Pancreatic Hormones and Diabetes Mellitus

The Endocrine Pancreas: Anatomy

Cell Types

A cell (α)	Glucagon
B cell (β)	Insulin
D cell (δ)	Somatostatin
PP cell (F cell)	Pancreatic polypeptide

Insulin

Biosynthesis

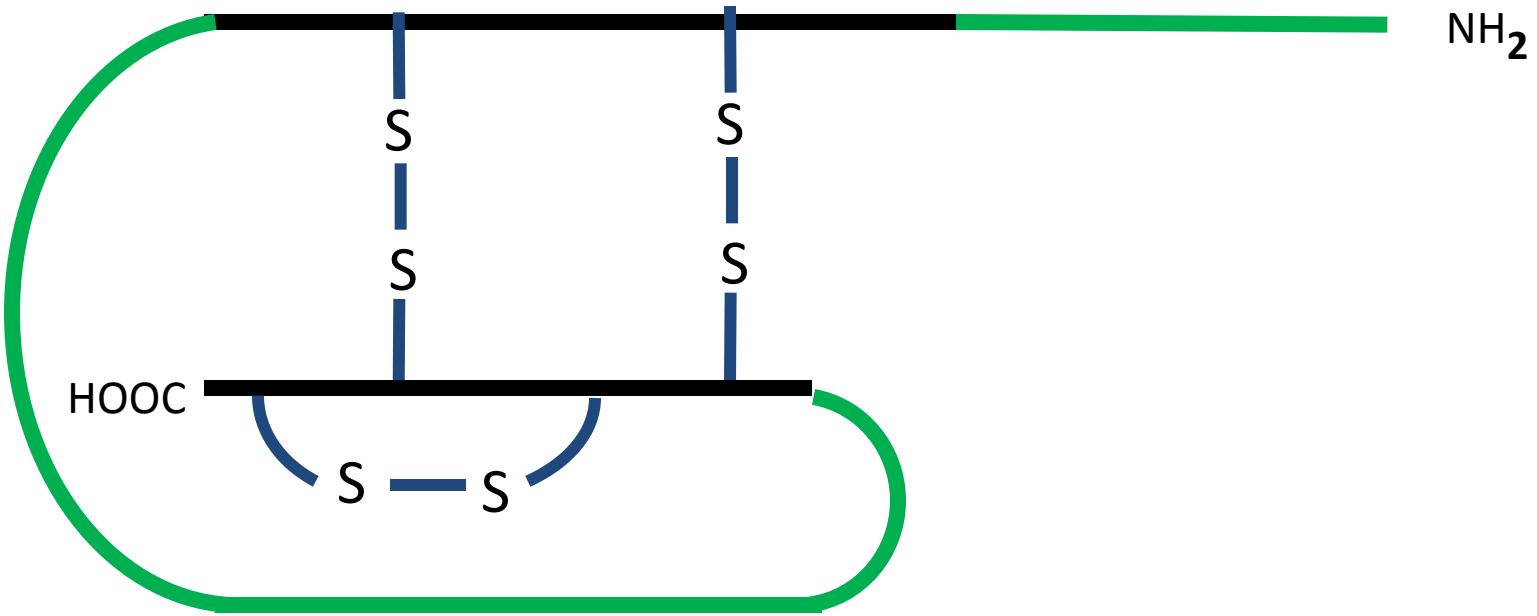
- Preproinsulin (M.W. 11500) → proinsulin → insulin + C - peptide

Biochemistry

- Proinsulin: (A+B chains)+(connecting segment)
- C-peptide: no known biological activity, degraded mainly in kidney.
- Insulin: A chain (21 a.as.) + B chain (30 a.as.).
- 2 –s-s-bonds (interchain), 1-s-s- (intrachain -A-).
- MW 5808, t½ 3-5 min.

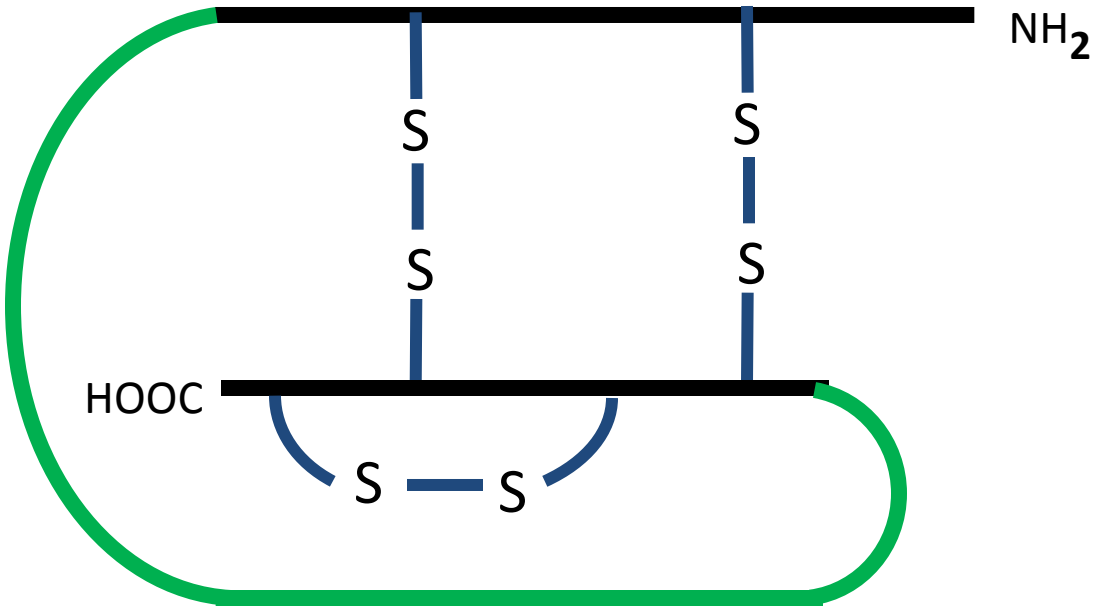
Synthesis of insulin - 1

Preproinsulin (110 a.as)



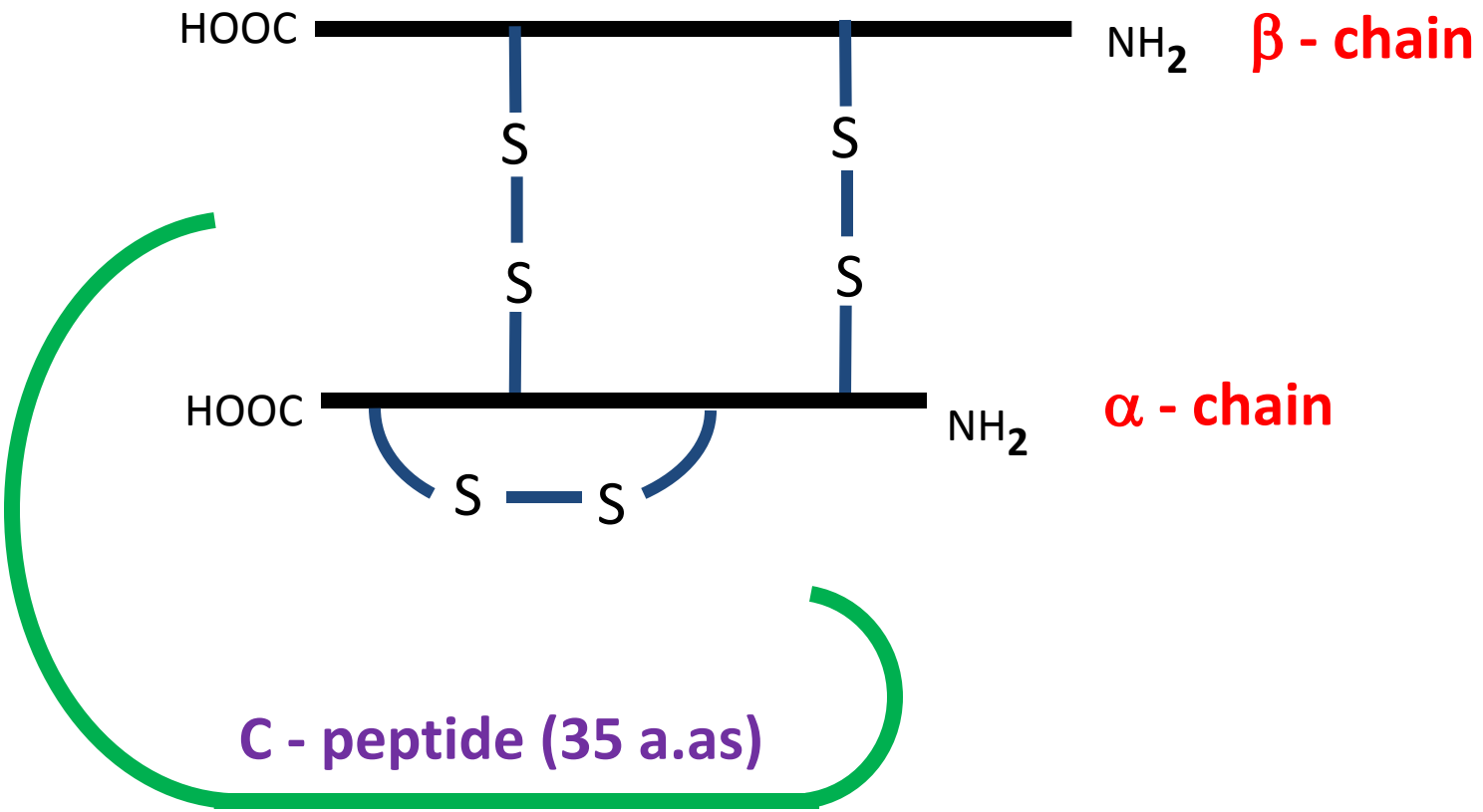
Synthesis of insulin - 2

Proinsulin (86 a.as)



Synthesis of insulin - 3

Insulin (21 + 30 a.as)



Insulin Secretion

- Basal: requires glucose presence
- Early phase: initial short-lived burst.
- Late Phase: rise again.
- ↑ glucose > 24h: desensitization
- Glucose metabolism (↑ ATP/ADP) → closes K^+ channels on β cells → depolarization → open Ca^{++} channels.
- cAMP: but not in absence of glucose.

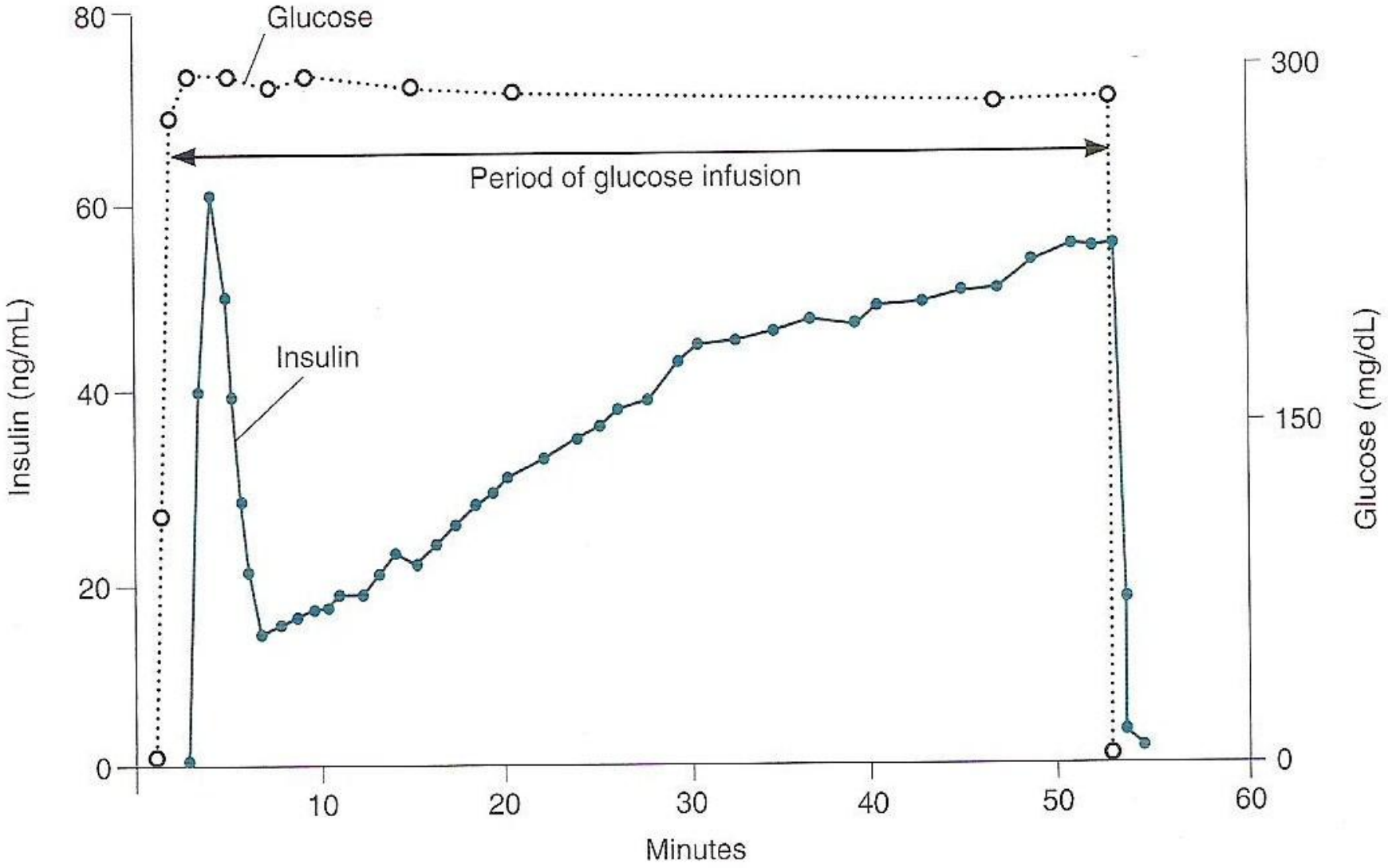


Figure 17–4. **Multiphasic response of the in vitro perfused pancreas during constant stimulation with glucose.** (Modified from Grodsky GM et al: Further studies on the dynamic aspects of insulin release in vitro with evidence for a two-compartmental storage system. Acta Diabetol Lat 1969;6[Suppl 1]:554.)

Insulin Secretion

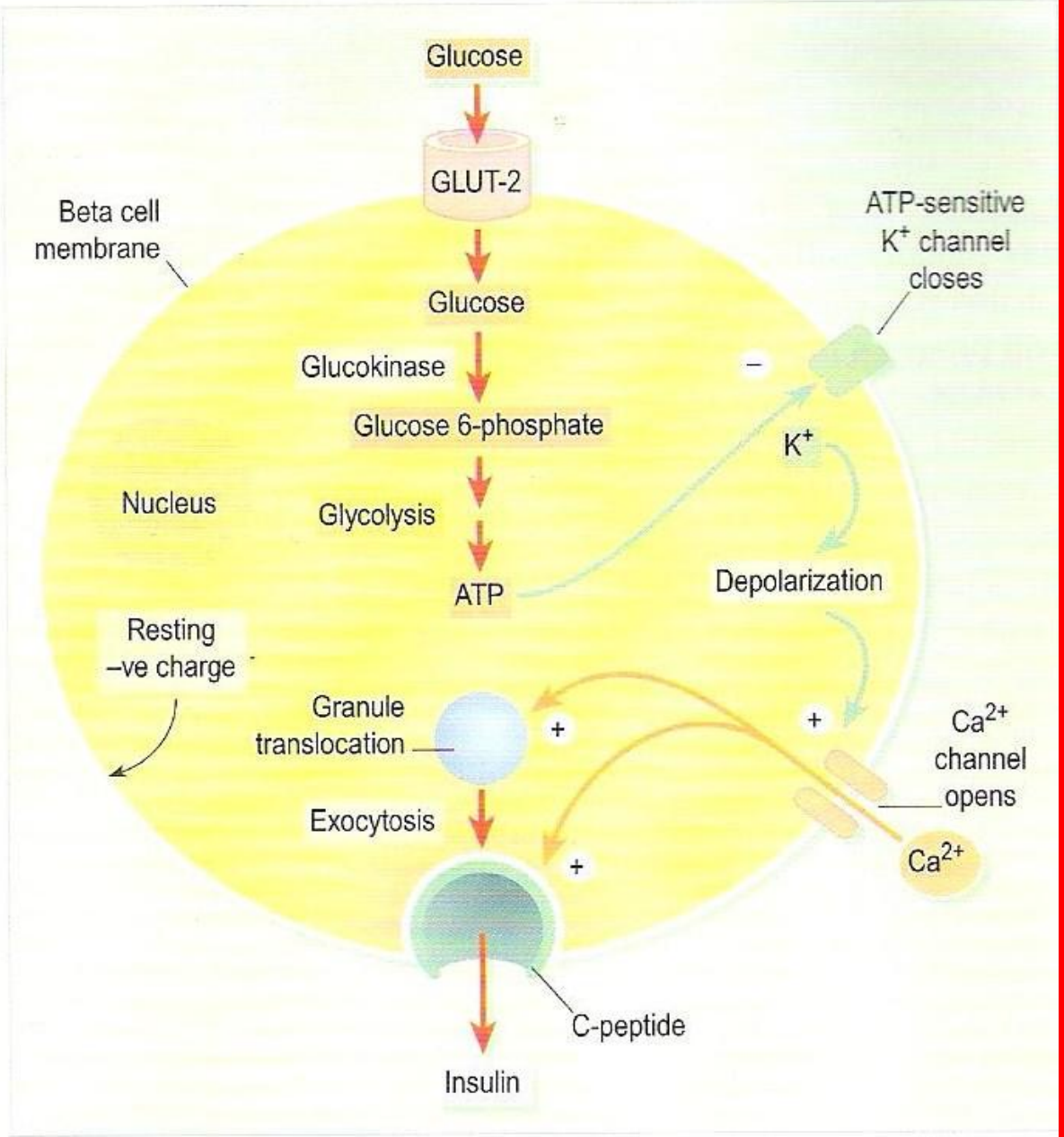


Fig. 3 **Insulin synthesis is coupled to its secretion.** GLUT is a glucose transporter.

