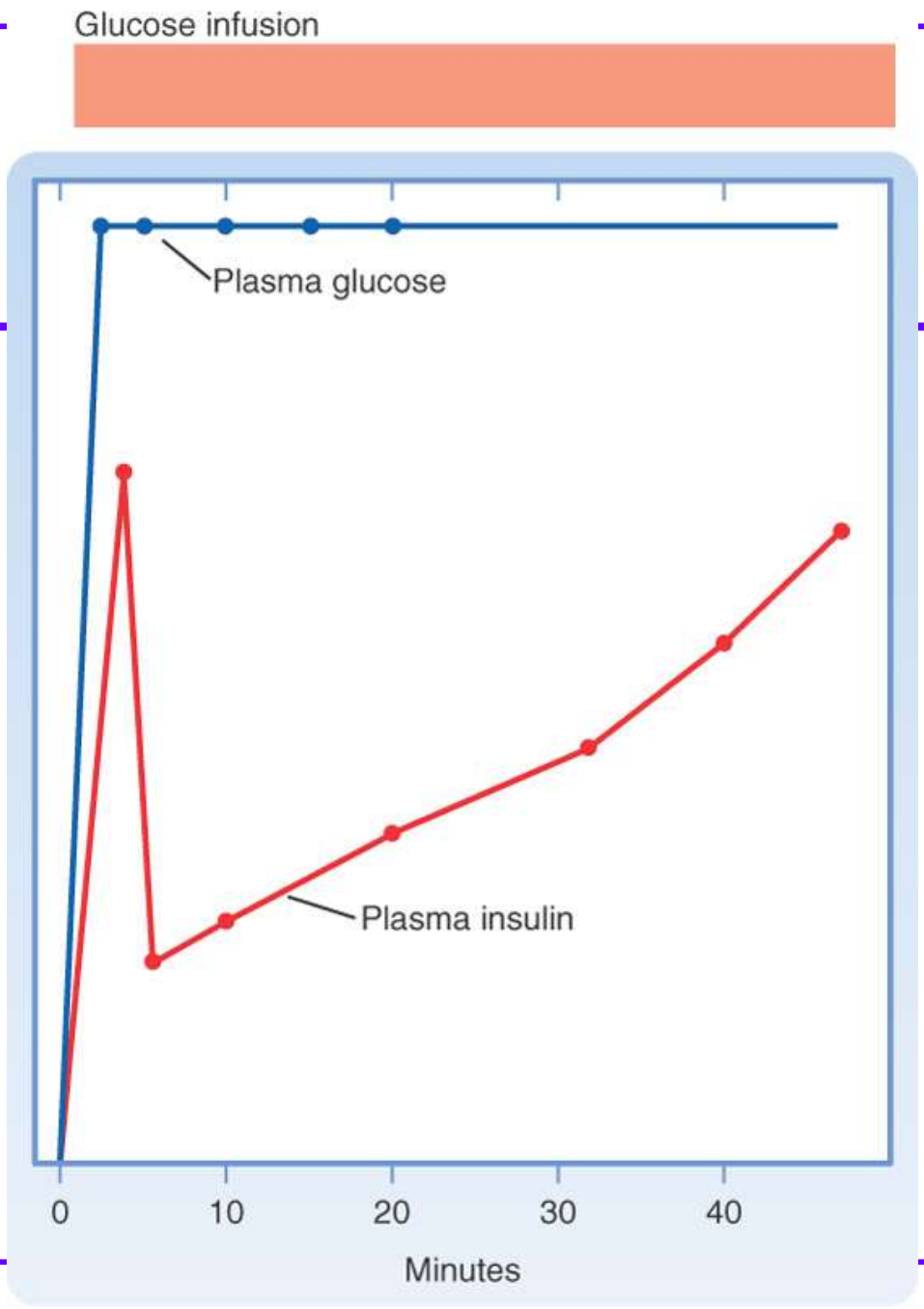
- It stimulates skeletal muscle fibers.
- It stimulates liver cells.
- It acts on fat cells
- It inhibits production of certain enzyme.

