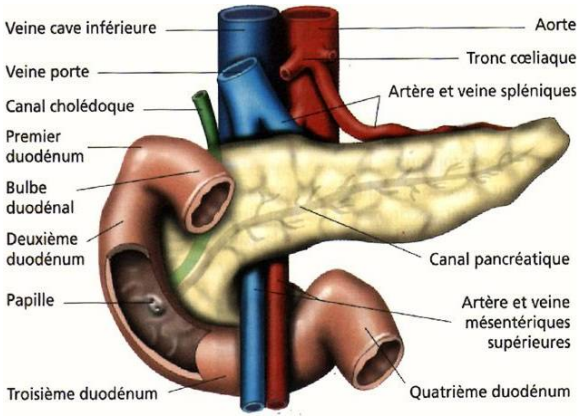
Endocrine Physiology

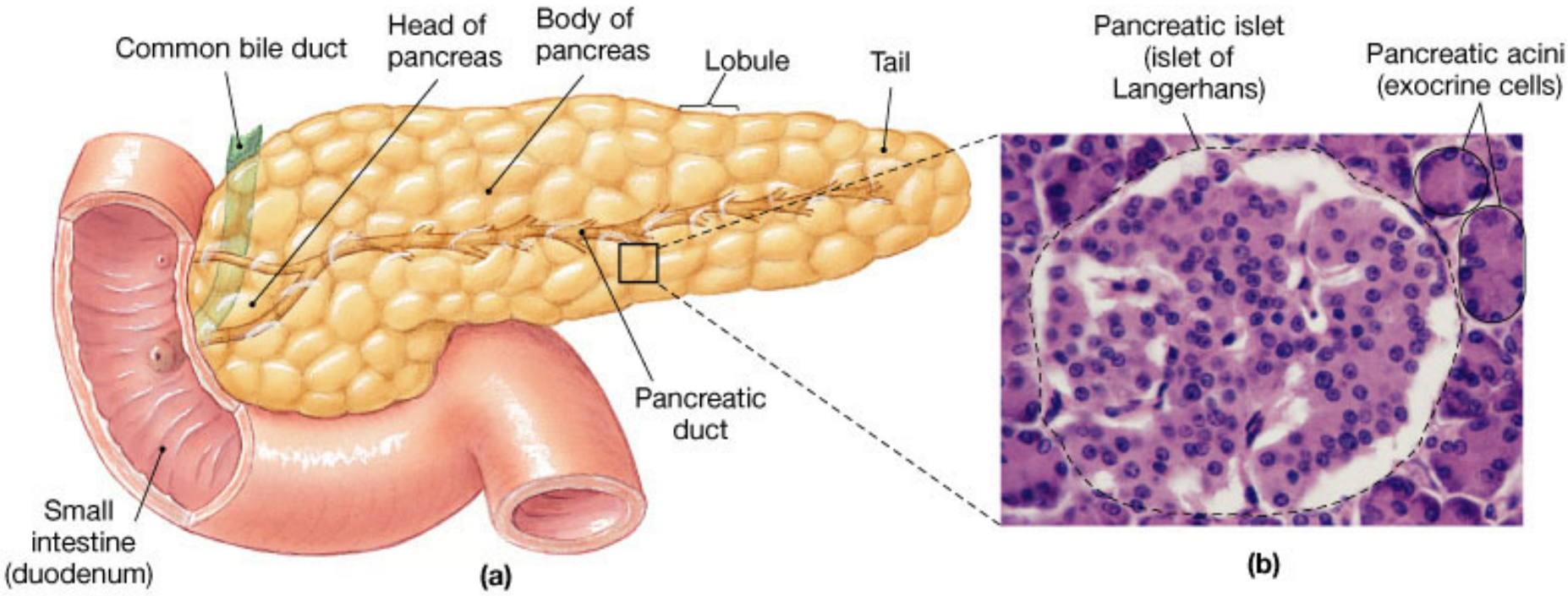
The Endocrine Pancreas



Pancreas

- 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.

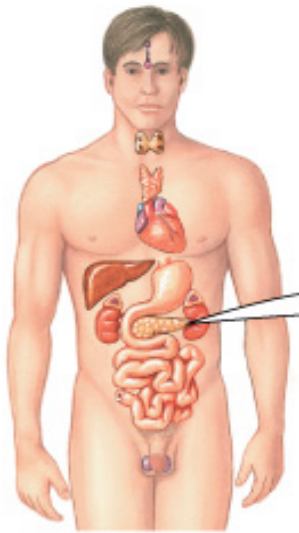
The Endocrine Pancreas

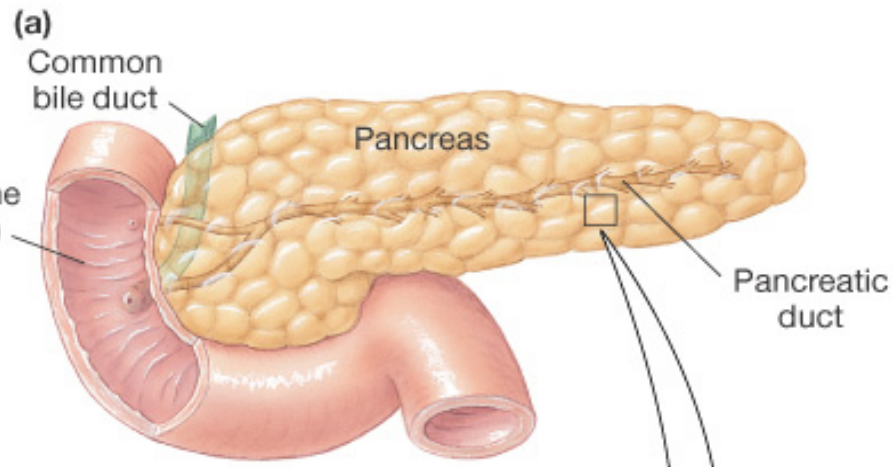


Islets of Langerhans

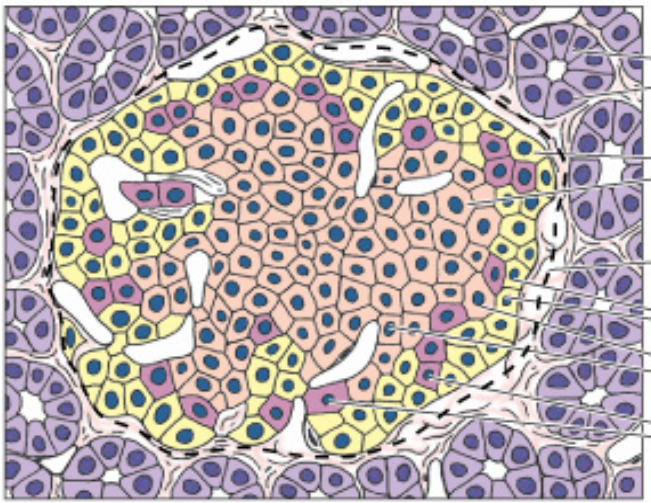
- 1 million islets
- 1-2% of the pancreatic mass
- Beta (β) cells produce insulin
- Alpha (α) cells produce glucagon
- Delta (δ) cells produce somatostatin
- F cells produce pancreatic polypeptide

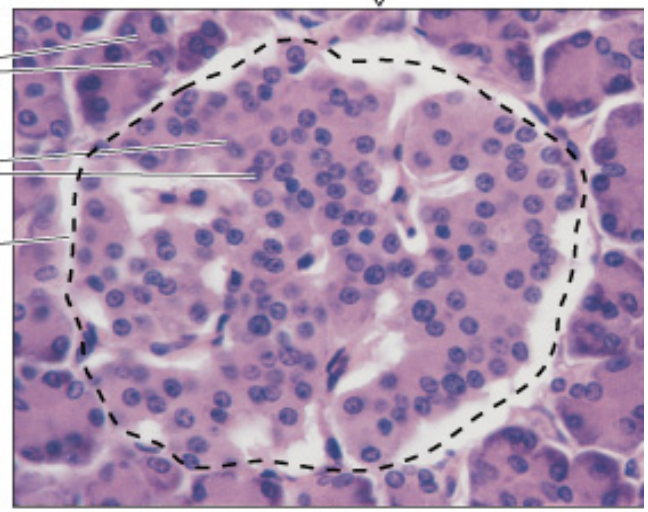
Islets of Langerhans





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





Insulin

- 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).