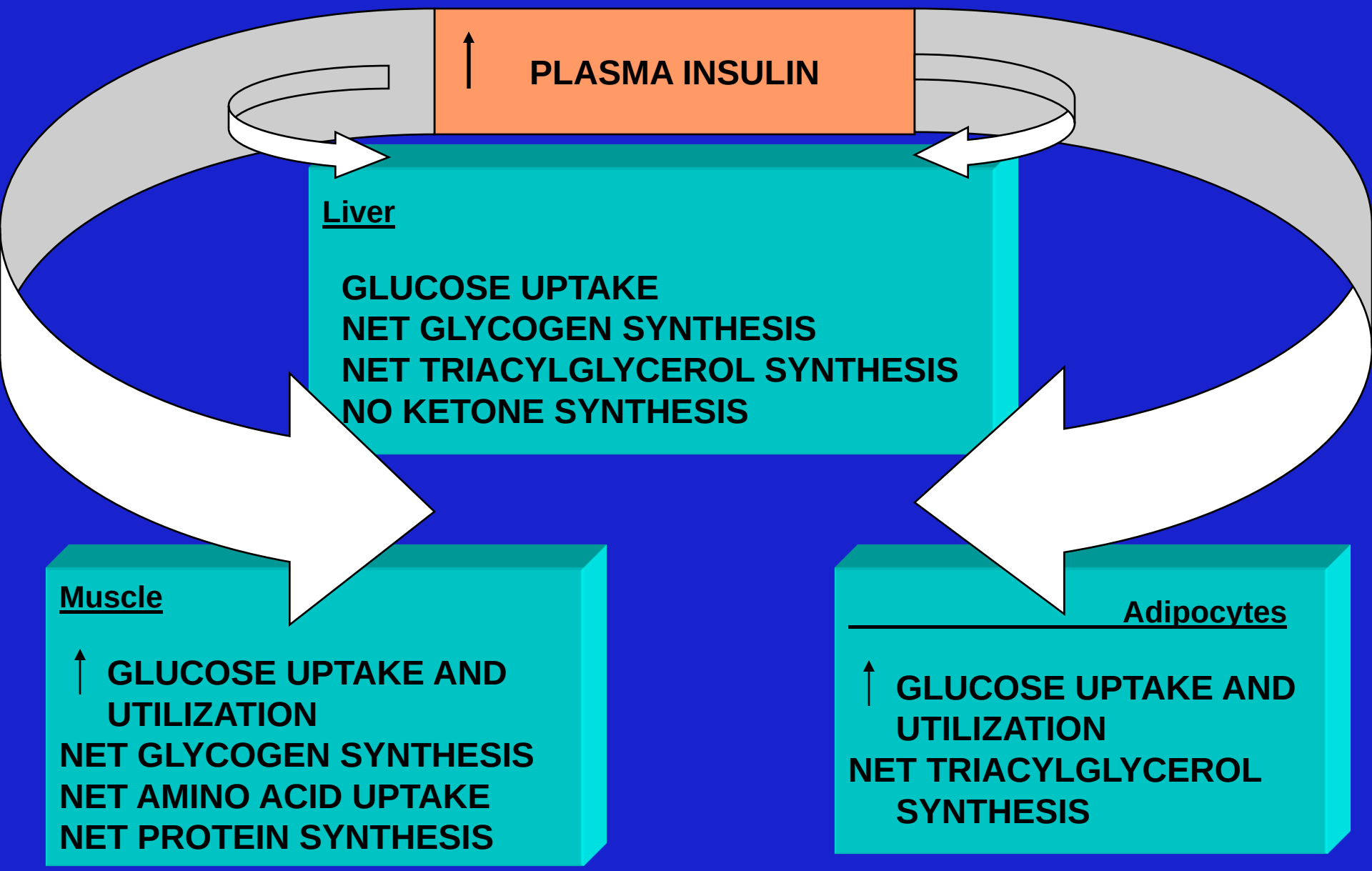
Metabolic Effects of Insulin

A. Paracrine Effects

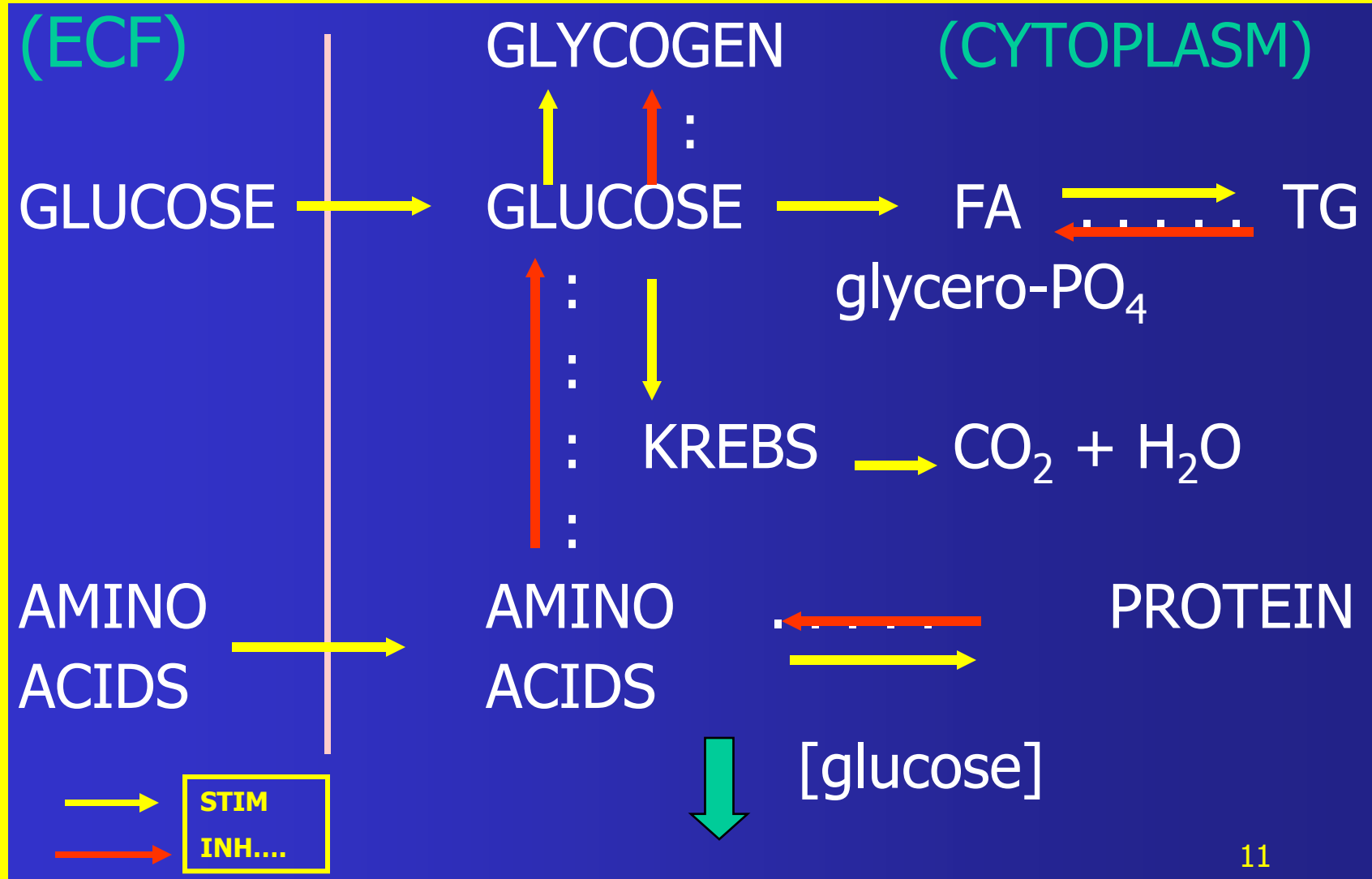
B + D cell (insulin + somatostatin) ↓ A cells (glucagon)

B. Endocrine Effects

1. liver: ↑glycogen synthesis and storage, glycolysis
   ↓ glycogen breakdown, gluconeogenesis, ketogenesis
   ↑ protein, TG, VLDL
2. Muscle: ↑ a.a. transport →↑ protein synthesis
   ↑ glycogen synthesis ↑ glucose transport
   ↑ glycogen synthase, ↓ glycogen phosphorylase
3. Adipose tissue:
   ↑ TG storage: ↑ lipoprotein lipase (endothelial cells)
   ↑ Glucose transport
   ↓ Intracellular lipolysis (↓ HSL)


↑ PLASMA INSULIN
Liver
GLUCOSE UPTAKE
NET GLYCOGEN SYNTHESIS
NET TRIACYLGLYCEROL SYNTHESIS
NO KETONE SYNTHESIS
Muscle
↑ GLUCOSE UPTAKE AND UTILIZATION
NET GLYCOGEN SYNTHESIS
NET AMINO ACID UPTAKE
NET PROTEIN SYNTHESIS
Adipocytes
↑ GLUCOSE UPTAKE AND UTILIZATION
NET TRIACYLGLYCEROL SYNTHESIS

Effects of Insulin



Effects of Insulin

CARBOHYDRATES

- Increased glucose uptake
- Increased glycolysis
- Increased glycogen synthesis
- Decreased glycogen catabolism
- Decreased gluconeogenesis

RESULT

- Decreased plasma glucose
- Increased glucose utilization
- Increased glycogen storage
- Net glucose uptake by the liver

Effects of Insulin

PROTEIN

Stimulation of amino acid uptake.

Stimulation of protein synthesis.

RESULT:

Decreased plasma amino acid levels.

Net protein anabolism.

Effects of Insulin

LIPIDS

Increased triacylglycerol (TG) synthesis.

Decreased TG catabolism.

Stimulation of endothelium lipoprotein lipase.

RESULT:

Decreased plasma glycerol/FFA.

Net fat storage.

Decreased utilization of fat for energy.

Activation of glycogen synthase and inactivation of glycogen phosphorylase

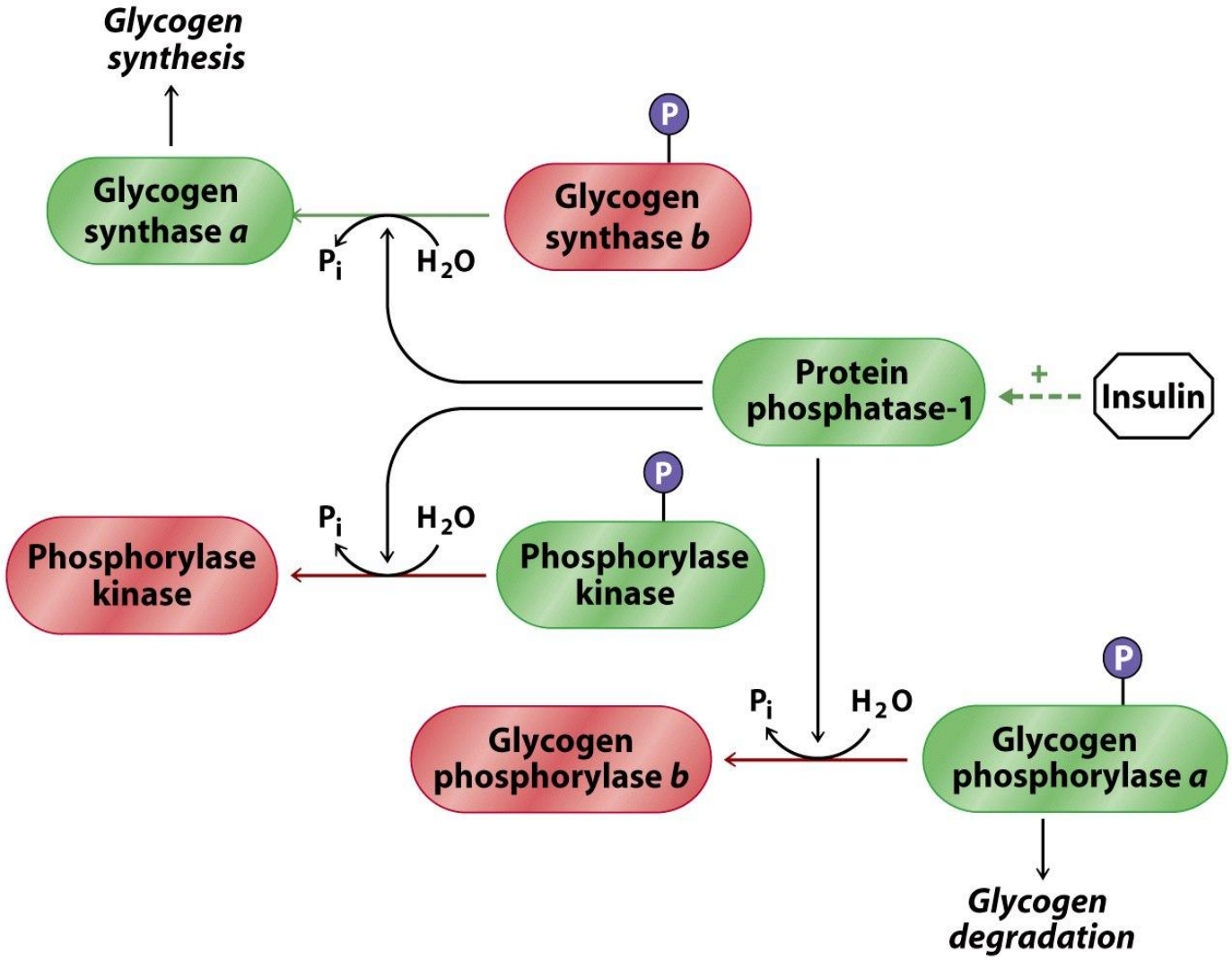
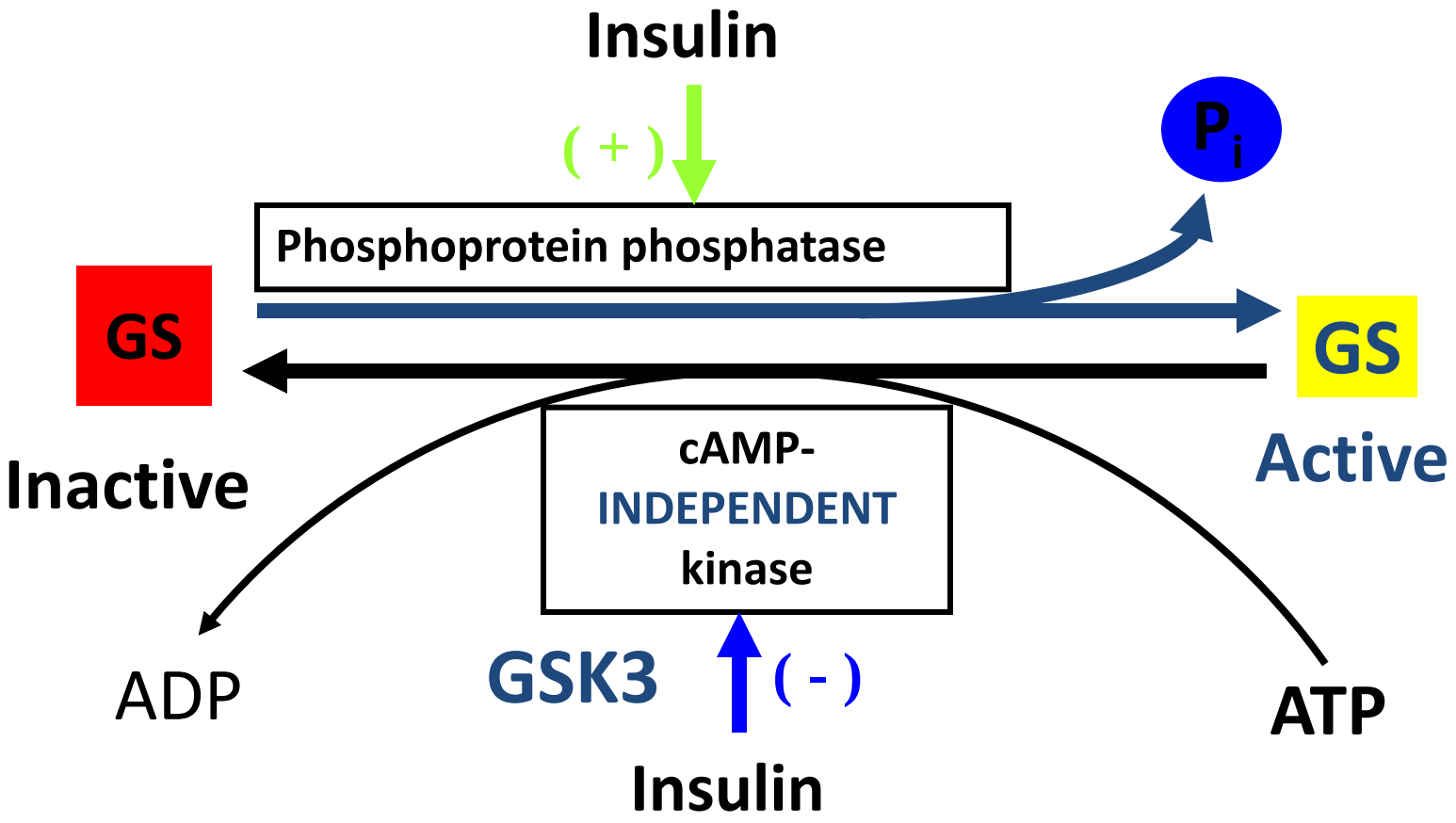