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



Blood [Glucose] & Insulin Secretion





Factors Affecting Insulin Secretion

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

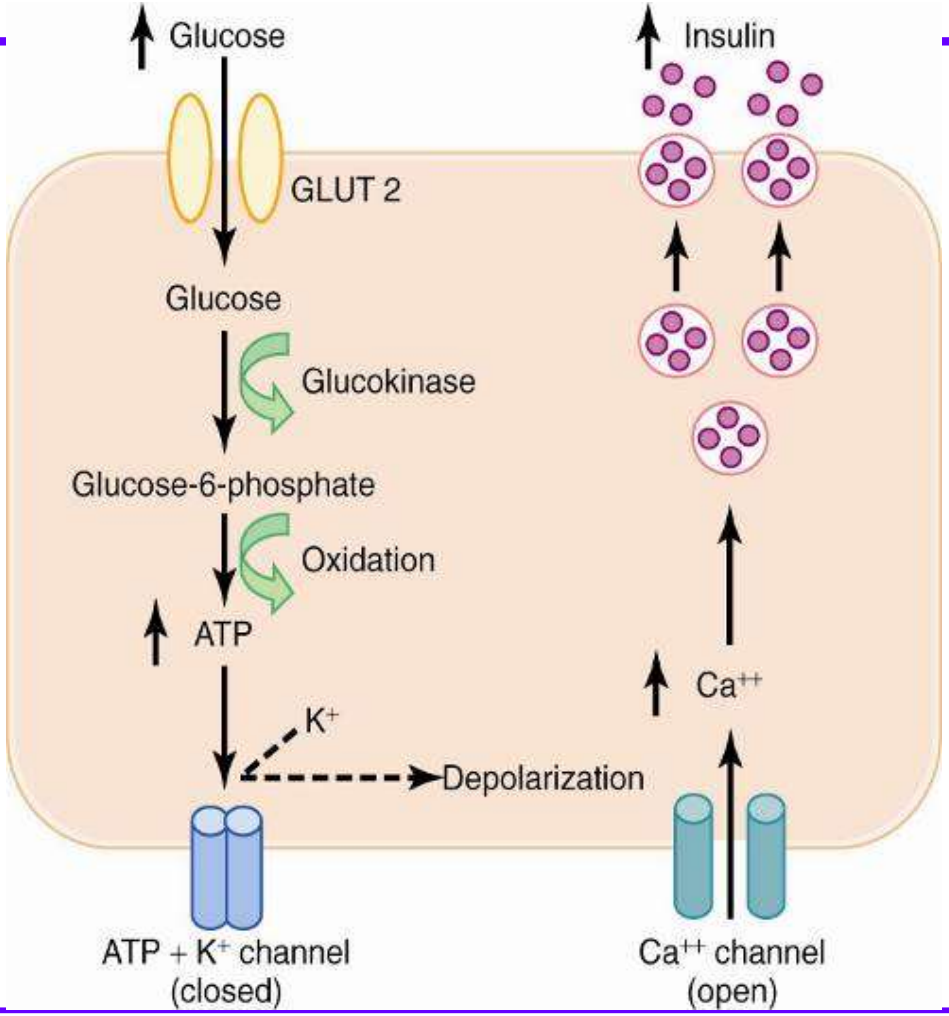
Incretin Hormones

- **Intestine derived hormones**

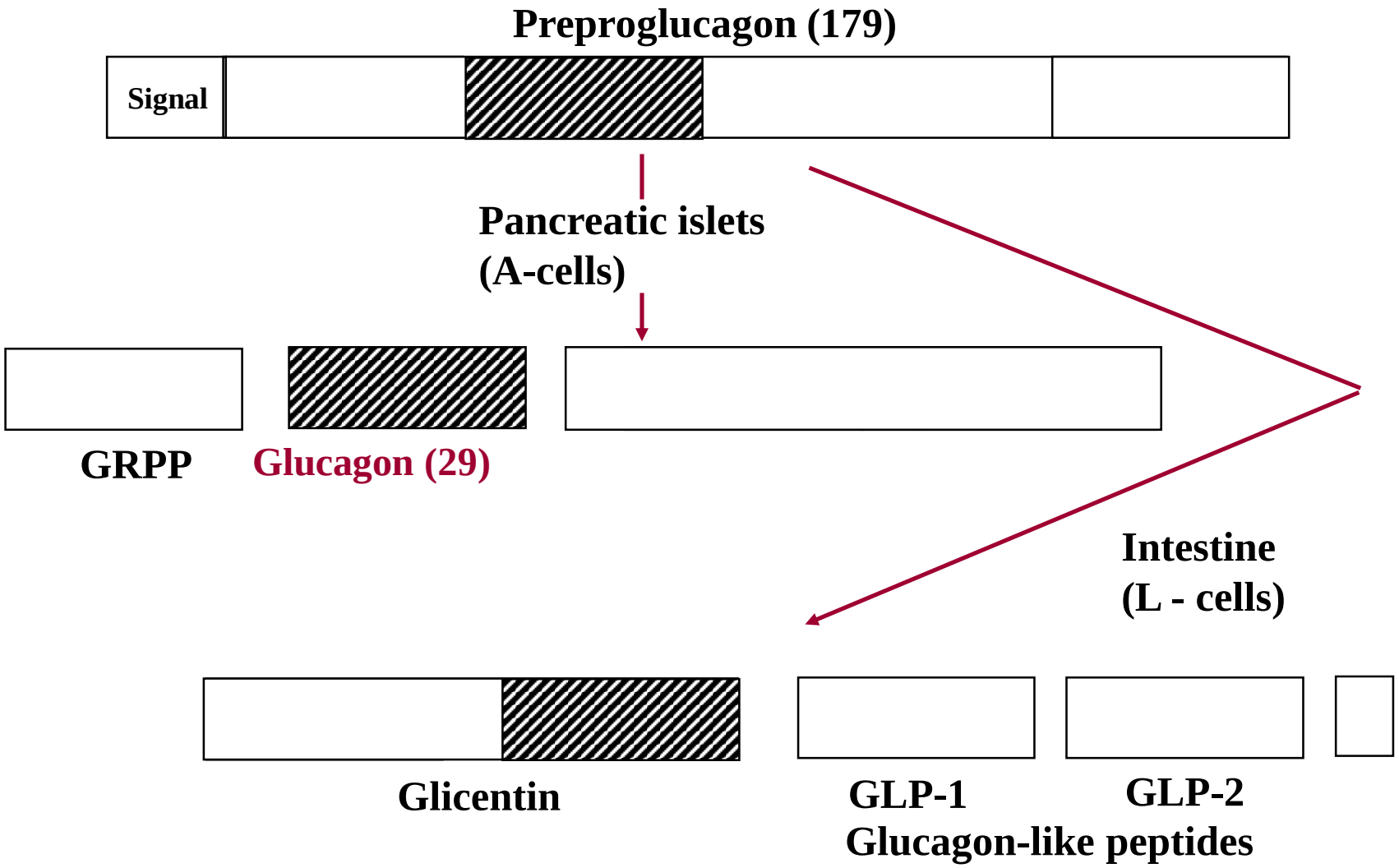
  - GLP-1, GIP
  - short $T_{1/2}$
  - secreted in response to GI glucose & fat