Insulin Structure

1- Large polypeptide 51 AA (MW 6000)

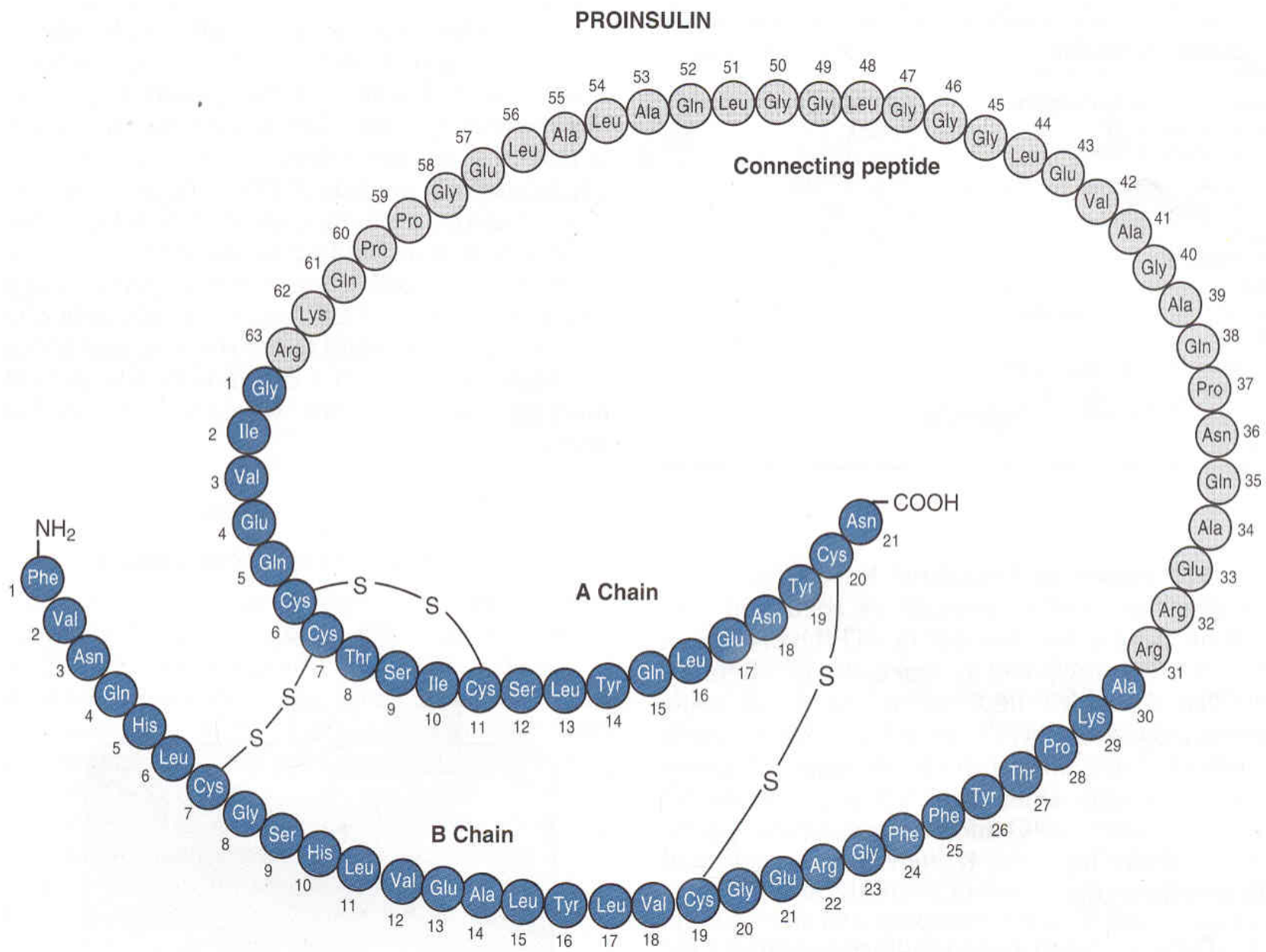
2- Tow chains linked by disulfide bonds.

A chain (21 AA)

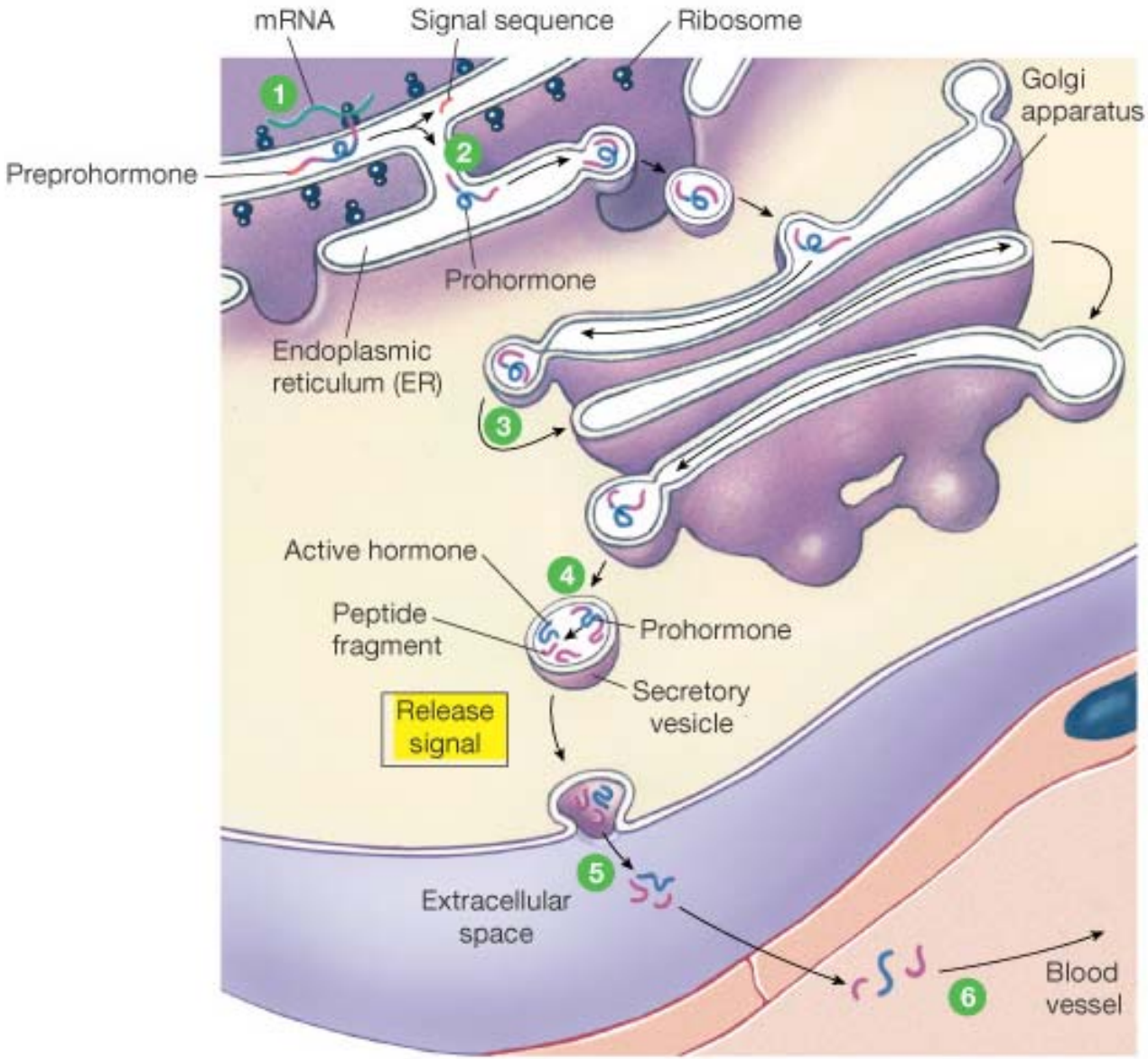
B chain (30 AA)

3 disulfide bonds.