Figure 12-17 Principles of Biochemistry, 4/e

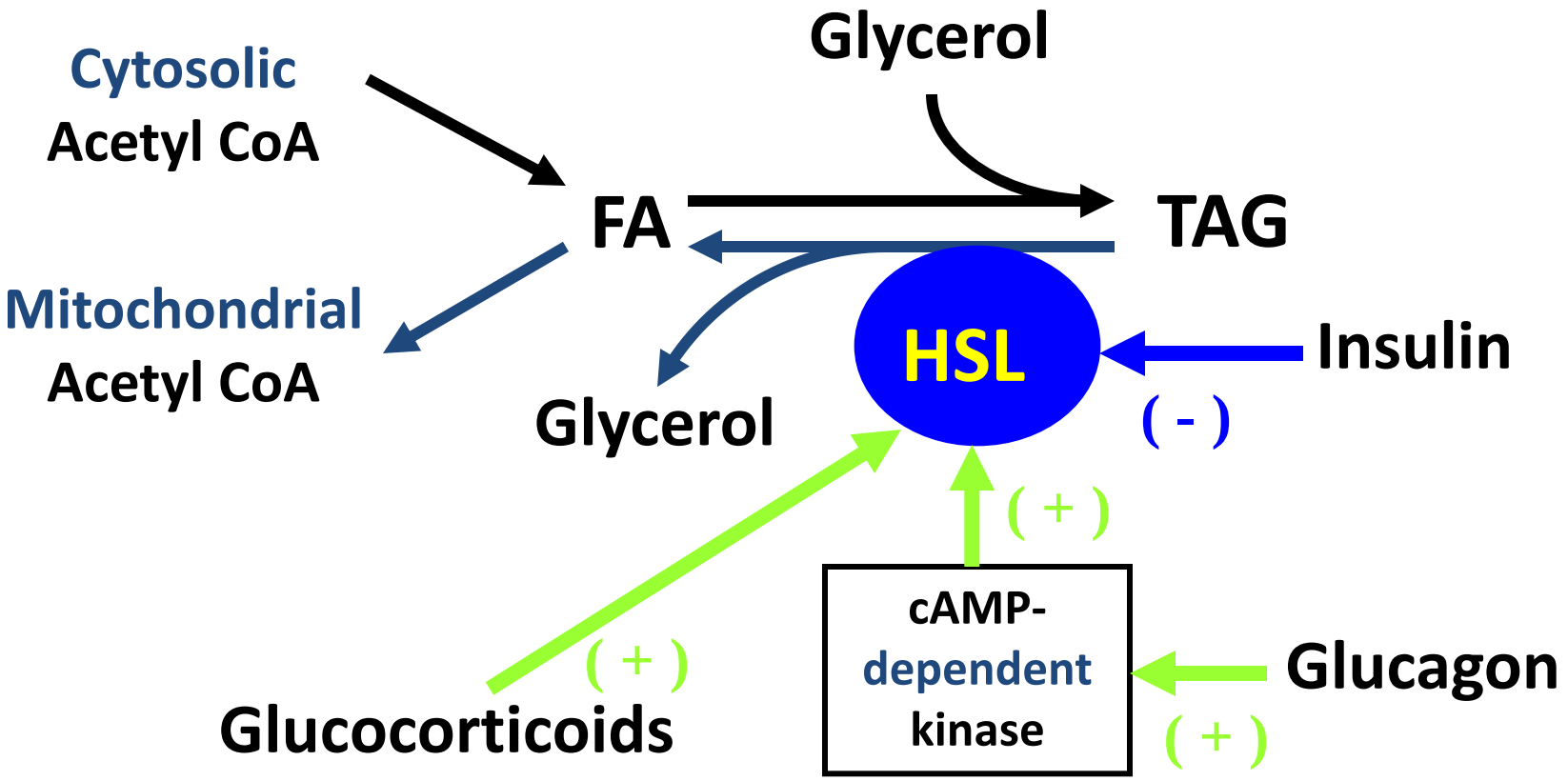
Binding of insulin by the liver or muscle cell leads to stimulation of protein phosphatase-1

Hydrolysis of phosphate catalyzed by protein phosphatase-1 increases the activity of glycogen synthase but deactivates glycogen phosphorylase.

Insulin switches ON glycogen synthetase (GS)



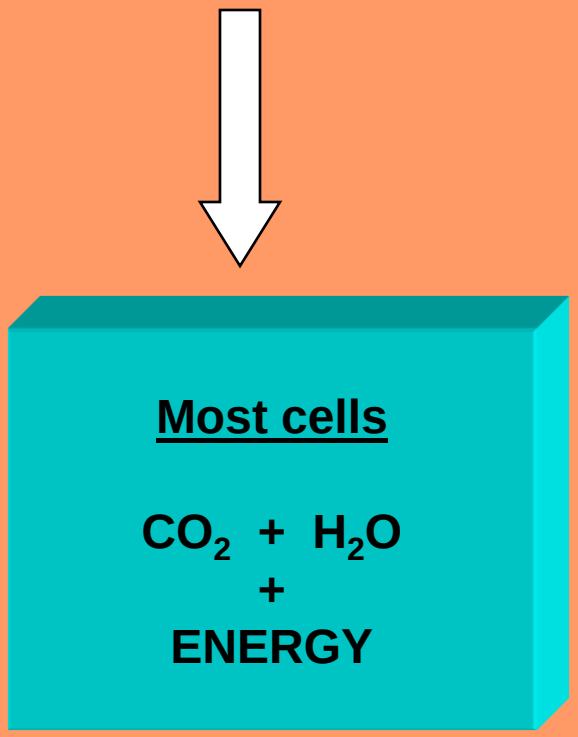
HSL and futile cycling



ABSORPTIVE STATE (ACTIONS OF INSULIN)	POSTABSORPTIVE STATE (DECREASED INSULIN)
PROTEINS ↑ AMINO ACIDS	PROTEINS ↓ AMINO ACIDS
TRIACYLGLYCEROL ↑ α-GLYCEROL PO_4 FATTY ACIDS	TRIACYLGLYCEROL ↓ GLYCEROL FATTY ACIDS
GLYCOGEN ↑ GLUCOSE	GLYCOGEN ↓ GLUCOSE

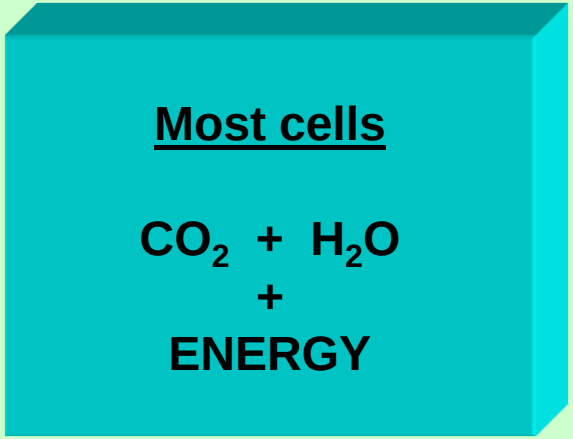
ABSORPTIVE STATE (ACTIONS OF INSULIN)

GLUCOSE

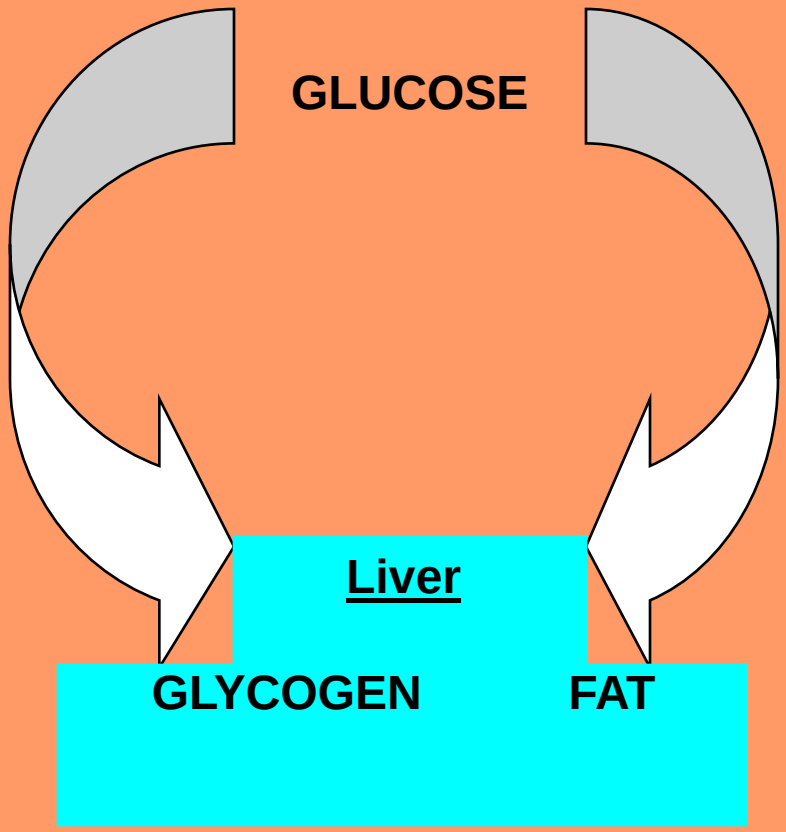


POSTABSORPTIVE STATE (DECREASED INSULIN)

FATTY ACIDS
and
KETONES

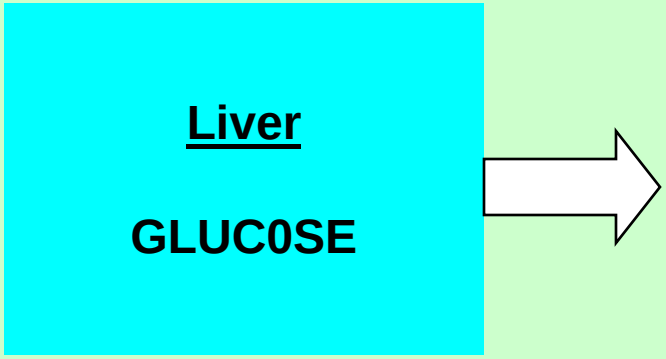


ABSORPTIVE STATE (ACTIONS OF INSULIN)



POSTABSORPTIVE STATE (DECREASED INSULIN)

PYRUVATE
LACTATE
GLYCEROL
and
AMINO ACIDS



Glucose Transporter Proteins

Energy-dependent Na^+- glucose cotransporter: intestine and kidney

Non-energy – dependent transporters: other sells

GLUT1: all human tissues, mainly brain, vascular system.
high affinity (basal glucose uptake).

GLUT3: all tissues, neurons
High affinity

GLUT2: low affinity
Important postprandially
Hepatic, intestinal, renal cells.

GLUT4: skeletal muscle, adipose tissue
Sequestered intracellularly
Insulin ↑ GLUT4 translocation