- **Simulate insulin secretion (glucose dependent)**
- **Inhibit glucagon secretion**
- **Slow gastric emptying**

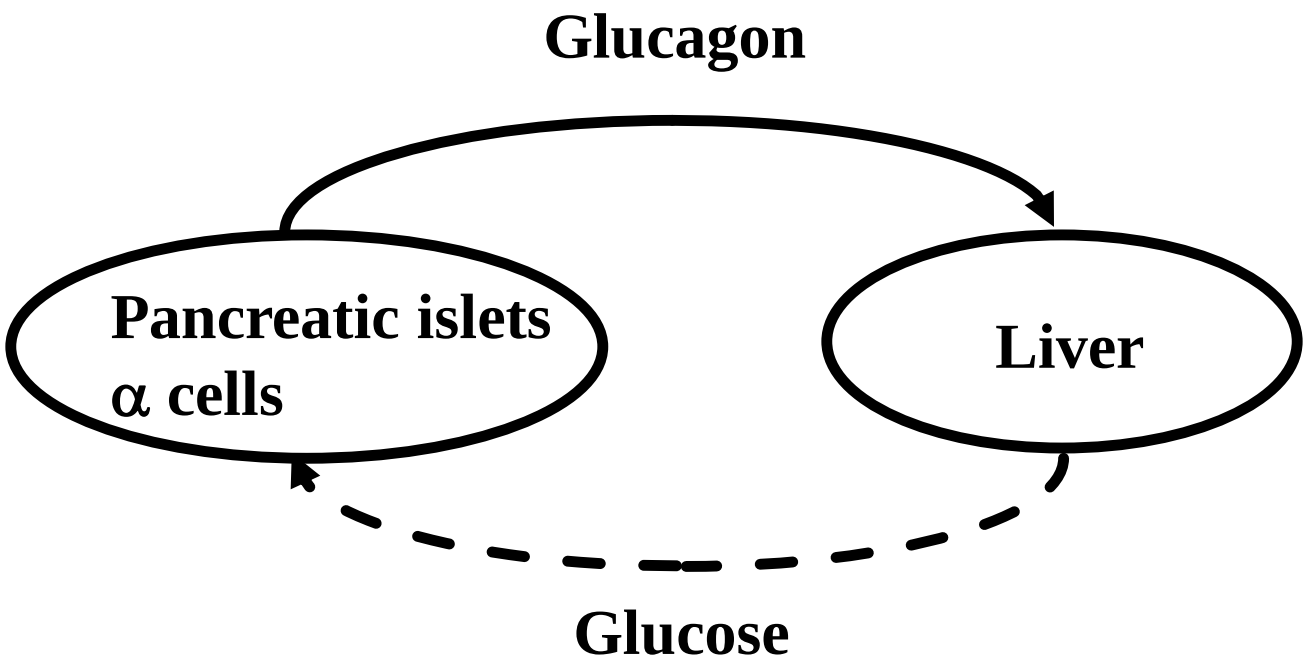
Mechanism of Glucose Stimulated Insulin Secretion