Insulin Structure



Protein and Polypeptide Synthesis and Release



1. Messenger RNA on the ribosomes of the ER binds amino acids into a peptide chain called a **preprohormone**. The chain is directed into the ER lumen by a **signal sequence** of amino acids.
2. Enzymes in the ER chop off the signal sequence, creating an inactive **prohormone**.
3. The prohormone passes from the ER through the Golgi apparatus.
4. Secretory vesicles containing enzymes and prohormone bud off the Golgi. The enzymes chop the prohormone into one or more active peptides plus additional peptide fragments.
5. The secretory vesicle releases its contents by exocytosis into the extracellular space.
6. The hormone moves into the circulation for transport to its target.

Insulin Synthesis

- insulin gene encodes a large precursor of insulin (preproinsulin)
- During translation, the signal peptide is cleaved (proinsulin)
- During packaging in granules by Golgi, proinsulin is cleaved into insulin and C peptide

Insulin Synthesis

DNA (chromosome 11) in β cells

↓

mRNA

↓

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

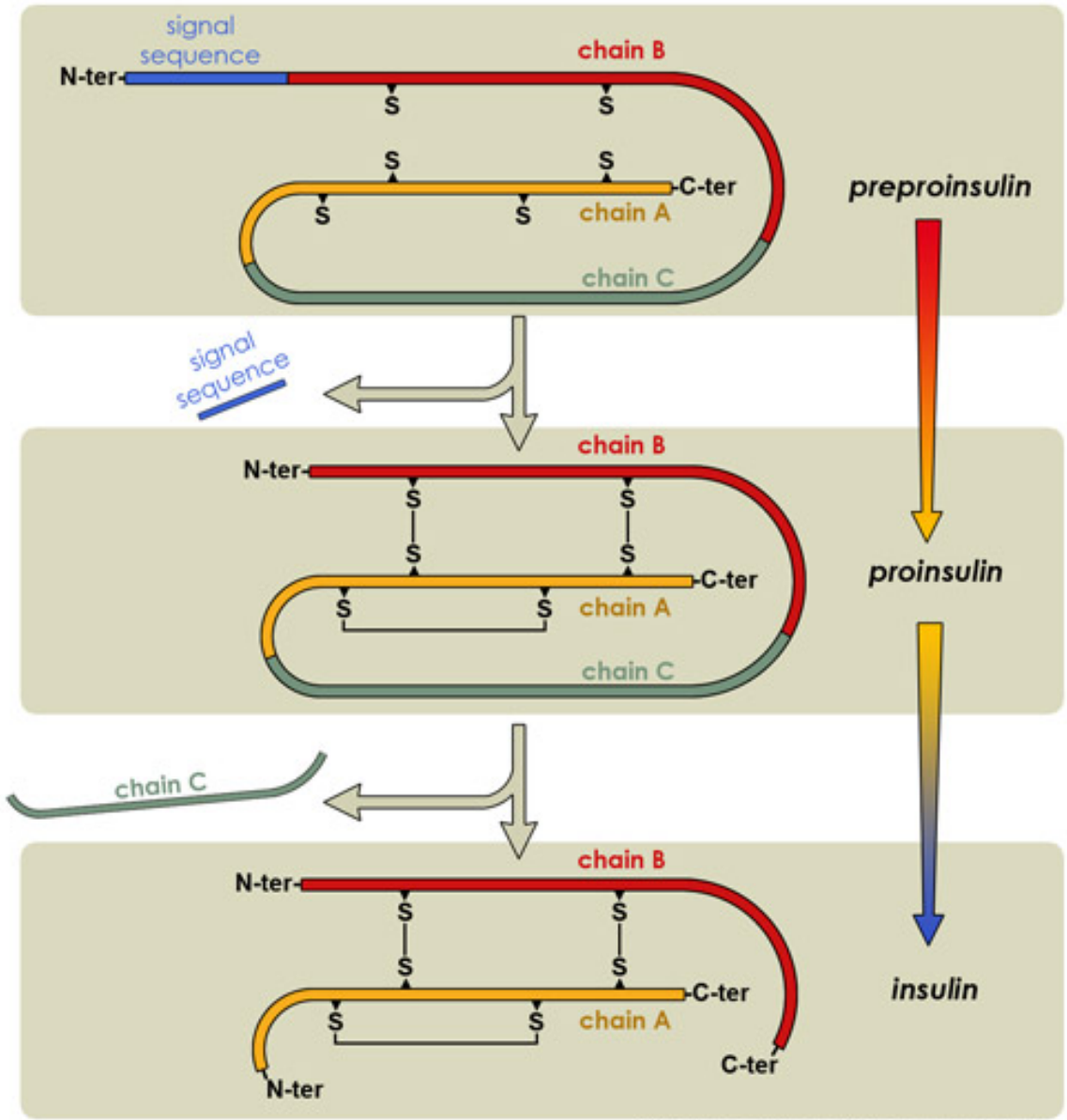
↓

proinsulin

↓

insulin

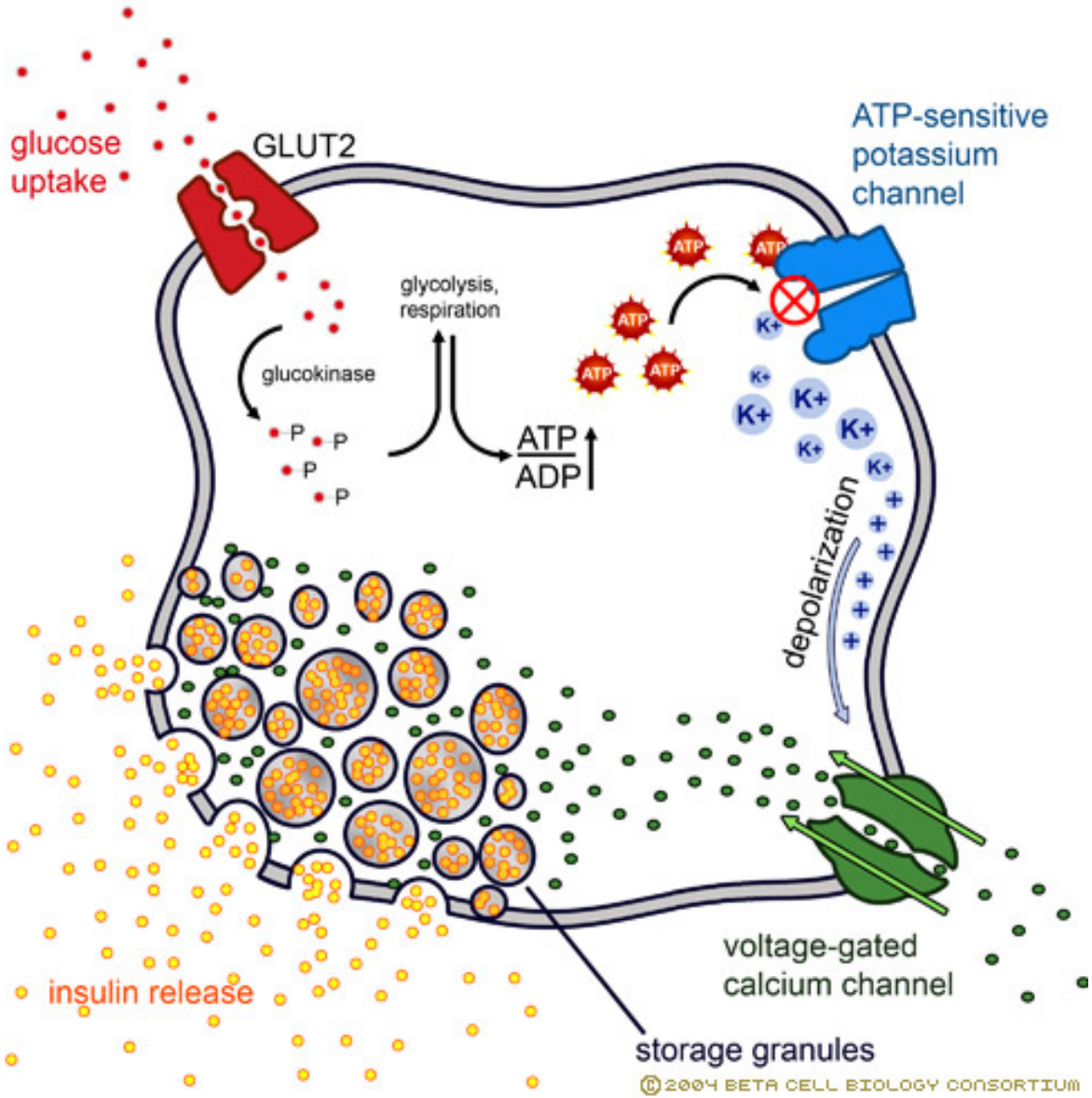
Insulin Synthesis

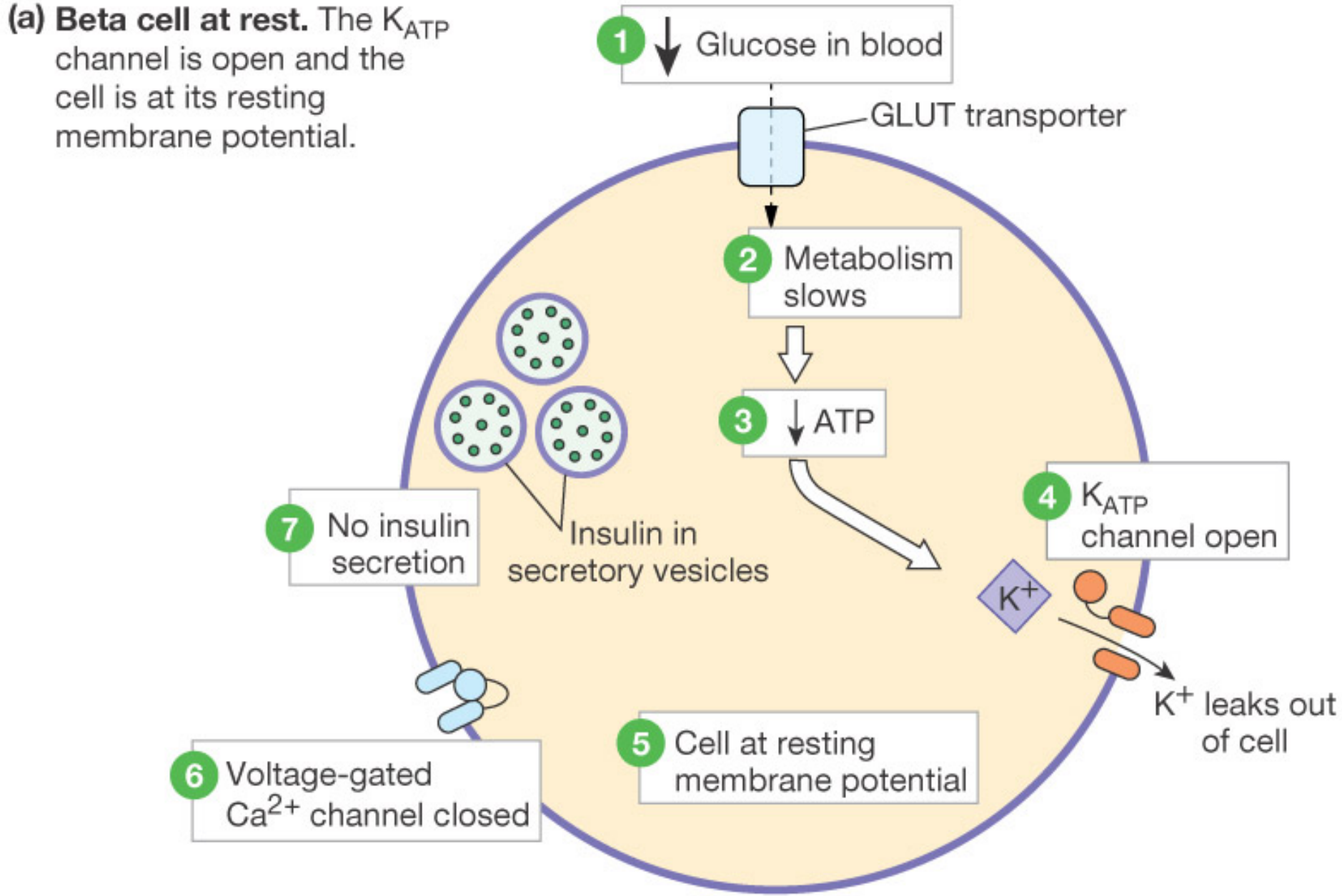


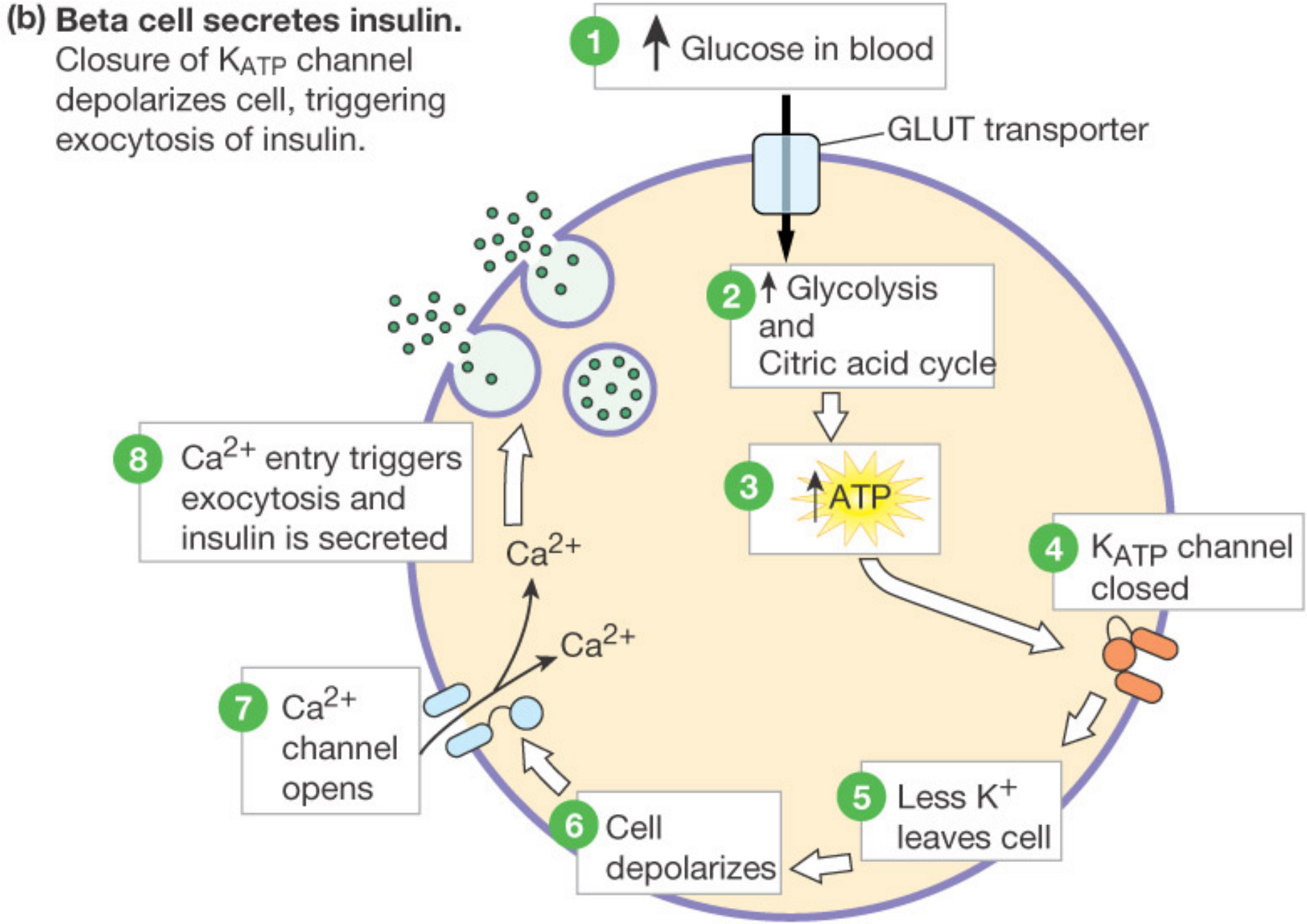
Insulin Synthesis

- 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







Regulation of Insulin Secretion

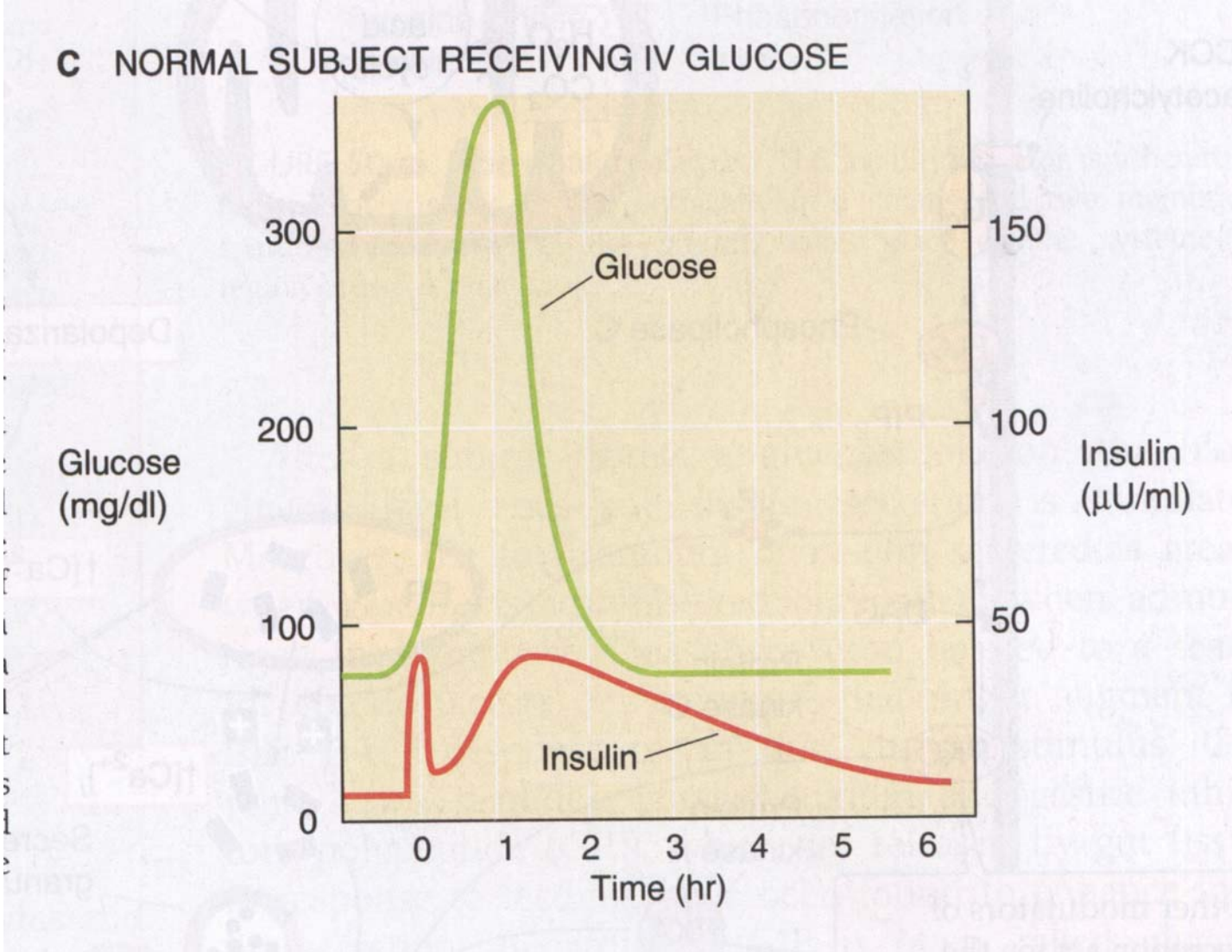
Regulators of insulin secretion

Stimulators of insulin secretion	Inhibitors of insulin secretion
↑ Serum glucose	↓ Glucose
↑ Serum amino acids	↓ Amino acids
↑ Serum free fatty acids	↓ Free fatty acids
↑ Serum ketone bodies	
Hormones	Hormones
Gastroinhibitory peptide (GIP)	Somatostatin
Glucagon	Epinephrine (α-receptor)
Gastrin	
Cholecystokinin (CCK)	
Secretin	
Vasoactive intestinal peptide (VIP)	
Epinephrine (β-receptor)	
Parasympathetic nervous system	Sympathetic nervous system stimulation