Glucose Transporter Proteins

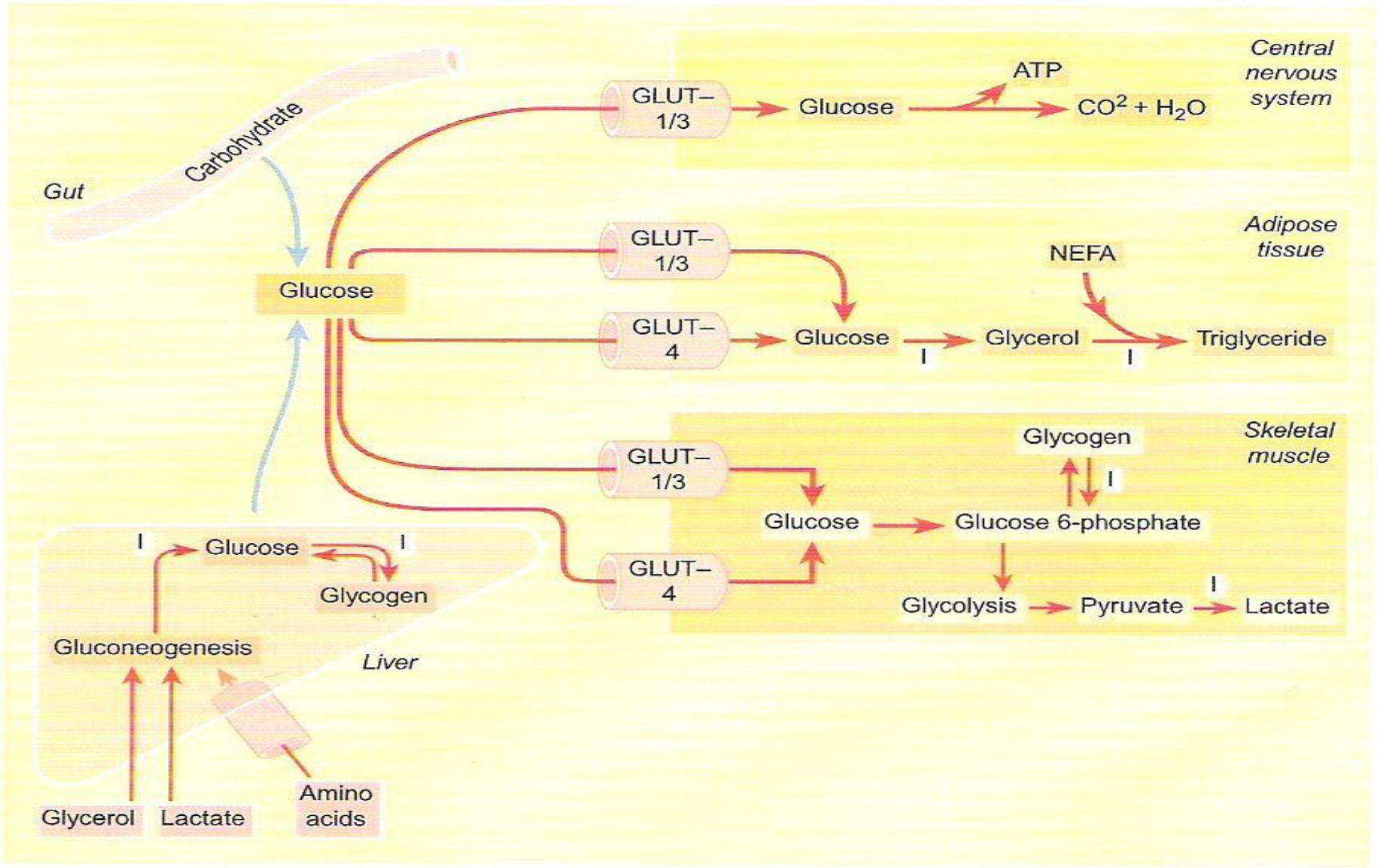
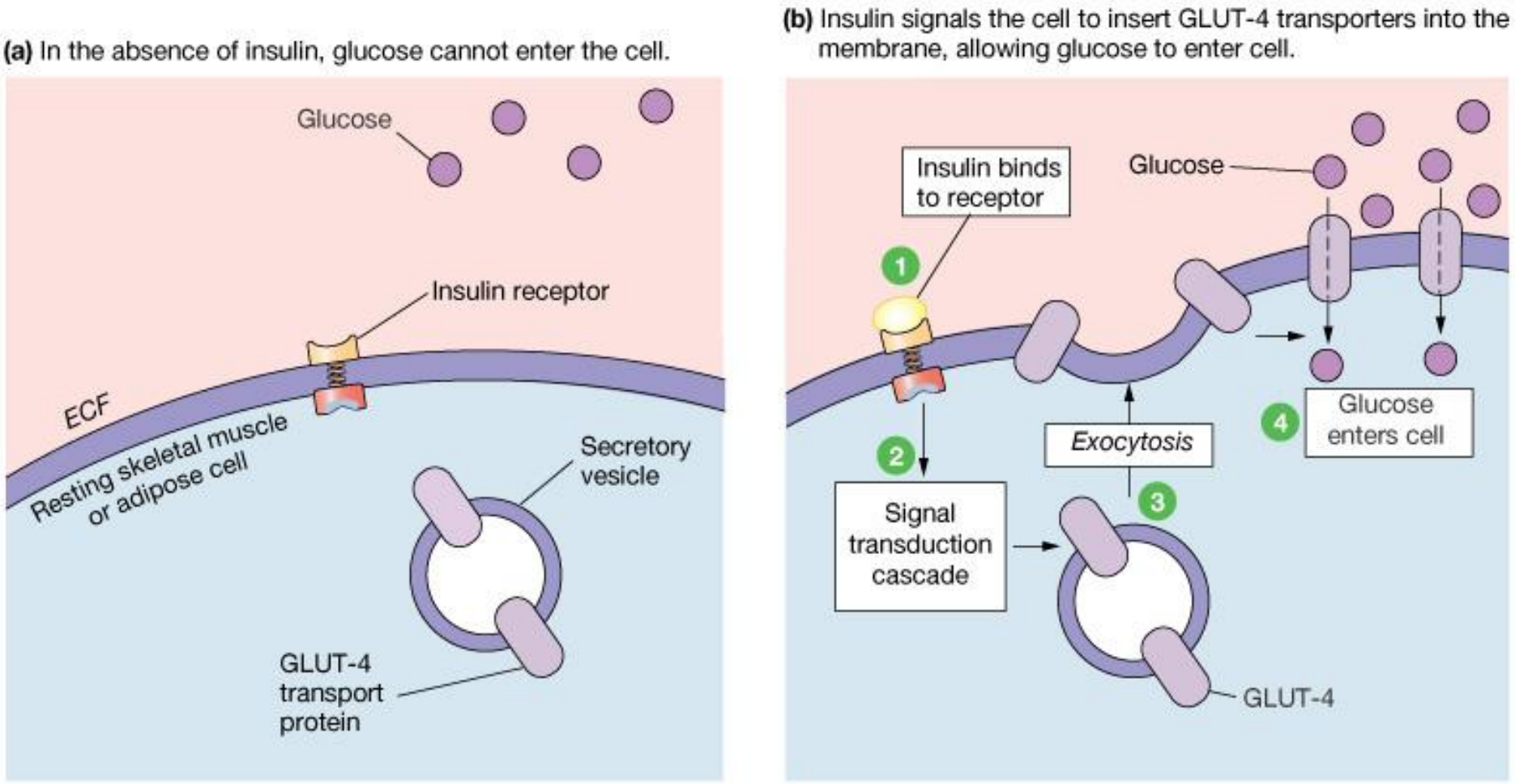
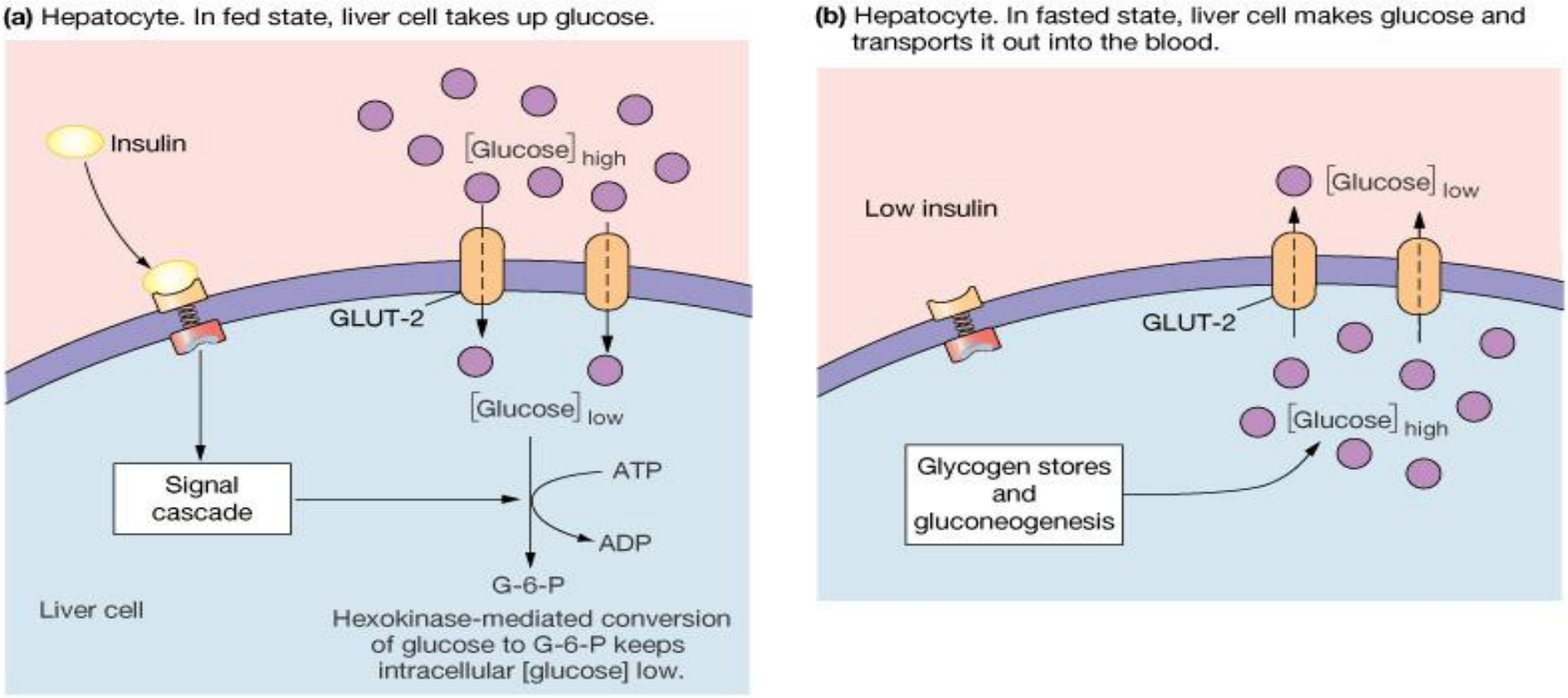


Fig. 1 **Overview of carbohydrate metabolism.** GLUT is a glucose transporter; I, indicates a site of action of insulin.

Insulin Stimulates Glucose Uptake in Skeletal Muscle and Fat cells: Insert Glucose Transporters



Insulin Stimulates Glucose Uptake in Liver cells: Form a polymer (glycogen)



Glucagon

Biochemistry

Pancreatic glucagon: single–polypeptide chain 29 a.as. MW 3485 synthesized in A cells.

Secretion

Glucose, GABA (B cells)↓ glucagon

Arg: ↑ glucagon, insulin

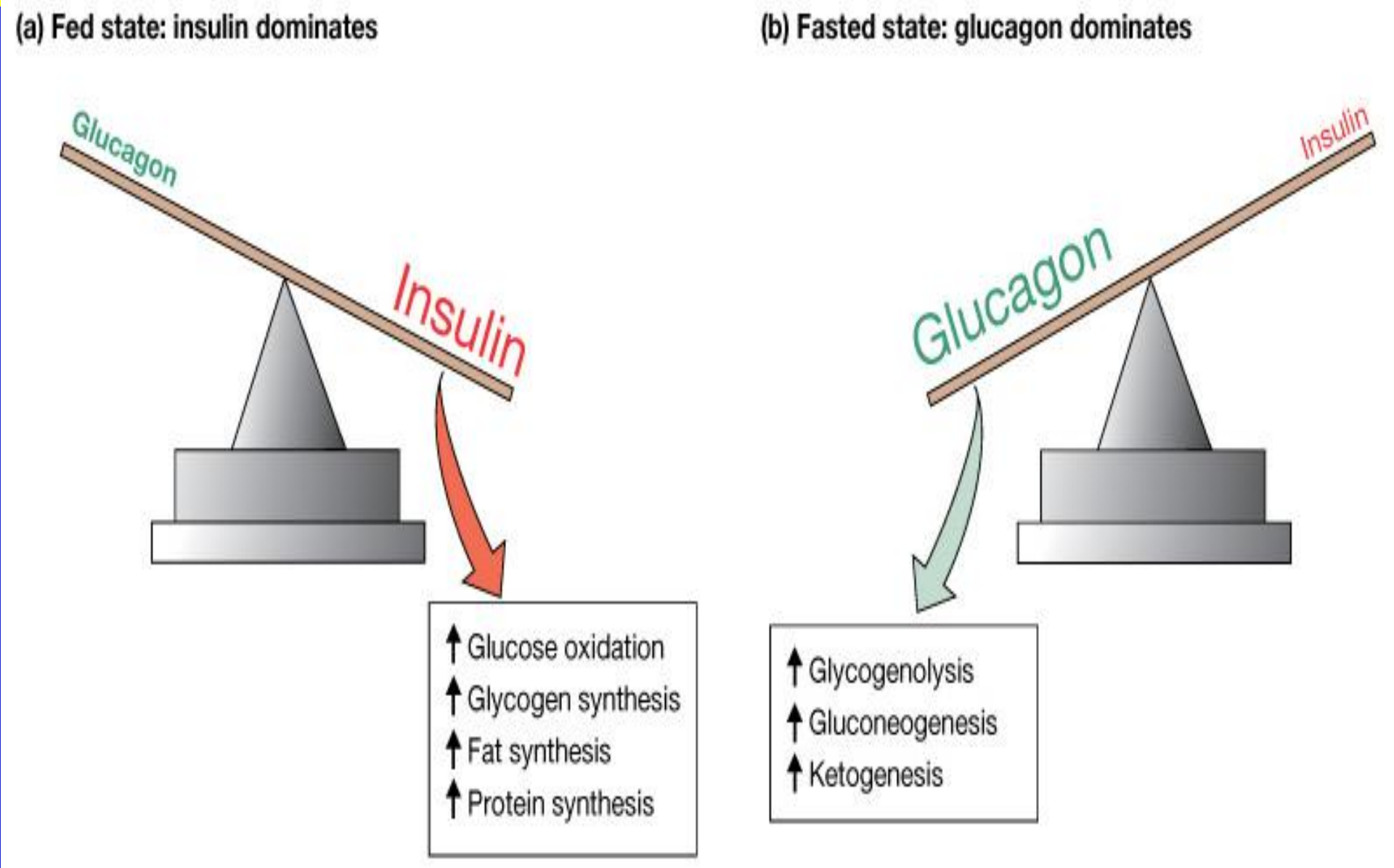
Catecholamines, CCK, gastrin, GIP, glucocorticoid ↑ glucagon

Action

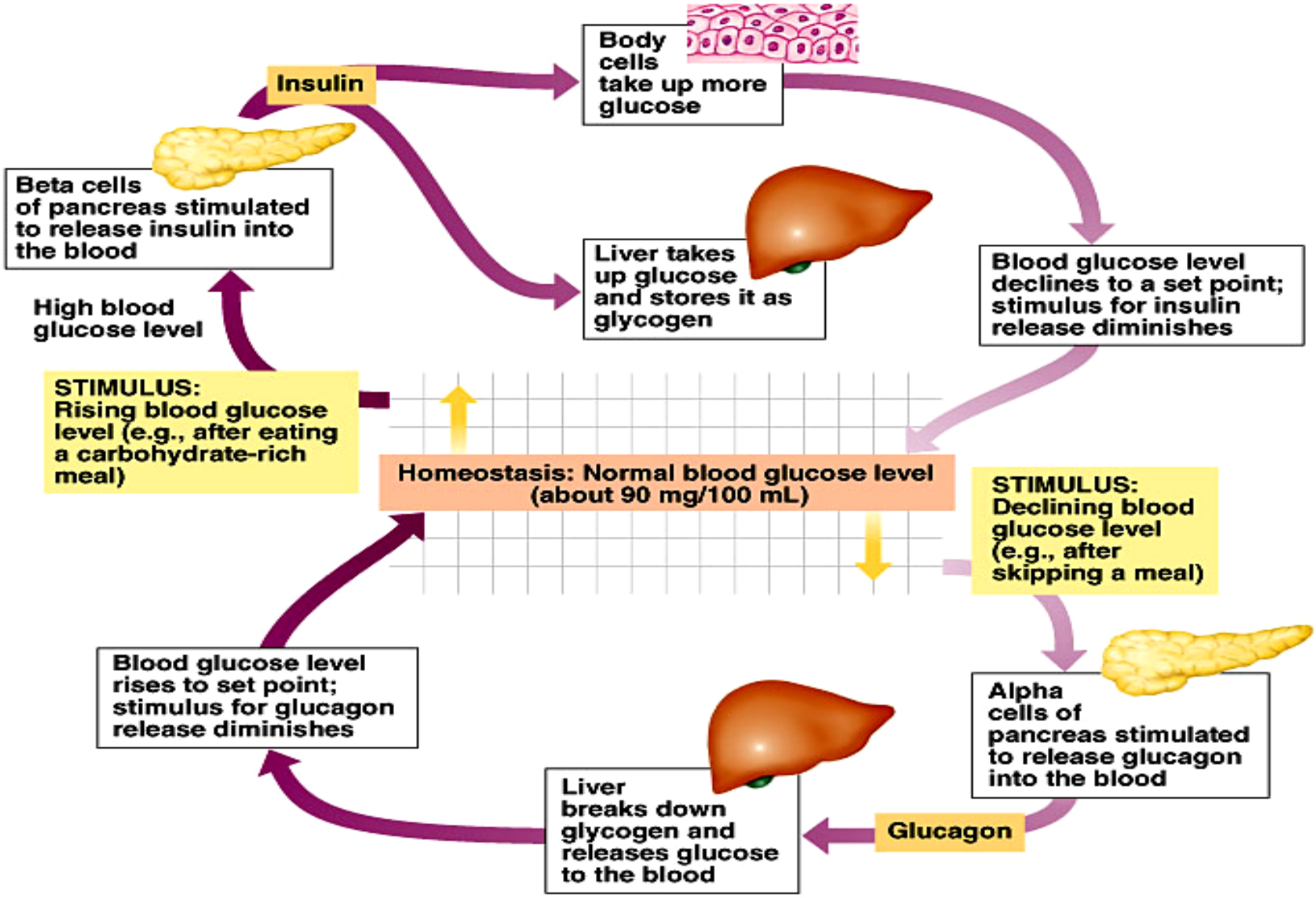
↑ Glycogenolysis, gluconeogenesis, ketogenesis.