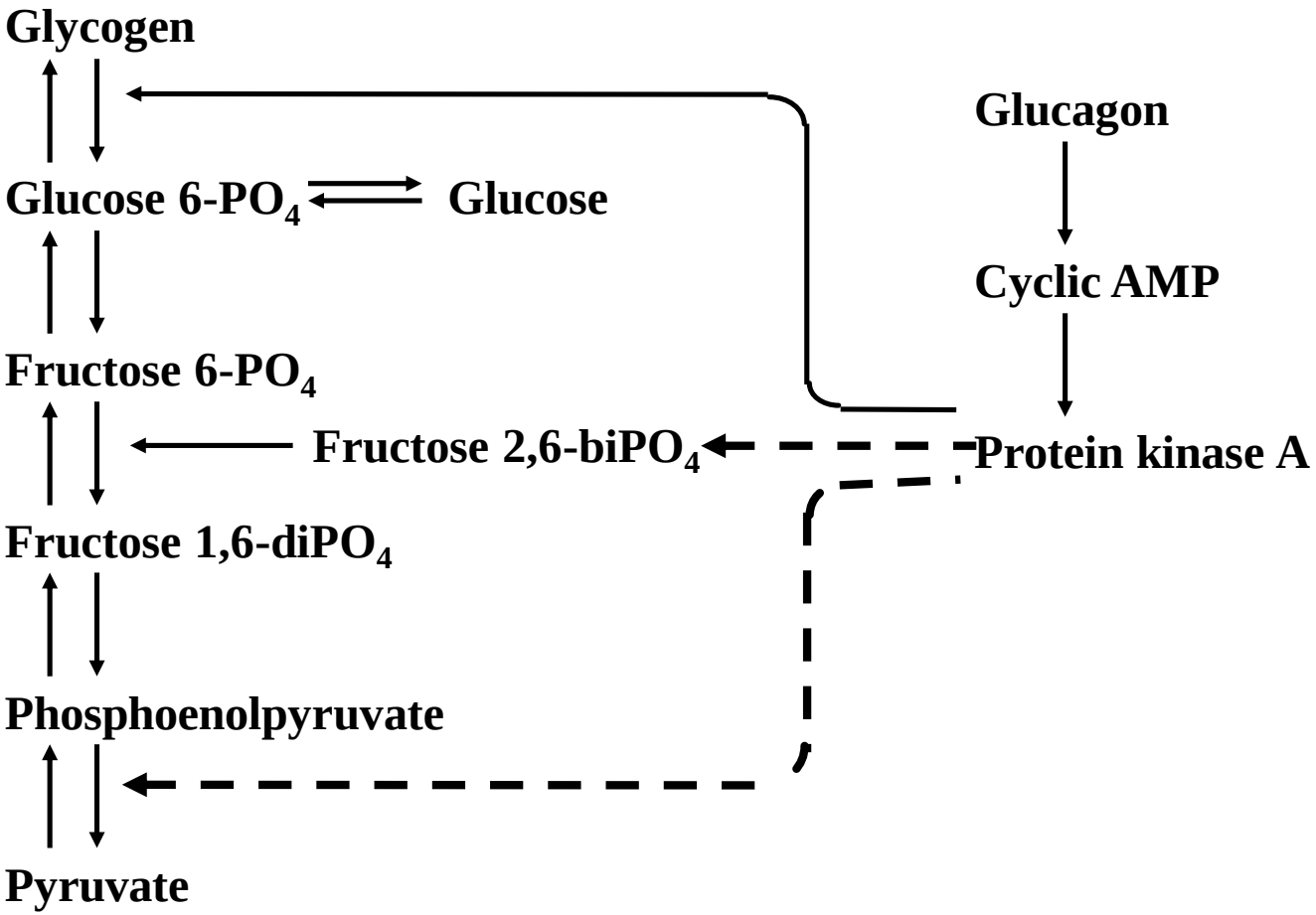
Processing of Preproglucagon



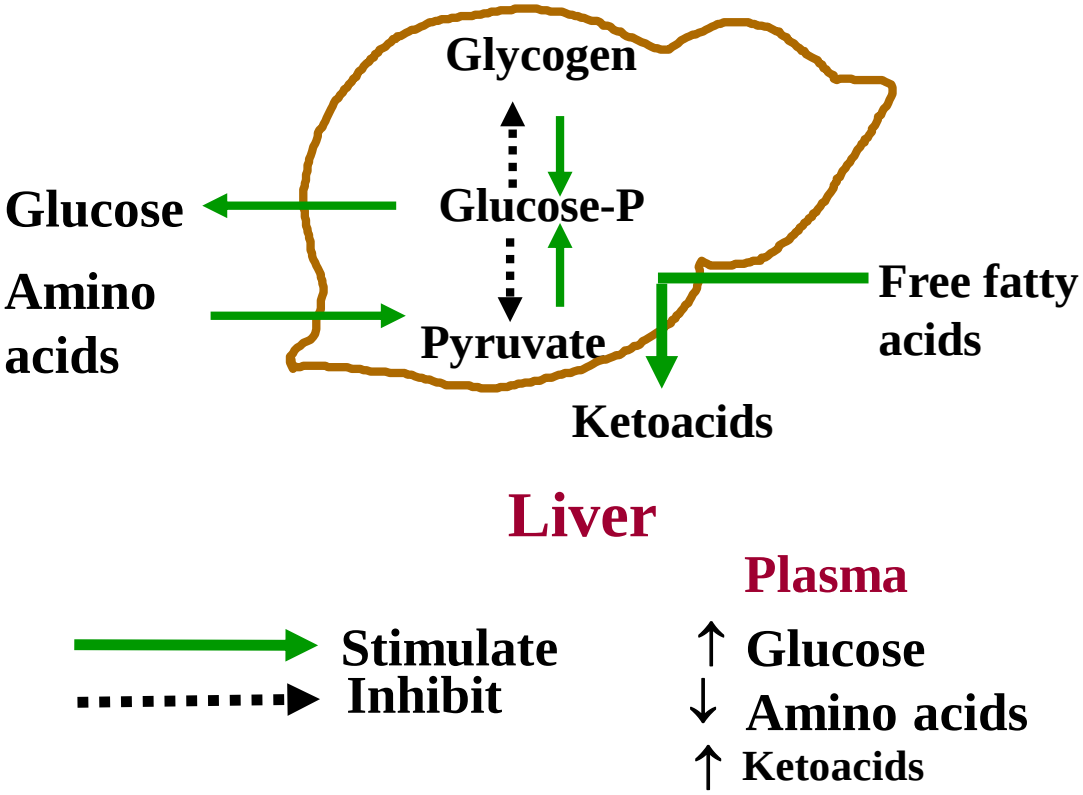