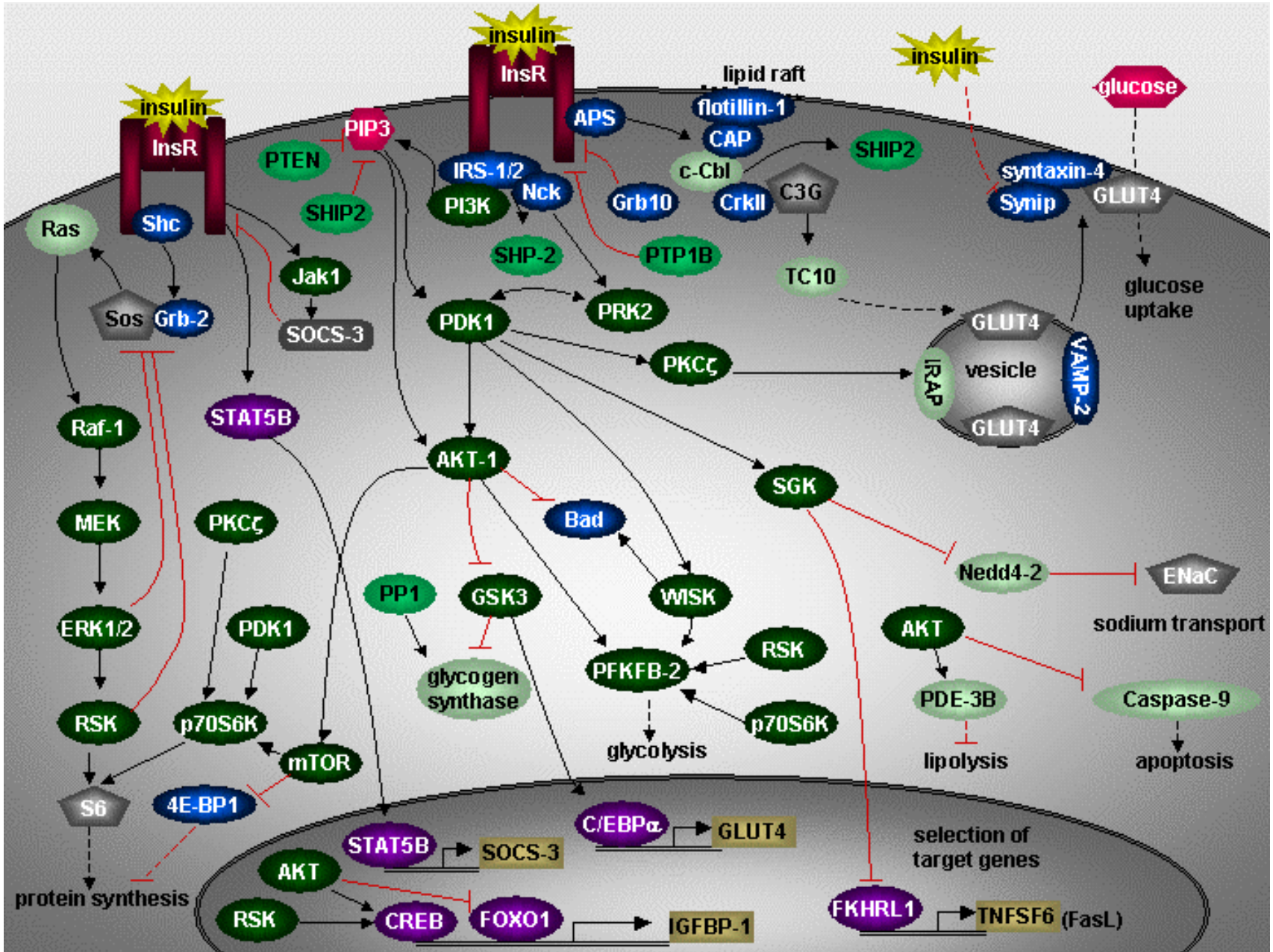
Regulation of Insulin Secretion

- No insulin is produced when plasma glucose below 50 mg/dl
- Half-maximal insulin response occurs at 150 mg/dl
- A maximum insulin response occurs at 300 mg/dl
- Insulin secretion is biphasic:
  - Upon glucose stimulation– an initial burst of secretion (5-15 min.)
  - Then a second phase of gradual increment that lasts as long as blood glucose is high

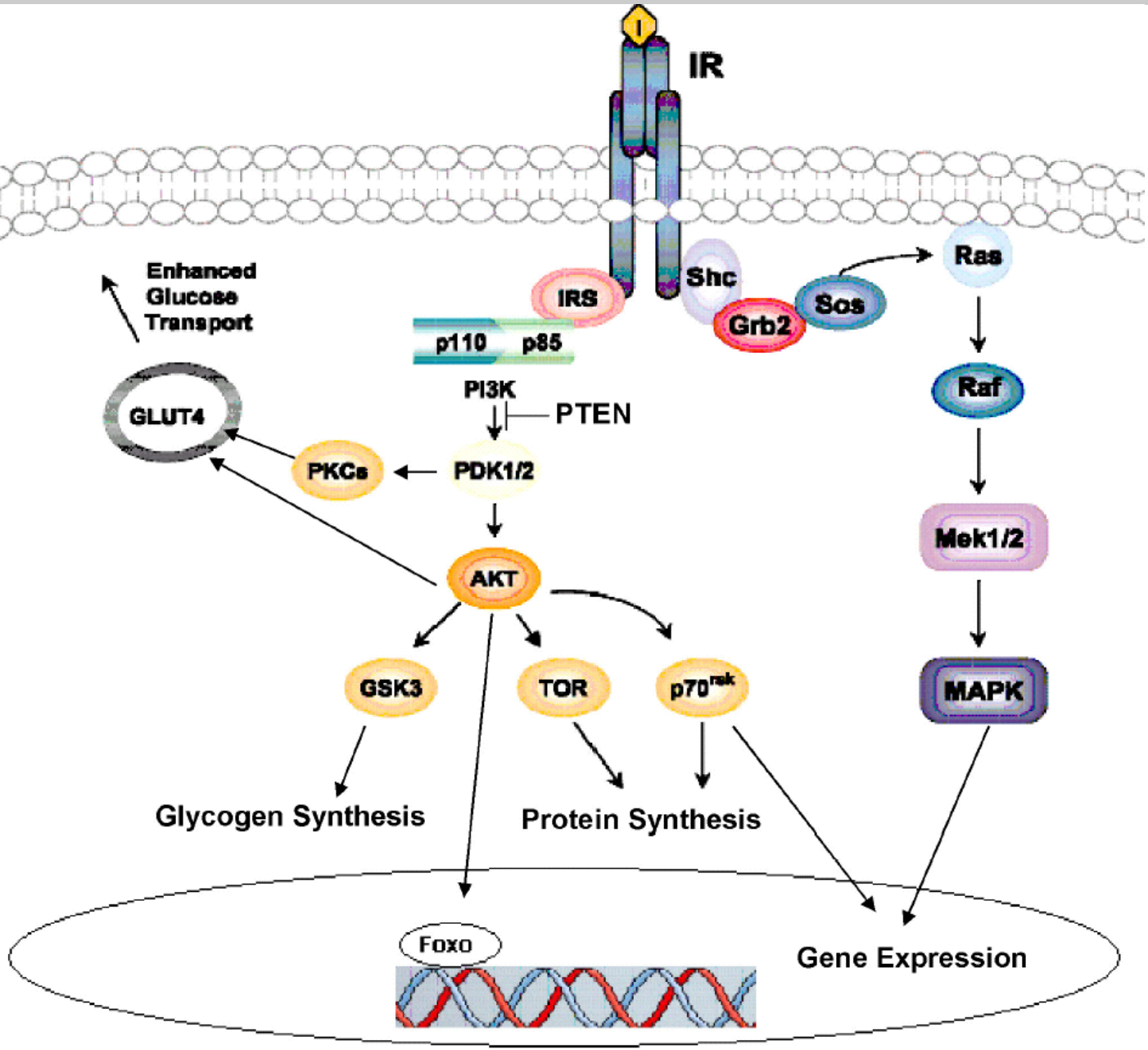
Insulin secretion is biphasic



Insulin Signaling



Insulin Signaling



Insulin Action on Cells:

- Insulin is the hormone of abundance.
- The major targets for insulin are:
  - liver
  - Skeletal muscle
  - adipose tissue
- The net result is fuel storage

Insulin Action on Carbohydrate Metabolism:

Liver:

- Stimulates glucose oxidation
- Promotes glucose storage as glycogen
- Inhibits glycogenolysis
- Inhibits gluconeogenesis

Muscle:

- Stimulates glucose uptake (GLUT4)
- Promotes glucose storage as glycogen

Insulin Action on Carbohydrate Metabolism :

Adipose Tissue:

- Stimulates glucose transport into adipocytes
- Promotes the conversion of glucose into triglycerides and fatty acids

Glucose Transport

- GLUT2 (liver, pancreas)
- **GLUT4**, insulin sensitive transporter (muscle, adipose tissue)
- GLUT3 (brain)

Glycogen Synthesis

- Short term storage of glucose
- Activates glycogen synthase
- Inhibit glycogen phosphorylase
- Glycolysis is also stimulated by insulin