↑ cAMP

Pancreatic Hormones, Insulin & Glucagon Regulate Metabolism



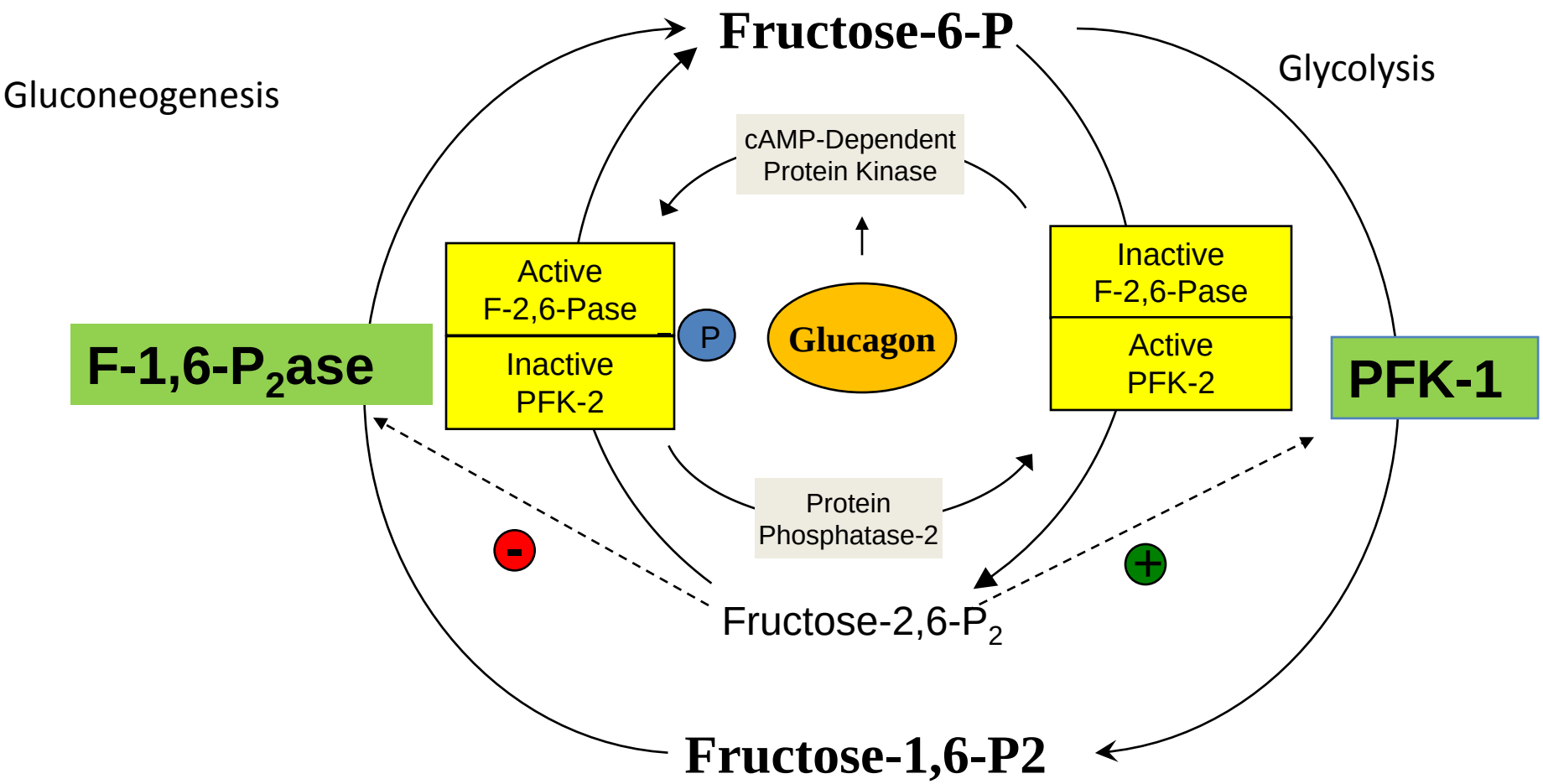
The Pancreas



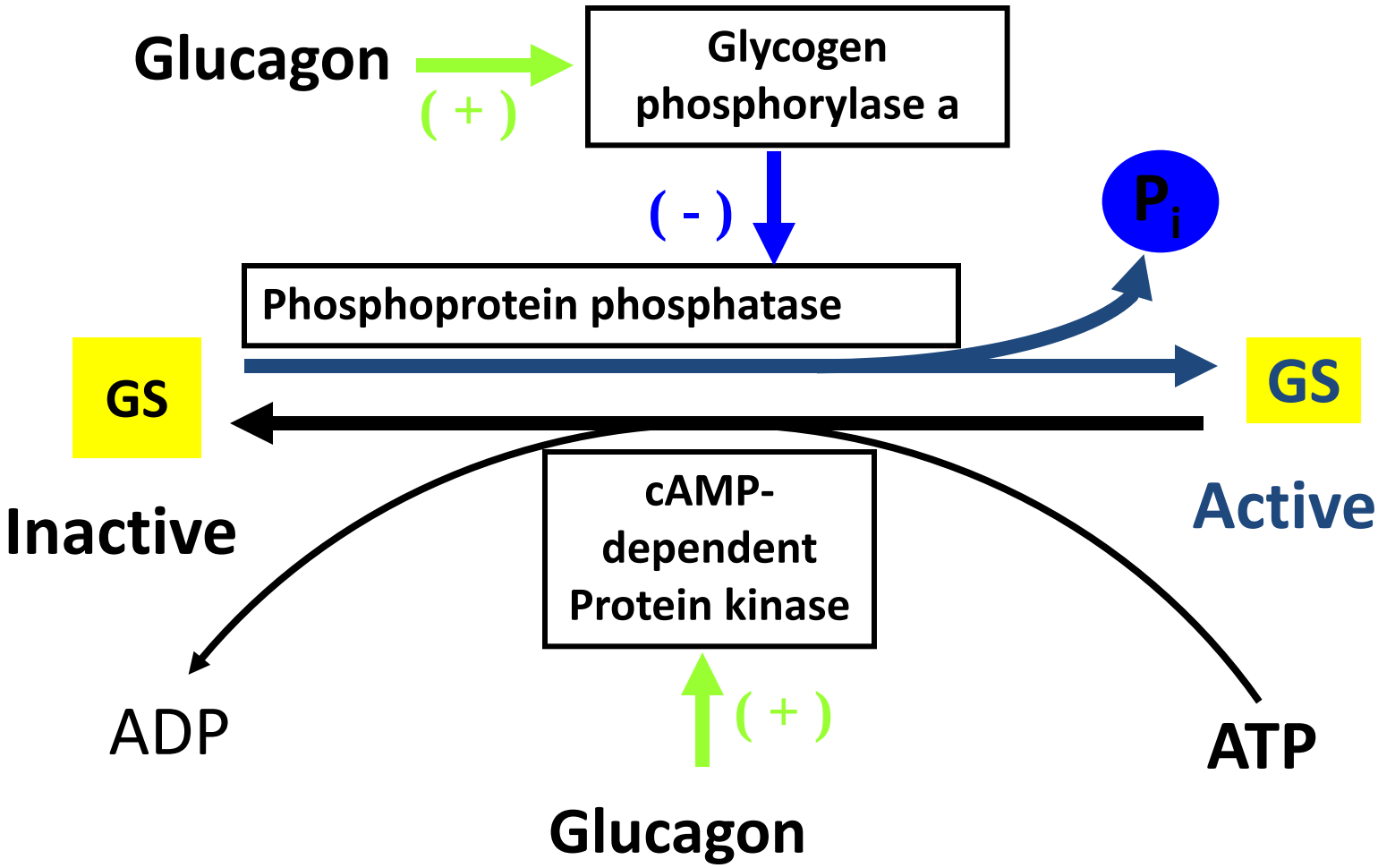
Glucose homeostasis

FIGURE 45.10 Glucose homeostasis maintained by insulin and glucagon.

6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2/F-2,6-P_2ase)



Glucagon switches OFF glycogen synthetase (GS)



Activation of glycogen phosphorylase and inactivation of glycogen synthase

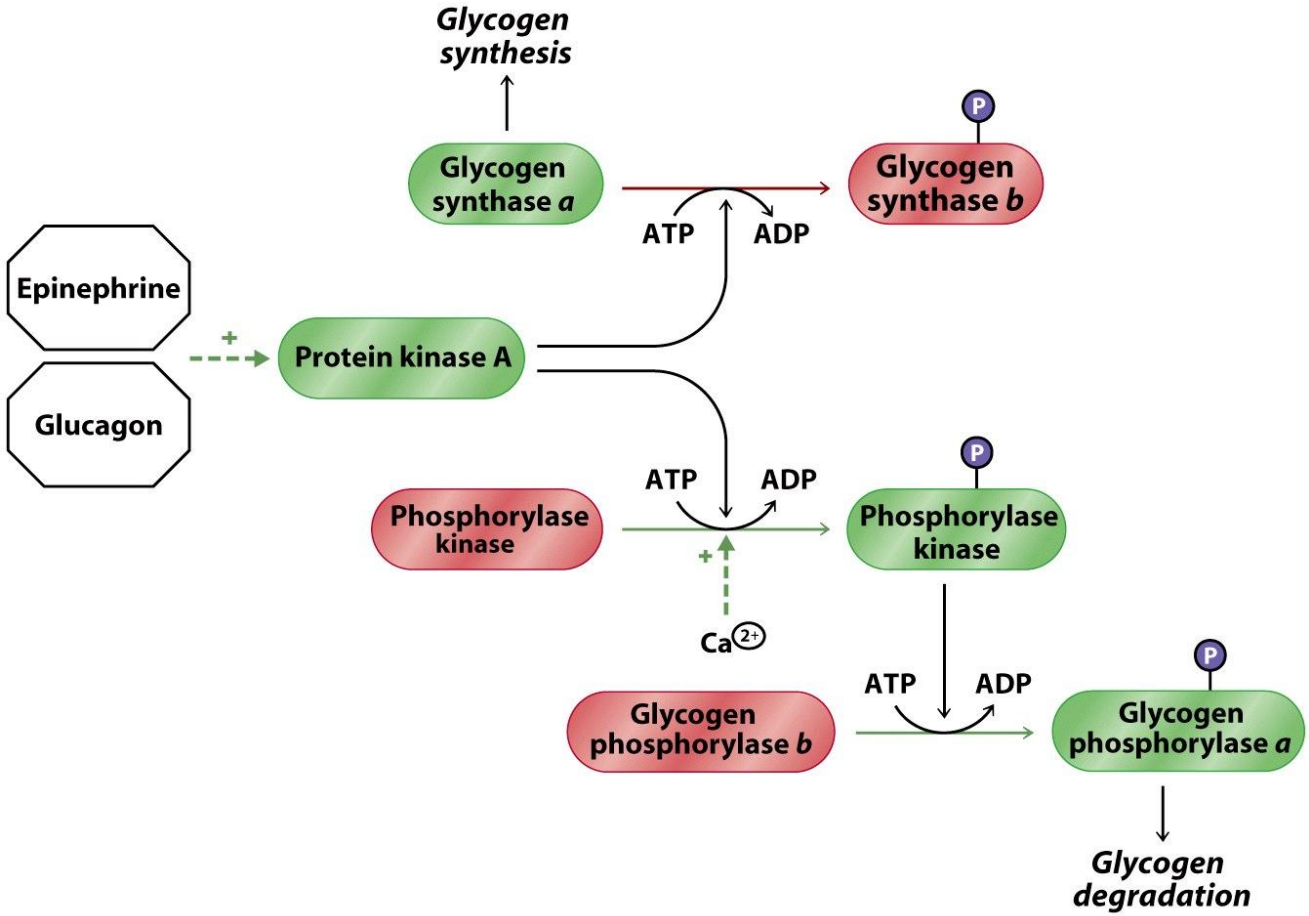
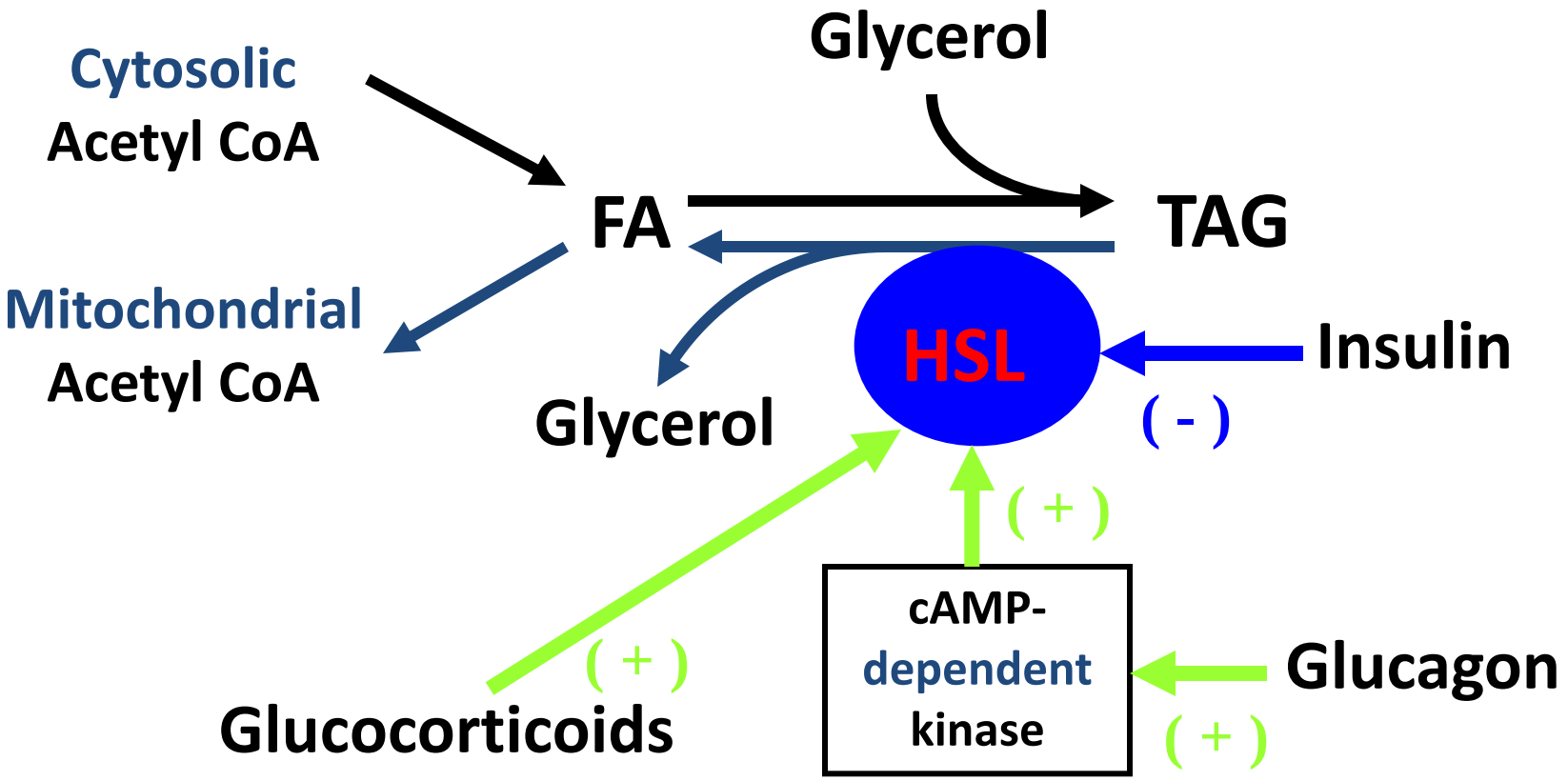


Figure 12-16 Principles of Biochemistry, 4/e

Glucagon as a signal of hunger. In its presence, the liver carries out glycogenolysis to provide glucose to the bloodstream and the rest of the body.
Epinephrine is a signal of stress. Stimulates muscle glycogenolysis to provide glucose to support contraction and movement