Metabolic Control by Glucagon



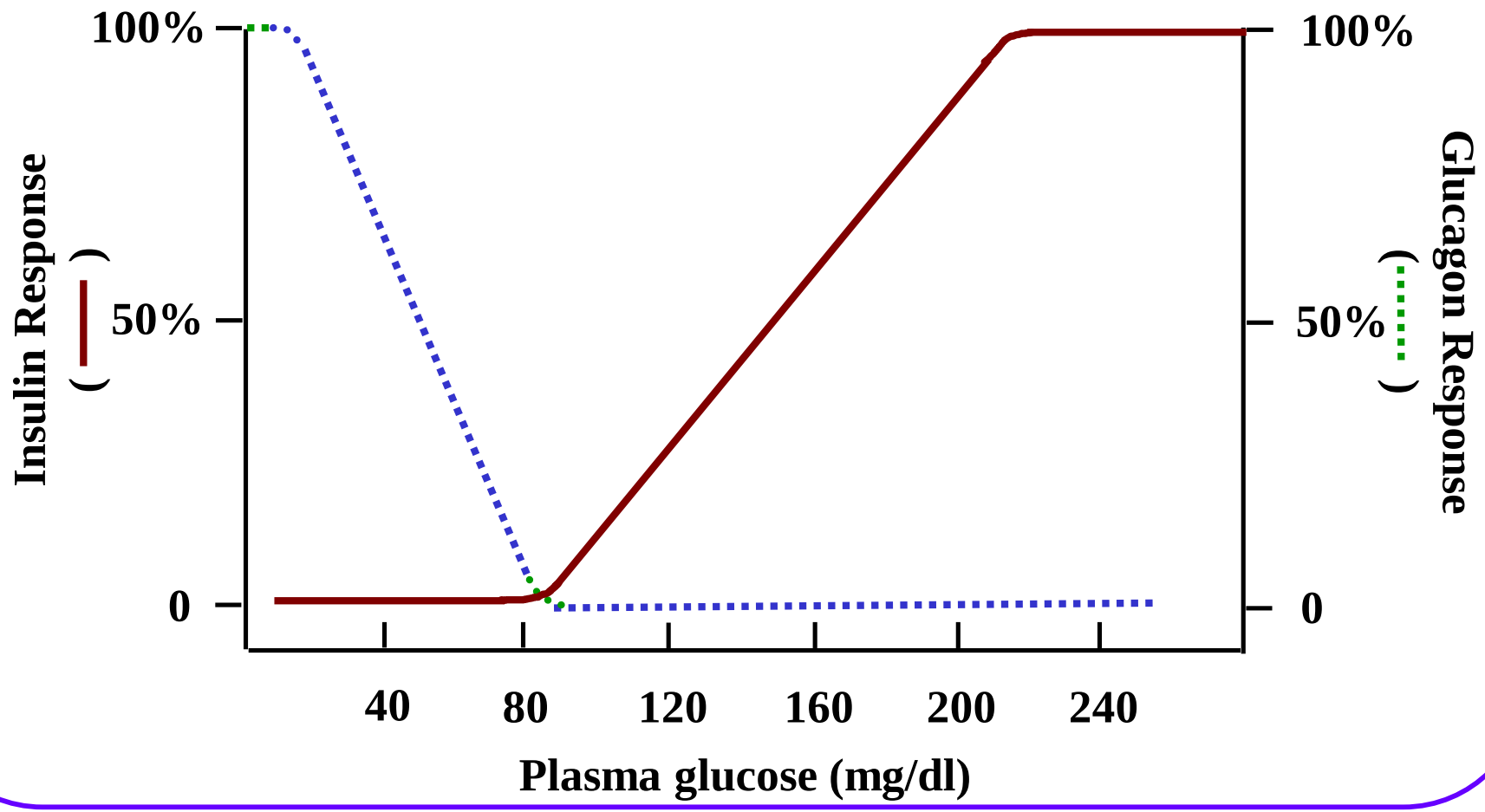
Effects of Glucagon on Glucose Output by Liver