Lipogenic and antilipolytic

- Insulin promotes lipogenesis and inhibits lipolysis
  - Promotes formation of α-glycerol phosphate and fatty acid synthesis
  - Stimulates fatty acid synthase (FAS)
  - Inhibits hormone sensitive lipase (HSL)
  - Activates lipoprotein lipase (LPL)

Protein Synthesis and Degradation

- Insulin promotes protein accumulation:

1. Stimulates amino acid uptake
2. Increases the activity of protein synthesis
3. Inhibits protein degradation

Action of insulin on Liver:

Actions of Insulin on Liver

- ↑ Glucose uptake (if blood glucose level is high)
- ↑ Glucose use
  - ↑ Glycogenesis, ↓ glycogenolysis
  - ↑ Glycolysis, ↓ gluconeogenesis
- ↑ Fatty acid synthesis and very-low-density lipoprotein formation, ↓ ketogenesis
- ↓ Urea cycle activity

Action of insulin on Fat:

Action of Insulin on Adipose Tissue

↑ Glucose uptake by increasing GLUT-4 availability

↑ Glucose use

- ↑ Glycolysis
- ↑ Production of α-glycerol phosphate

↑ Esterification of fats

↓ Lipolysis

Action of insulin on Muscle:

Action of Insulin on Muscle

- ↑ Glucose uptake by increasing GLUT-4 availability
- ↑ Glucose use
  - ↑ Glycogenesis, ↓ glycogenolysis
  - ↑ Glycolysis
- ↑ Amino acid uptake (particularly branched-chain amino acids)
- ↑ Protein synthesis, ↓ proteolysis

Insulin action (summary):

Dominates in Fed State Metabolism

- ↑ glucose uptake in most cells
- ↑ glucose use & storage
- ↑ protein synthesis
- ↑ fat synthesis