HSL and futile cycling

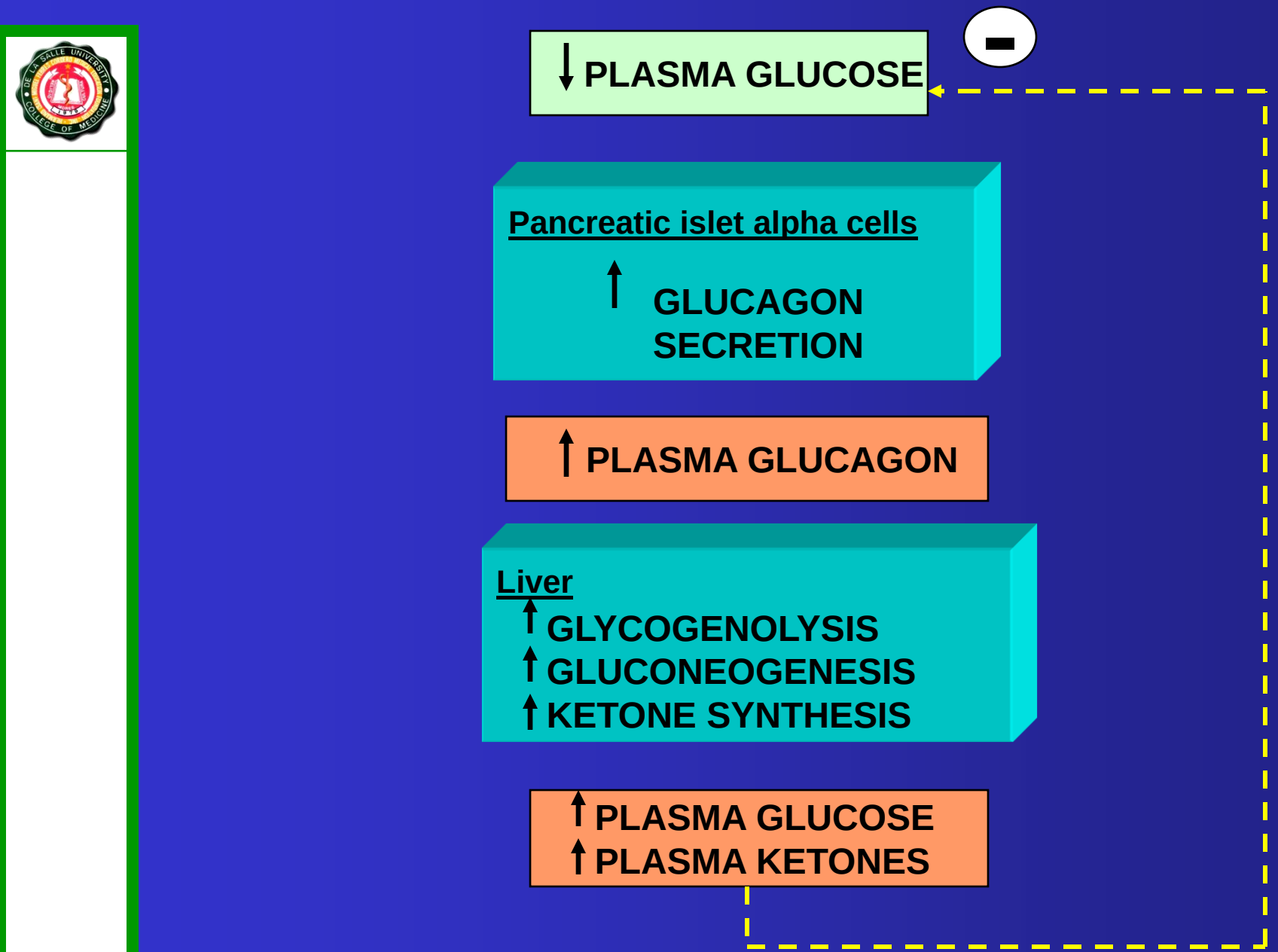


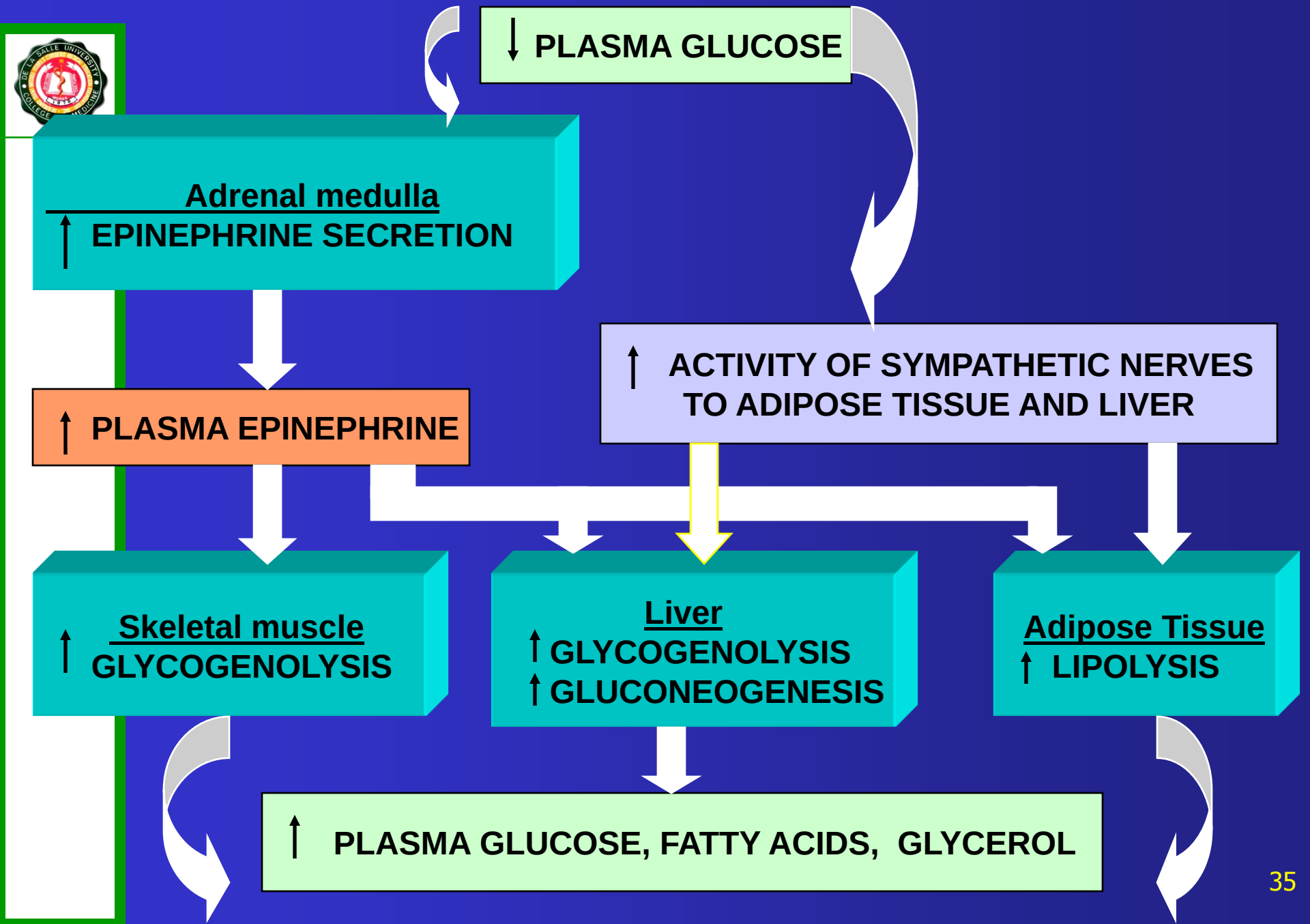
Actions of insulin and glucagon

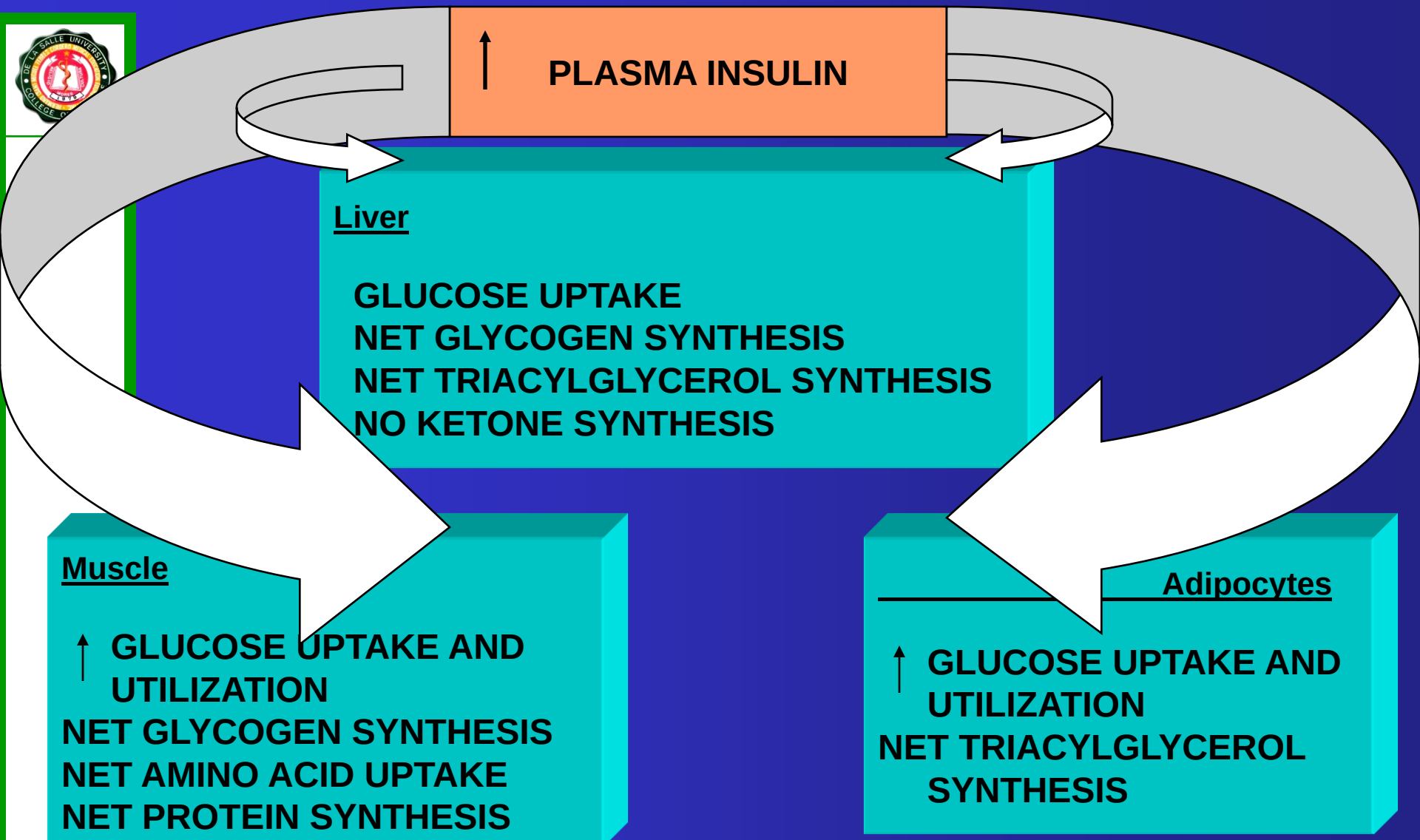
Insulin	Glucagon
Signal of **feeding**.	Signal of **fasting**.
Target tissues: liver, adipose skeletal muscle	Target tissues: liver, adipose
Affects metabolism of: carbohydrates, lipids proteins	Affects metabolism of: carbohydrates, lipids
Actions are **anabolic**	Actions are **catabolic**