Metabolic Effects of Glucagon



Blood [Glucose] & Secretion of Insulin & Glucagon



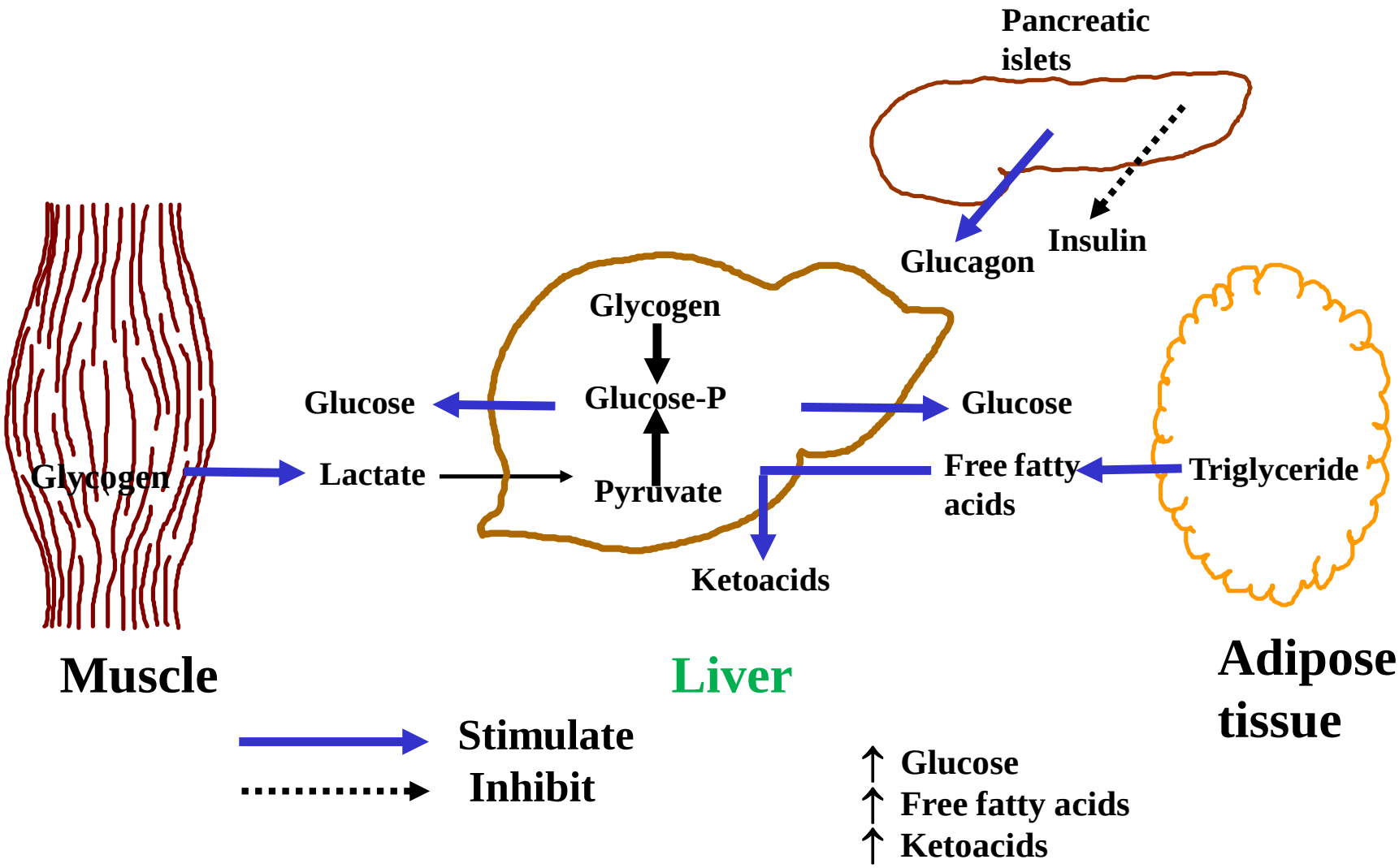
Factors Affecting Glucagon Secretion

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

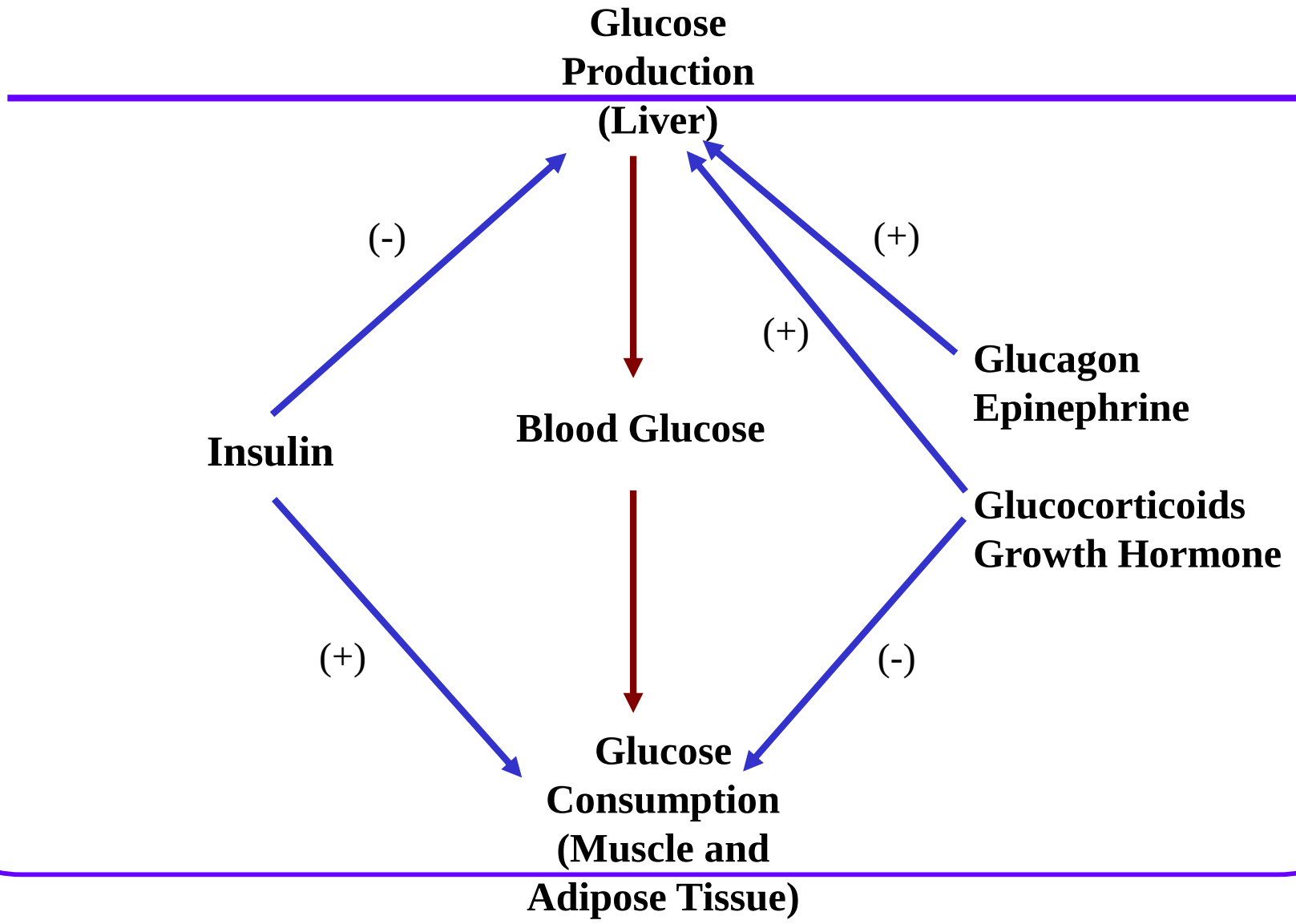
Fuel Metabolism in Anabolic & Catabolic States

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



Hormonal Interactions in the Maintenance of Blood [Glucose]

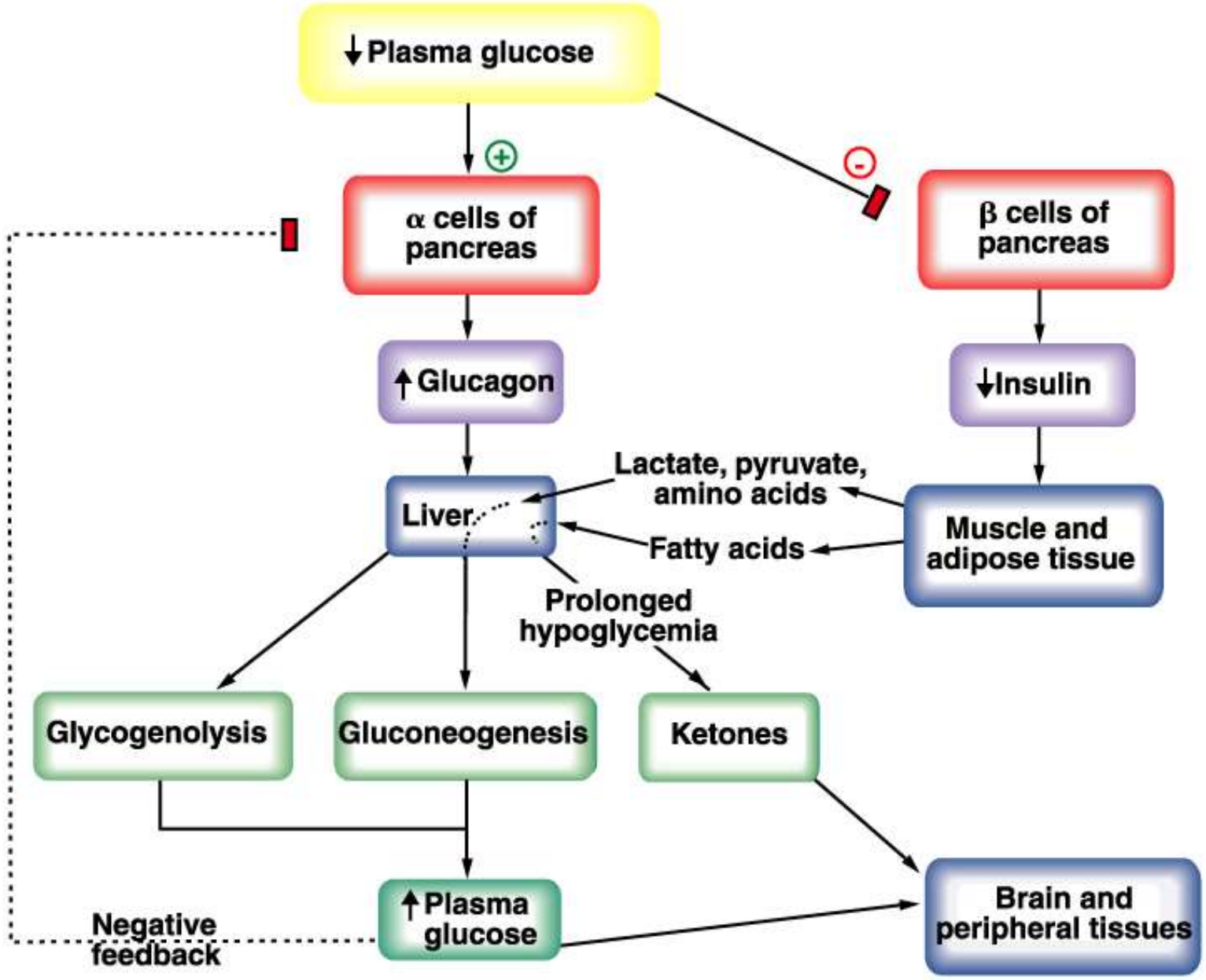


Responses to Decreasing Plasma [Glucose]