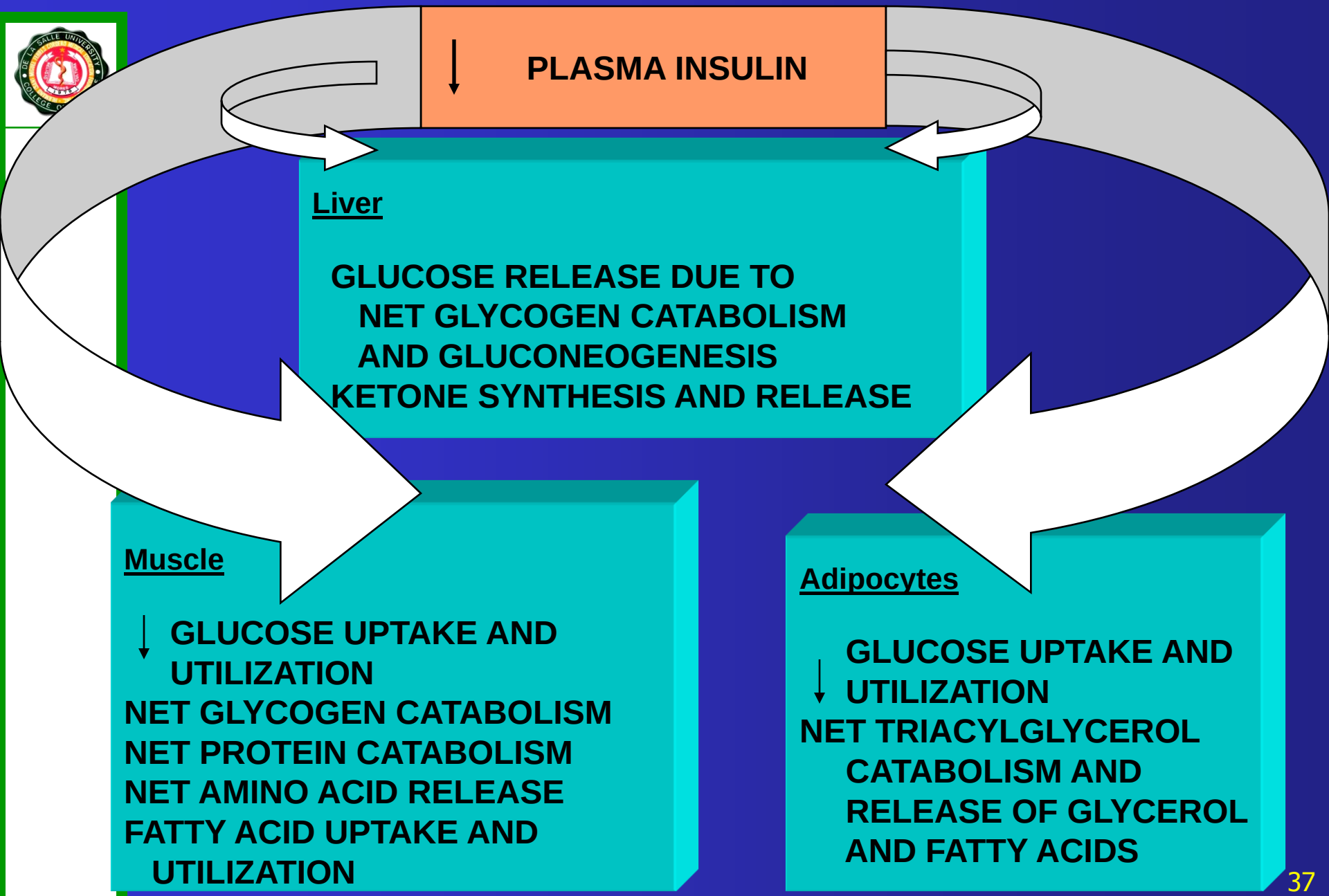
Control of insulin & glucagon secretion

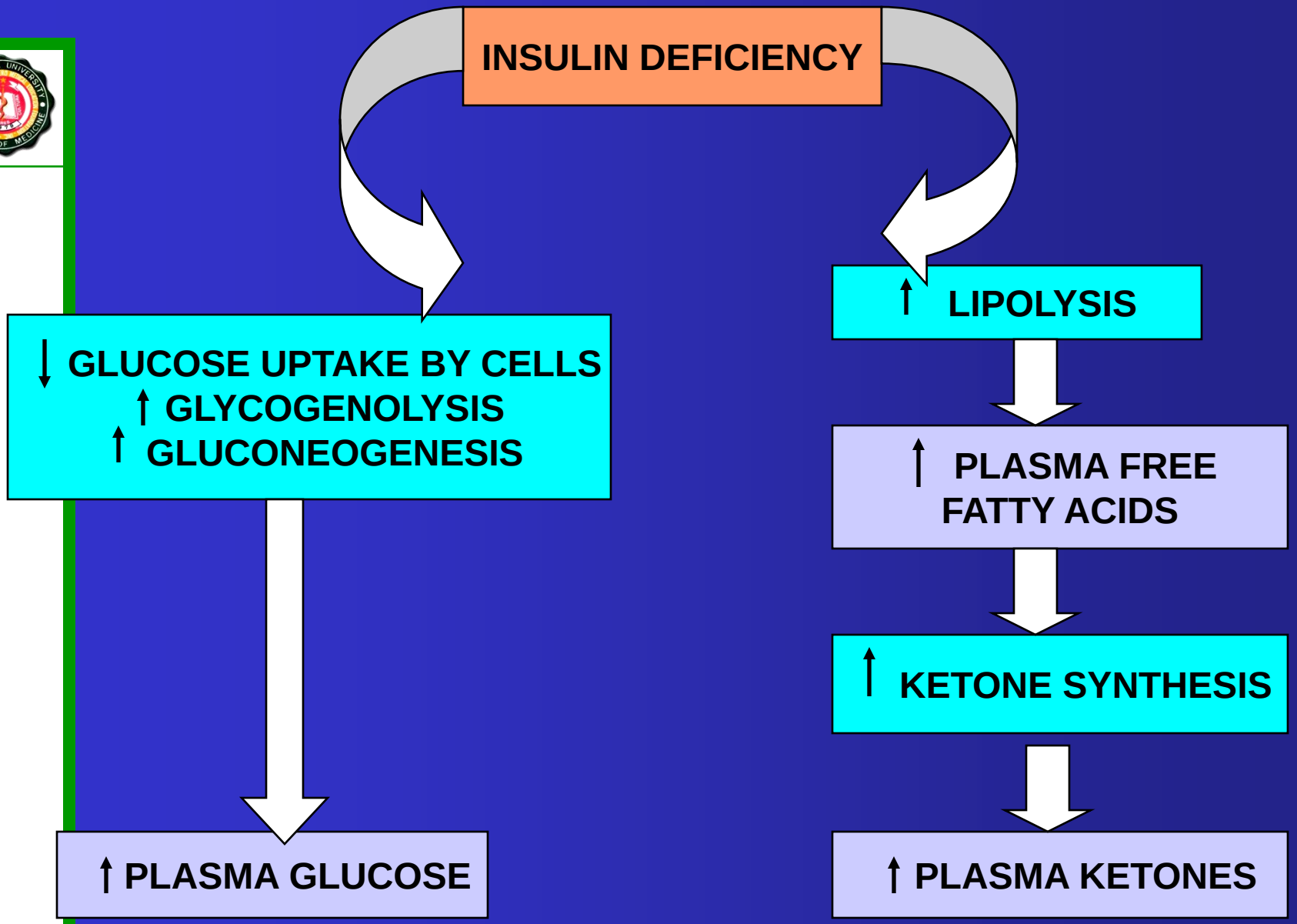
Factor	Insulin	Glucagon
Nutrients:		
glucose ↑ 5mM	+	-
glucose ↓ 5mM	-	+
↑ amino acids	+	+
↑ fatty acids	+	No effect
Hormones/neurotransmitters:		
GI tract	+	No effect
epinephrine	-	+
norepinephrine	-	+

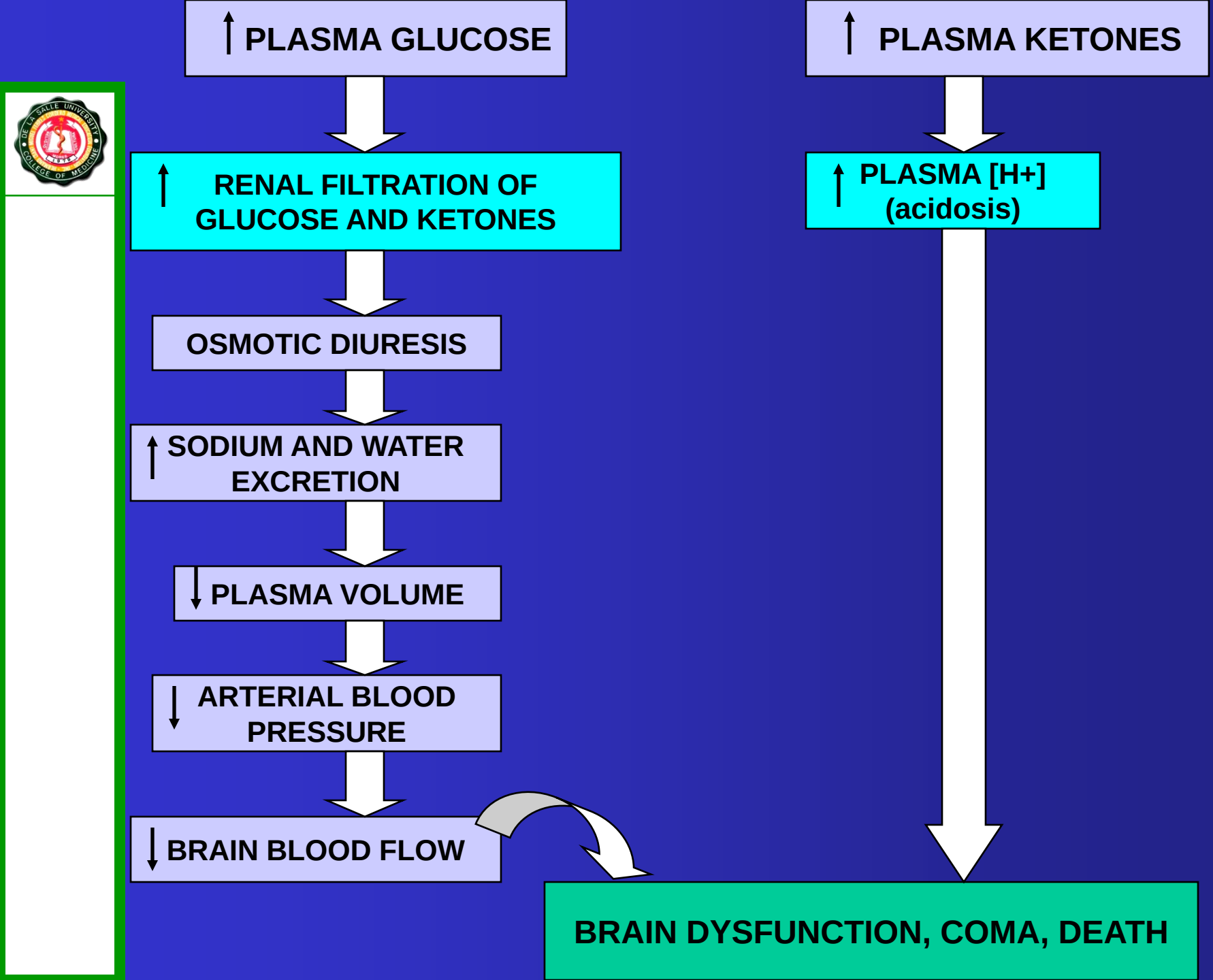

↓ PLASMA GLUCOSE
−
Pancreatic islet alpha cells
↑ GLUCAGON SECRETION
↑ PLASMA GLUCAGON
Liver
↑ GLYCOGENOLYSIS
↑ GLUCONEOGENESIS
↑ KETONE SYNTHESIS
↑ PLASMA GLUCOSE
↑ PLASMA KETONES


↓ PLASMA GLUCOSE
Adrenal medulla
↑ EPINEPHRINE SECRETION
↑ PLASMA EPINEPHRINE
↑ ACTIVITY OF SYMPATHETIC NERVES TO ADIPOSE TISSUE AND LIVER
↑ Skeletal muscle GLYCOGENOLYSIS
Liver
↑ GLYCOGENOLYSIS
↑ GLUCONEOGENESIS
Adipose Tissue
↑ LIPOLYSIS
↑ PLASMA GLUCOSE, FATTY ACIDS, GLYCEROL


↑ PLASMA INSULIN
Liver
GLUCOSE UPTAKE
NET GLYCOGEN SYNTHESIS
NET TRIACYLGLYCEROL SYNTHESIS
NO KETONE SYNTHESIS
Muscle
↑ GLUCOSE UPTAKE AND UTILIZATION
NET GLYCOGEN SYNTHESIS
NET AMINO ACID UPTAKE
NET PROTEIN SYNTHESIS
Adipocytes
↑ GLUCOSE UPTAKE AND UTILIZATION
NET TRIACYLGLYCEROL SYNTHESIS


↓ PLASMA INSULIN
Liver
GLUCOSE RELEASE DUE TO
NET GLYCOGEN CATABOLISM
AND GLUCONEOGENESIS
KETONE SYNTHESIS AND RELEASE
Muscle
↓ GLUCOSE UPTAKE AND
UTILIZATION
NET GLYCOGEN CATABOLISM
NET PROTEIN CATABOLISM
NET AMINO ACID RELEASE
FATTY ACID UPTAKE AND
UTILIZATION
Adipocytes
↓ GLUCOSE UPTAKE AND
UTILIZATION
NET TRIACYLGLYCEROL
CATABOLISM AND
RELEASE OF GLYCEROL
AND FATTY ACIDS


INSULIN DEFICIENCY
↓ GLUCOSE UPTAKE BY CELLS
↑ GLYCOGENOLYSIS
↑ GLUCONEOGENESIS
↑ PLASMA GLUCOSE
↑ LIPOLYSIS
↑ PLASMA FREE FATTY ACIDS
↑ KETONE SYNTHESIS
↑ PLASMA KETONES


↑ PLASMA GLUCOSE
↑ PLASMA KETONES
↑ RENAL FILTRATION OF GLUCOSE AND KETONES
↑ PLASMA [H+] (acidosis)
OSMOTIC DIURESIS
↑ SODIUM AND WATER EXCRETION
↓ PLASMA VOLUME
↓ ARTERIAL BLOOD PRESSURE
↓ BRAIN BLOOD FLOW
BRAIN DYSFUNCTION, COMA, DEATH

Somatostatin

- Preprosomatostatin 128 a.as → somatostatin-28 → somatostatin-14
- Hypothalamus: somatostatin-14, somatostatin-28 (5-10%)
- Pancreatic D cells: only somatostatin-14
- Small intestine: somatastatin-28 (70-75%), somatostatin-14 (25-30%)
- **Potency:** somatostatin-28 is 10× more active than somatastatin-14 for ↓GH and insulin
- Somatostatin-14 more effective ↓ glucagon

Somatostatin …

Release:

glucose, arg. G.I. hormones ↑ insulin + somatostatin

Receptor:

Five somatostatin receptors (SSTR 1-5)

SSTR 5: ↓ insulin

SSTR 2: ↓ G.H., glucagon

Octreotide SSTR 2 > SSTR 5 somatostatin agonist treat acromegaly without much effect on carbohydrate tolerance.

Diabetes Mellitus

Classification

Type 1 Diabetes mellitus (previously IDDM)

- Pancreatic islet B cell destruction
- 95% due to autoimmune process
- 5% idiopathic

Type 2 Diabetes Mellitus (previously NIDDM)

- Spectrum of defects, more prevalent
- Insulin resistance with impairment in compensatory insulin secretion

Other specific Type

- Rare monogenic defects of:
  - Pancreatic B cell function
  - Insulin action

Type 1 Diabetes Mellitus

Characteristics

- Severe form: associated with ketosis.
- Most common in young individuals, occasionally occurs in non-obese adults.
- Circulating insulin: absent, ↑ glucagon, no response to insulinogenic stimuli.
- Liver, muscle, fat: fail to take up absorbed nutrients; deliver glucose, amino acids, fatty acids.
- Incomplete oxidation of F.As: ↑ ketone bodies.
- Treatment: insulin.

Type 1 Diabetes Mellitus …

Genetics of Type 1 Diabetes

- Genetic influences: less marked than type 2 (30-40% twins).
- Viruses (mumps, rubella, coxsackievirus β4).
- Environmental toxins (nitrophenylurea, rat poison, HCN)
- HLA- class II molecules (DQ and DR).
- DR3 and DR4: major susceptibility risk factors for type 1.
- Reason: mystery, theory (immune system targets B cell proteins homologous to certain viral or other foreign peptides (partially digested cow's milk).
- Most common antibodies: against glutamic acid decarboxylase (GAD).

Type 2 Diabetes Mellitus

Characteristics

- Insulin resistance with relative rather than absolute insulin deficiency.
- Adults > 40 years, some degree of obesity.
- Ketosis: rare
- Aggravated by: genetic factors, aging sedentary life, visceral obesity.
- Hyperglycemia: impede insulin signaling and pancreatic β cell function
- Strong genetic predisposition, complex and poorly defined.

Type 2 Diabetes Mellitus

Subgroups

A. Obese type 2 Diabetes.

B. Nonobese type 2 Diabetes.

C. Metabolic syndrome (Syndrome X):

- Hyperglycemia, hyperinsulinemia, hypertension → coronary artery disease and stroke.
- Hypertriglyceridemia (↑VLDL, ↓HDL), Atherosclerosis, obesity.

Type 2 Diabetes Mellitus

Other Specific Types of Diabetes

1. **Genetic Defects of Pancreatic B cell Function**
   - Late childhood before age 25 years.
   - Maturity-Onset Diabetes of the Young = MODY "6 types".
   - Gene defect in glucose-induced insulin release.
   - MODY2: abnormal glucokinase
2. **Mutation of Mitochondrial DNA**

   Mutation of Mito DNA impairs leucine transfer into Mito.

Type 2 Diabetes Mellitus …

Other Specific Types of Diabetes …

3. **Mutant Insulins**
4. **Genetic defects in insulin action**

   Mutations of insulin receptor or postreceptor signaling.
5. **Diseases of the Exocrine Pancreas**

   Damage of ⅔ of the pancreas can cause diabetes
6. **Endocrinopathies**

   Acromegaly, ↑glucocorticoids (Cushing's syndrome), ↑catecholamines (pheochromocytoma), ↑thyroid hormone (thyrotoxicosis), ↑glucagon (glucagonoma), ↑pancreatic somatostatin: peripheral responsiveness to insulin is impaired, ↑somatostatin and catecholamines ↓ insulin

Clinical Features of Diabetes Mellitus

Type 1 Diabetes

- Absolute deficiency of insulin.
- Excessive accumulation of circulating glucose and F.As.
- Hyperosmolarity, hyperketonemia → osmotic diuresis → ↑ urine (↑ glucose, Na^+, H_2O in urine).
- Thirst, blurred vision (exposure of lenses and retinas to hyperosmolar fluids)
- Weight loss: depletion of (H_2O, glycogen, TG stores, muscle mass).
- loss of plasma volume (hypotension, dizziness).
- Loss of muscles (weakness).
- Ketoacidosis → dehydration, anorexia, nausea, vomiting.

Clinical Features of Diabetes Mellitus

Type 2 Diabetes

- Polyuria, thirst, blurred vision, fatigue, osmotic diuresis.
- Diabetes associated with upper fat deposits (android). "visceral" obesity "mesenteric region." correlates with insulin resistance, subcutaneous fat of the abdomen has little association with insulin insensitivity.

Laboratory Findings in Diabetes Mellitus

1. Urine glucose and ketone bodies, blood glucose – basal and after glucose administration.
2. Glycosylated hemoglobin: assessment of therapeutic management.
3. Insulin, C-peptide, GH, glucagon.
4. Atherosclerosis: serum cholesterol, TG, HDL, LDL.

Urinalysis

1. **Glycosuria**
   - Problems: urine glucose reflects blood glucose at time of urine formed.
   - Non-diabetic glycosuria due to glucose: abnormal renal glucose handling; pregnancy.
2. **Ketonuria**
   - 3 major ketone bodies: β - hydroxybutyric acid, acetoacetic acid, acetone,
   - Other conditions: starvation, high-fat diet, alcoholic ketoacidosis, fever.
3. **Proteinuria**
   - Sign of renal complications of diabetes.

Blood Glucose Testing

1. **Normal Values**

   Fasting plasma glucose 70-110 mg/dl.