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

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


↓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

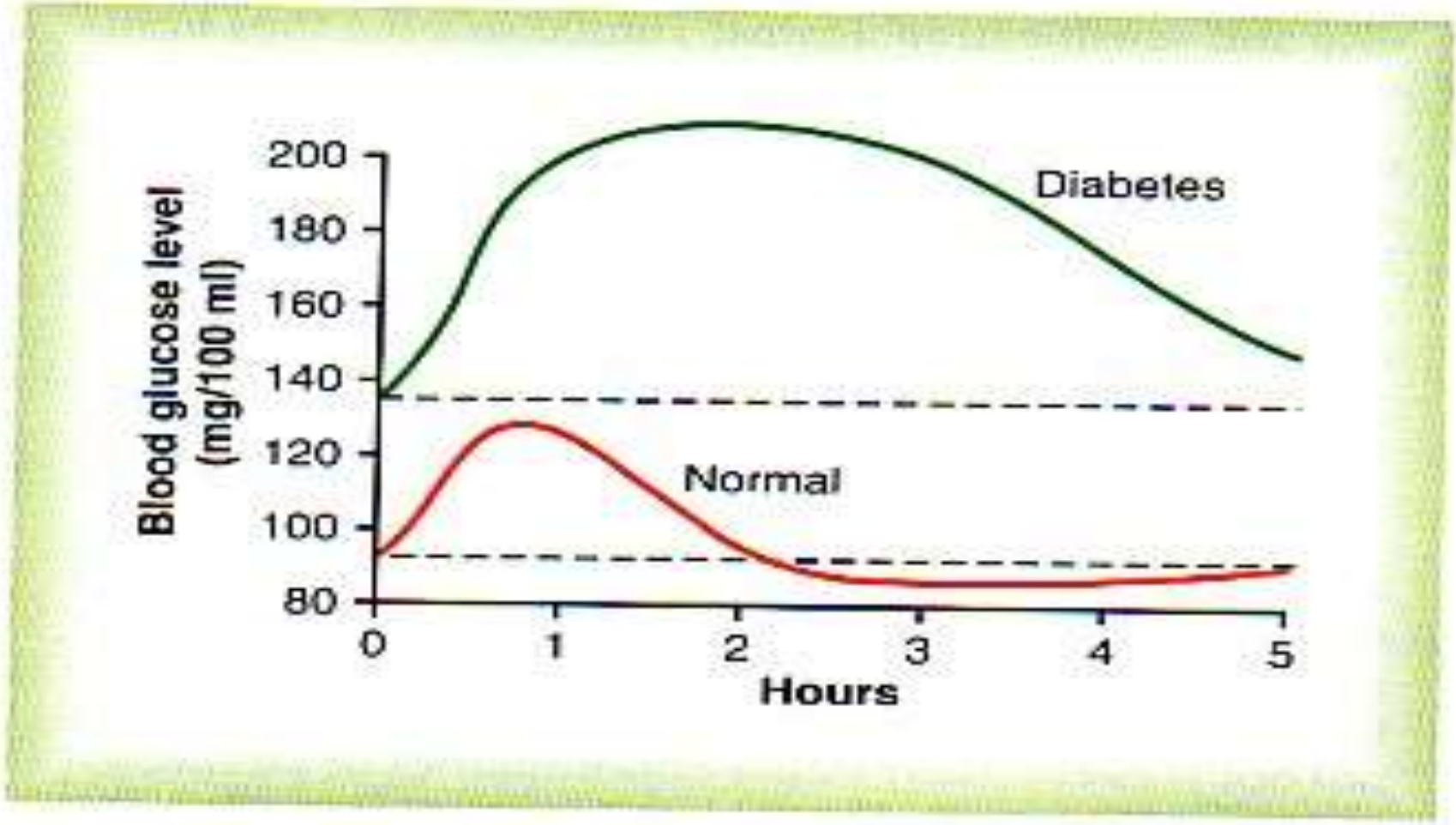
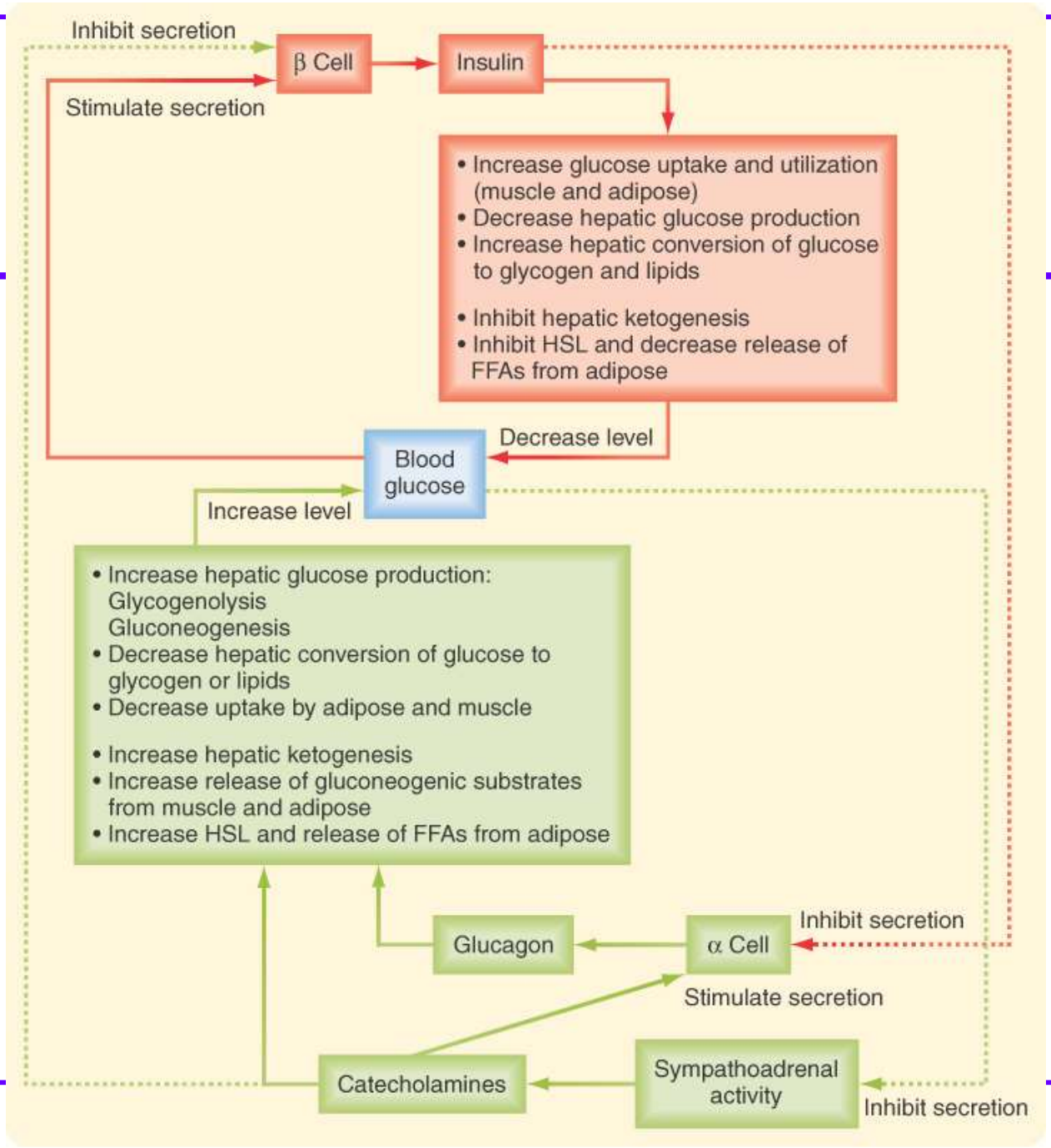


Figure 78–12

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

Comparison of Type I and Type II 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



Glucose Homeostasis & Diabetes

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

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


THANK YOU