2. **Venous Blood Samples**

   Samples in tubes with Na fluoride.

   Enzymatic methods (glucose oxidase, hexokinase), colorimetric method.

3. **Capillary Blood Samples**

   Paper strip methods (glucose oxidase, glucose dehydrogenase, hexokinase)

4. **Interstitial Fluid Glucose Samples**

   Two continuous glucose monitoring systems:

   a. Inserting a subcutaneous sensor

   b. Glucowatch: interstitial fluid extracted through intact skin by low electric current.

Laboratory Findings in Diabetes Mellitus

Serum Ketone Determination

Glycated Hemoglobin Assays

Glycohemoglobin (GHb): reaction between glucose + Hb major from: HbA_{1c} elevated with chronic hyperglycemia

HbA_1: means Hb_{1c} +Hb_{1a} +Hb_{1b}

HbA1 reflects state of glycemia over preceding 8-12 wks.

Lipoproteins in Diabetes

Type 2 diabetic dyslipidemia: TG 300-400mg/dl, low HDL (<30mg/dl), smaller dense LDL (carries ↑ free cholesterol).

Diagnosis of Diabetes Mellitus

Diagnostic Criteria

1. Symptoms: (thirst, ↑ urination, unexplained weight loss)
2. Random blood glucose > 200 mg/dL
3. Fasting Plasma Glucose: > 126 mg/dL
4. Two-hour plasma glucose: > 200 mg/dL (75g oral glucose tolerance test)

   Impaired–Fasting glucose (IFG) added to impaired-glucose tolerance (IGT).

1. IFG: > 100 mg/dL < 126 mg/dL.
2. IGT: 2hr plasma glucose > 140 mg/dL < 200 mg/dL

Diabetes Mellitus: Type II a Group of Diseases

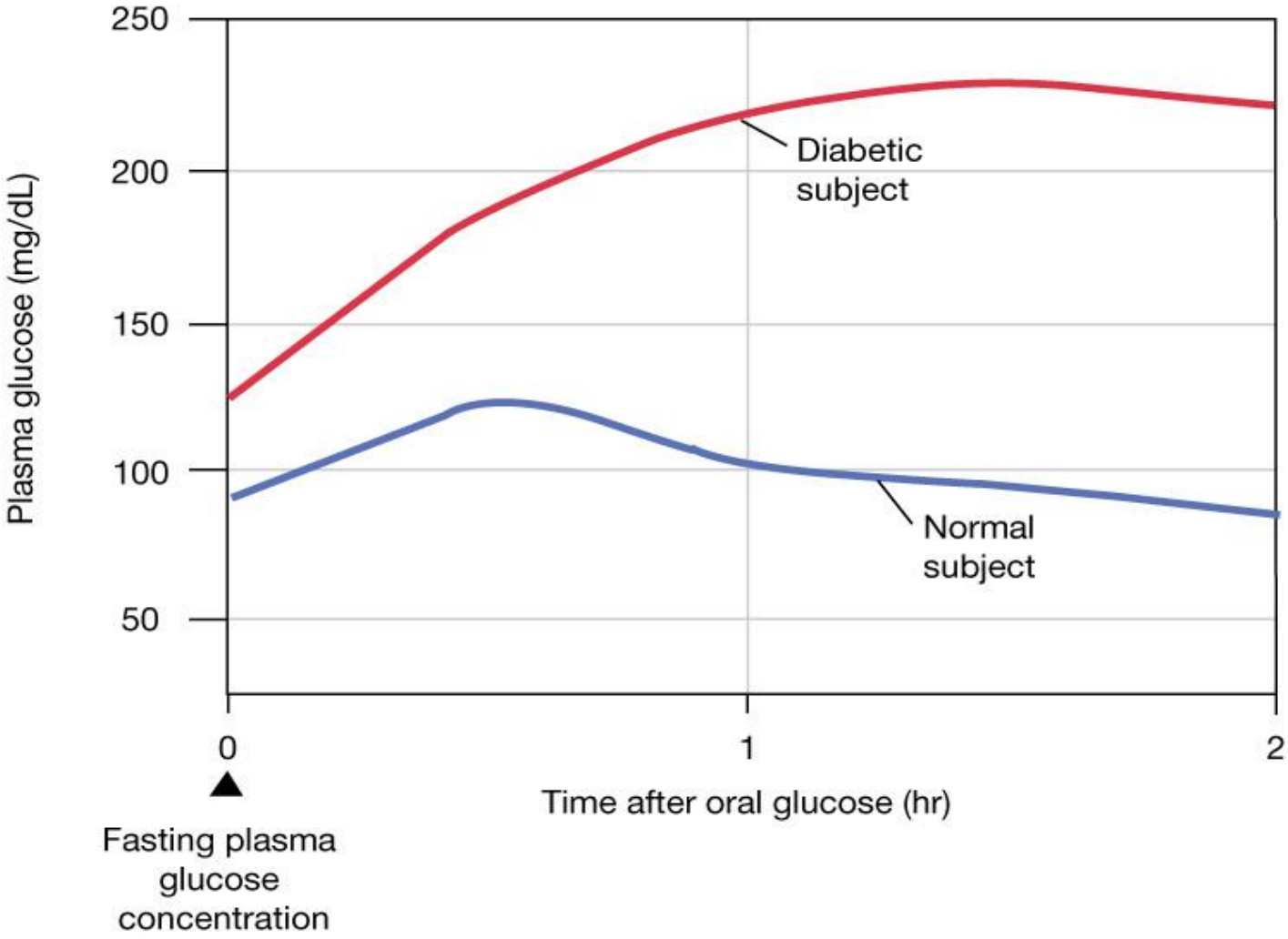


Figure 22-16: Normal and abnormal glucose tolerance tests

Treatment of Diabetes Mellitus

Diet

- A fundamental element of therapy in all diabetic patients.
- Obese type 2: weight loss, limit carbohydrate intake.
- Both type: limit cholesterol 300 mg daily; 10-20 % total calories, proteins, saturated fat < 8-9%, same polyunsaturated. Remained calories individualized ratio of monounsaturated fat and of carbohydrate (containing 20-35g dietary fiber).

Oral Agents for Treatment of Hyperglycemia

For type 2 diabetes

1. Drugs ↑ insulin secretion: sulfonylureas; meglitinide and D-phenylalanine derivative, nateglinide (bind sulfonylurea receptor).
2. Drugs: alter insulin action (Metformin on liver). (Thiazolidinediones on skeletal muscle, adipose tissue)
3. Drugs: affect absorption of glucose (α-glucosidase inhibitors acarbose and miglitol).

Oral Agents for Treatment of Hyperglycemia …

For type 2 diabetes …

1. **Drugs that stimulate insulin secretion**

- Sulfonylureas stimulate insulin release from pancreatic B cells.
- Binding to surface receptors closes K+ channels → depolarization of B cells →↑ Ca^{++} entry →↑ insulin release.
- Not used for type 1 (require functioning B cells).

Mechanism of Action of Sulfonylurea

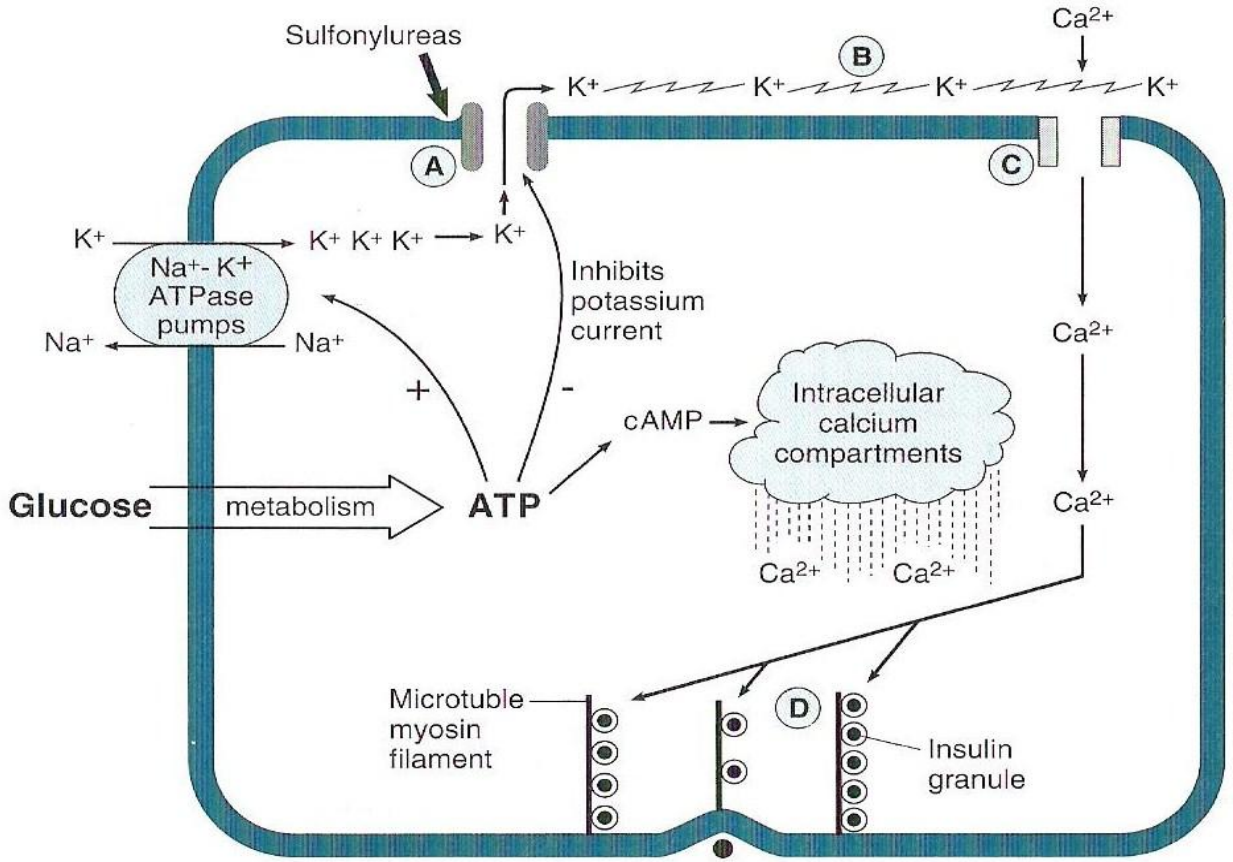


Figure 17–8. Proposed mechanism for sulfonylurea stimulation of insulin release by the pancreatic B cell. Energy-dependent pumps maintain a high intracellular concentration of potassium (K^+). In the resting B cell, K^+ diffuses from the cell through non-energy-dependent potassium channels (A). This current of potassium ions generates an electrical potential that polarizes the resting cell membrane (B) and closes a voltage-gated calcium channel (C), thereby preventing extracellular calcium from entering the cell. When sulfonylureas bind to a specific receptor on the potassium channel (or when glucose metabolism generates ATP), the potassium channel closes. This depolarizes the cell, allowing calcium to enter and cause microtubules to contract (D), moving insulin granules to the cell surface for emeiocytosis. (Modified and reproduced, with permission, from Karam JH: Type II diabetes and syndrome X. Endocrinol Metab Clin North Am 1992;21:339.)

Oral Agents for Treatment of Hyperglycemia …

For type 2 diabetes …

2. **Drugs that alter Insulin Action**
   - Biguanides: Do not require functioning pancreatic B cells. e.g. Metformin.
   - Reduces both Fasting levels and postprandial hyperglycemia in type 2.
   - ↓ hepatic gluconeogenesis, ↓ G.I absorption of glucose, ↑glucose uptake by skeletal muscle.
   - Improve fasting and postprandial hyperglycemia and hypertriglyceridemia in obese diabetics.
   - Thiazolidinediones: ↑ GLUT1, and GLUT4, ↓ FFA, ↓ glucose output

Oral Agents for Treatment of Hyperglycemia …

For type 2 diabetes …

3. Drugs that affect glucose absorption

- α-Glucosidase inhibitors: acarbose, miglitol.
- Potent inhibitors of glucoamylase, α-amylase, sucrase)

Treatment of diabetes Mellitus …

Insulin

- For type 1 diabetics as well as for type 2 diabetics (not responding to diet and oral hypoglycemic drugs).
- Highly purified human insulin preparations: ↓ complications (insulin allergy, insulin resistance).

Acute Complications of Diabetes Mellitus

Hypoglycemia

Most common complications in insulin –treated diabetics.

Clinical Features

- Neuroglycopenia: Insufficient glucose for CNS , confusion, coma, even death (severe hypoglycemia)
- Autonomic hyperactivity: adrenergic (tachycardia, palpitations) parasympathetic (nausea, hunger)

Management

- Unaware: nocturnal, screening 2-3 am.
- Reduction of evening insulin, increase bedtime snack.

Treatment

Glucose administration.

Acute Complications of Diabetes Mellitus …

Coma

Causes: from diabetes mellitus or its treatment

A. Hyperglycemic coma

Severe insulin deficiency (diabetic ketoacidosis).

Mild or moderate insulin deficiency (hyperglycemic, hyperosmolar, nonketotic coma).

B. Hypoglycemic Coma

Excessive doses of insulin or certain oral hypoglycemic agents.

C. Lactic Acidosis

Severe tissue anoxia.

Chronic Complications of Diabetes Mellitus

Diabetic Vascular Disease: Vascular system (also complications in nerves, skin, lens)

A. Microvascular Disease: Capillaries and arterioles (thickening of capillary basement membrane). Often retina, kidney, heart.

B. Macrovascular Disease: large blood vessels (atherosclerosis). Myocardial infarction, strokes, peripheral gangrene.

Chronic Complications of Diabetes Mellitus …

1. **Ophthalmologic Complications**
   a. **Diabetic Retinopathy**
      - Type1: more than 5 years, all type 2 patients. Hypertension accelerates retinopathy.
      - Non-proliferative retinopathy: early stage dot hemorrhages, retinal edema. Capillaries leak proteins, lipids, and red cells into retina (common in type 2).
      - Proliferative retinopathy: growth of new capillaries and fibrous tissues within retina and vitreous chamber. Both types of diabetes (common type 1), vitreous hemorrhage or retinal detachment 80% after 15 years.

   b. **Cataract :** Due to glycosylation of lens protein, excess sorbitol.

   c. **Glaucoma:** Neovascularization of iris.

Chronic Complications of Diabetes Mellitus …

2. Renal Complications (Diabetic Neuropathy)

- Type 1 diabetics (no intensive insulin therapy) → 30-40% chance after 20 years. Lower frequency in type 2.
- Initially proteinuria, subsequently ↑ urea and creatinine. Microalbuminuria with ↑ blood pressure (↓ protein diet, antihypertensive therapy).
- Progressive nephropathy: proteinuria, nephritic syndrome, hyperalbuminemia, edema, ↑ LDL, hypertension, atherosclerosis (chronic, cerebral).
- Treatment: Dialysis, Renal transplantation.

Chronic Complications of Diabetes Mellitus …

3. Neurologic Complications (Diabetic Neuropathy)

a. Peripheral Sensory Neuropathy

Sensory loss proceeded by paresthesias (tingling, itching) increasing pain (lower extremities)

b. Motor Neuropathy

Delayed motor nerve conduction, muscle weakness and atrophy.

c. Autonomic Neuropathy

Diabetes of long duration, G.I. system (nausea, remitting), Gall – bladder function altered (stone formation). Orthostatic hypotension, diabetic diarrhea.

No effective treatment.

Chronic Complications of Diabetes Mellitus …

4. Cardiovascular Complications

a. Heart Diseases

Coronary atherosclerosis → heart failure

M.I. 3-5 × common (leading cause of death in type 2).

Reason: unknown (hyperlipidemia, abnormal platelet adhesiveness, coagulation factors, hypertension and oxidative stress and inflammation).

b. Peripheral vascular Disease

Ischemia of lower extremities, impotence, gangrene of the feet.

Avoid tobacco (reduces peripheral blood flow).

Hypertension: should be controlled.

Chronic Complications of Diabetes Mellitus …

5. **Skin Changes**

   Diabetic dermopathy: atrophic brown spots on the skin.

6. **Bone and Joint Complications**

   Chronic progressive stiffness of hands; Glycosylation of collagen, 5-6 years after onset of type 1.

   Bone demineralization, Gout (obese diabetics).

7. **Infection**

   Candidal infections, atherosclerosis.

THE END!!!!