Insulin: Summary

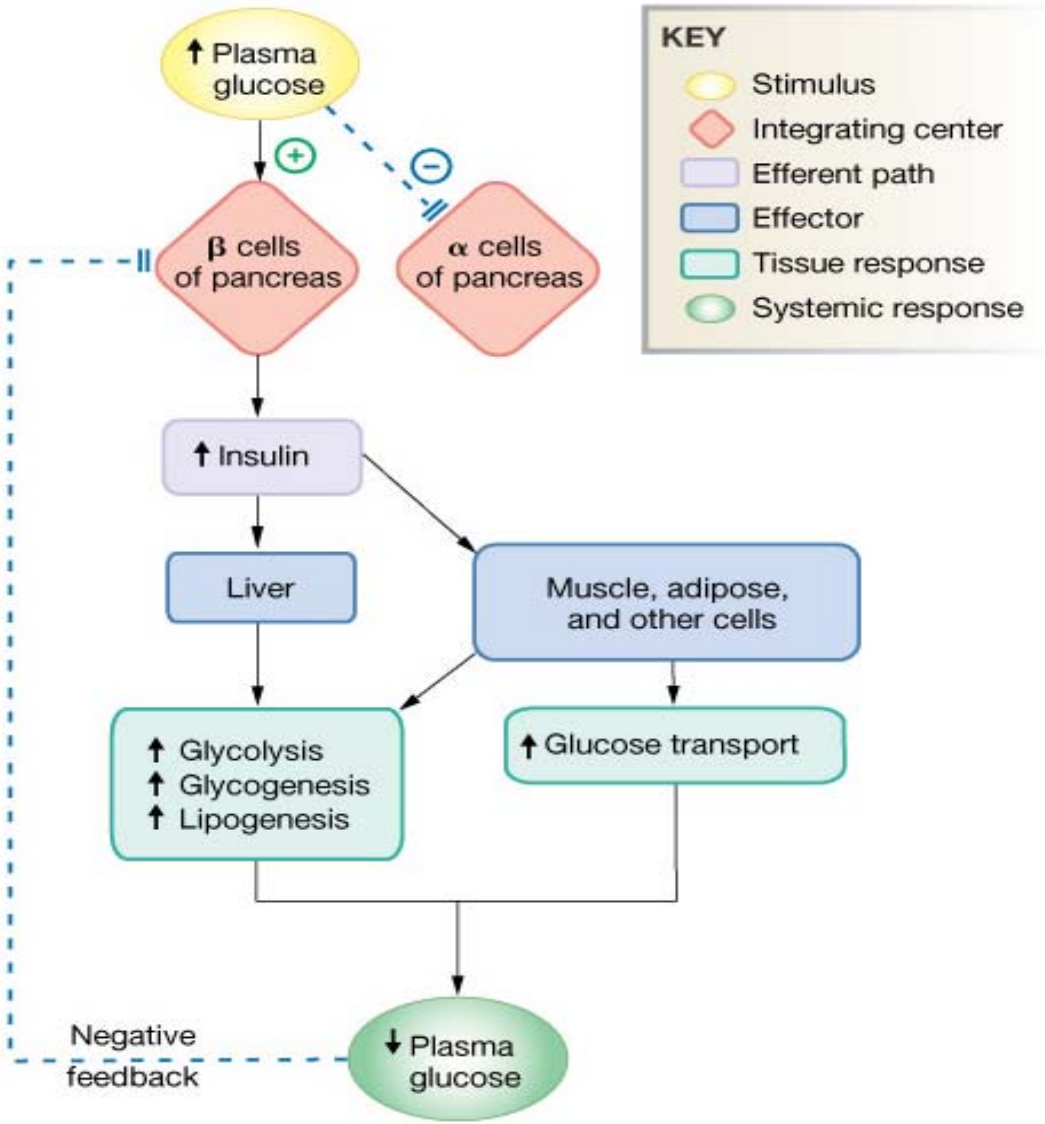


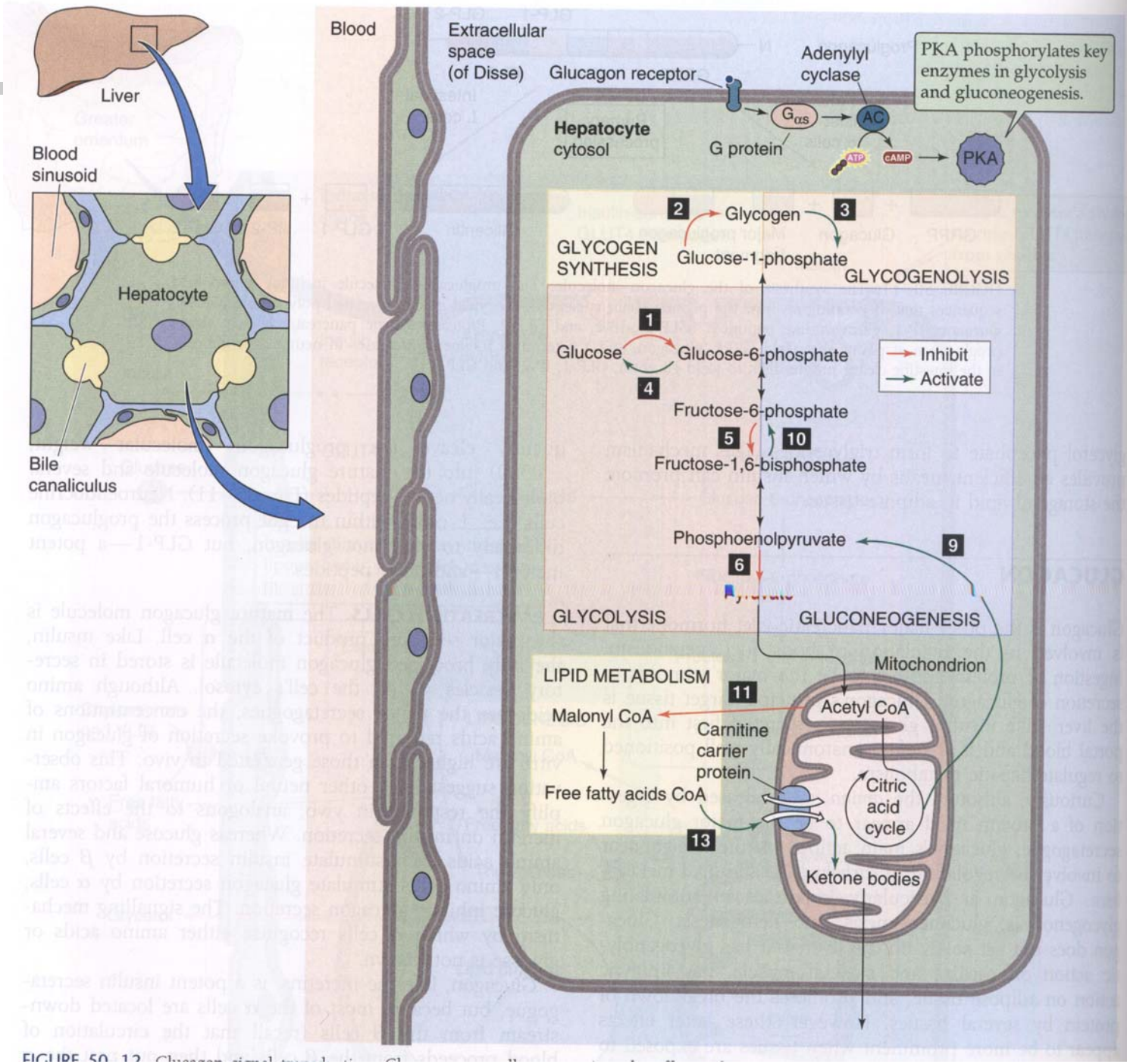
Table 22-3: Insulin

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

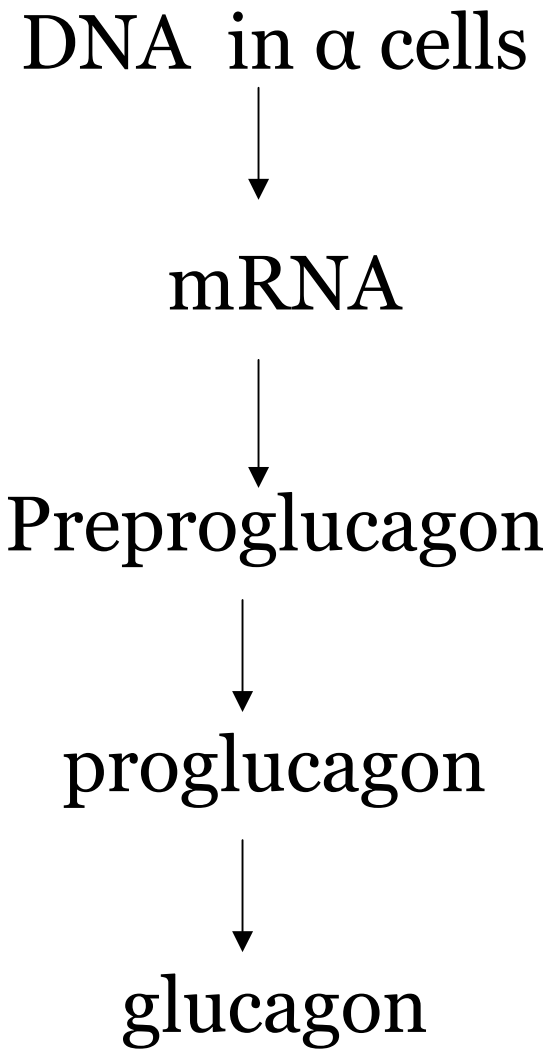
Glucagon

- A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent
- Produced by α cells in the pancreas
- Its major target is the liver, where it promotes:
  - Glycogenolysis – the breakdown of glycogen to glucose
  - Gluconeogenesis – synthesis of glucose from lactic acid and noncarbohydrates
  - Release of glucose to the blood from liver cells

Glucagon Signaling



SYNTHESIS



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 Action on Cells:

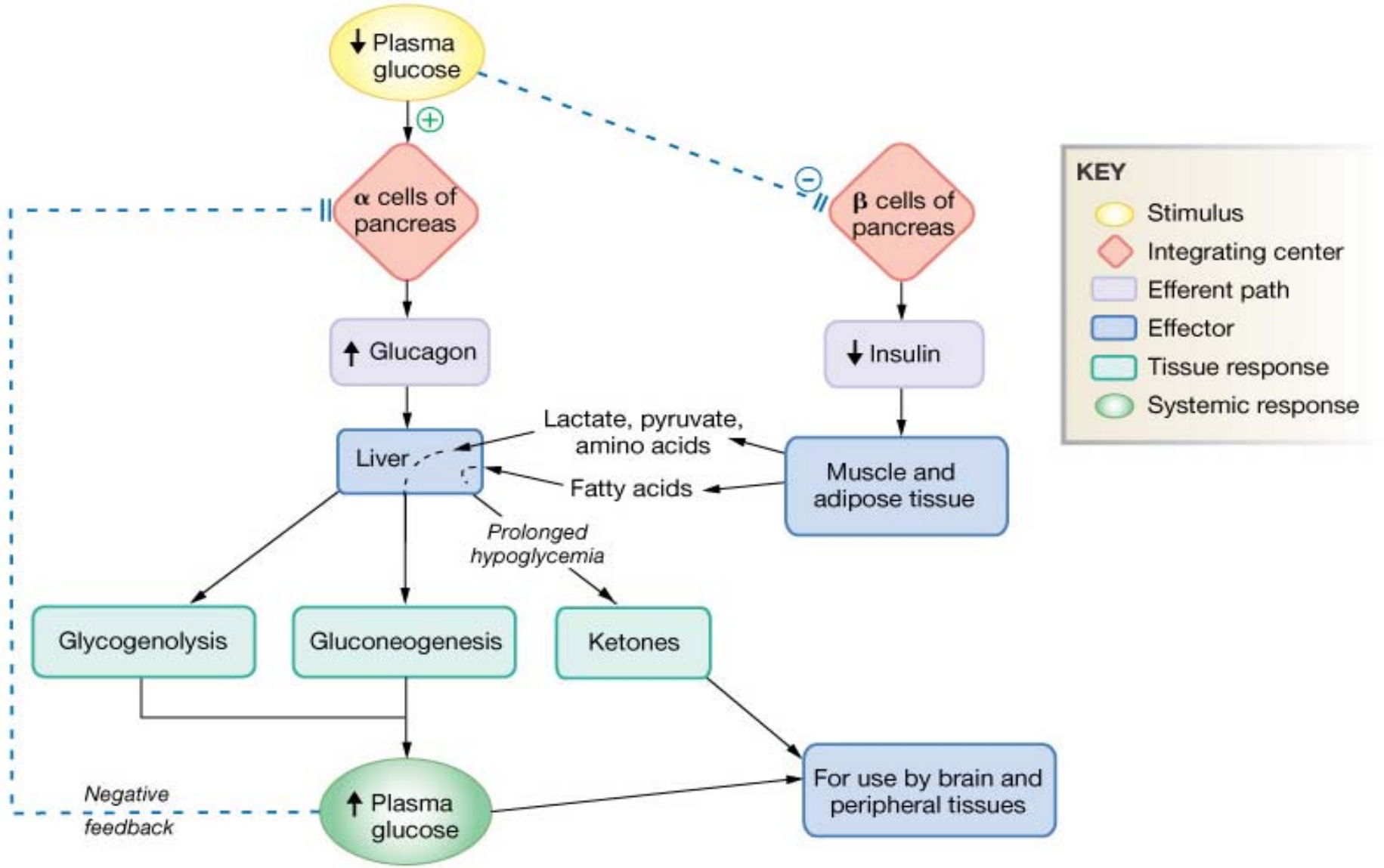
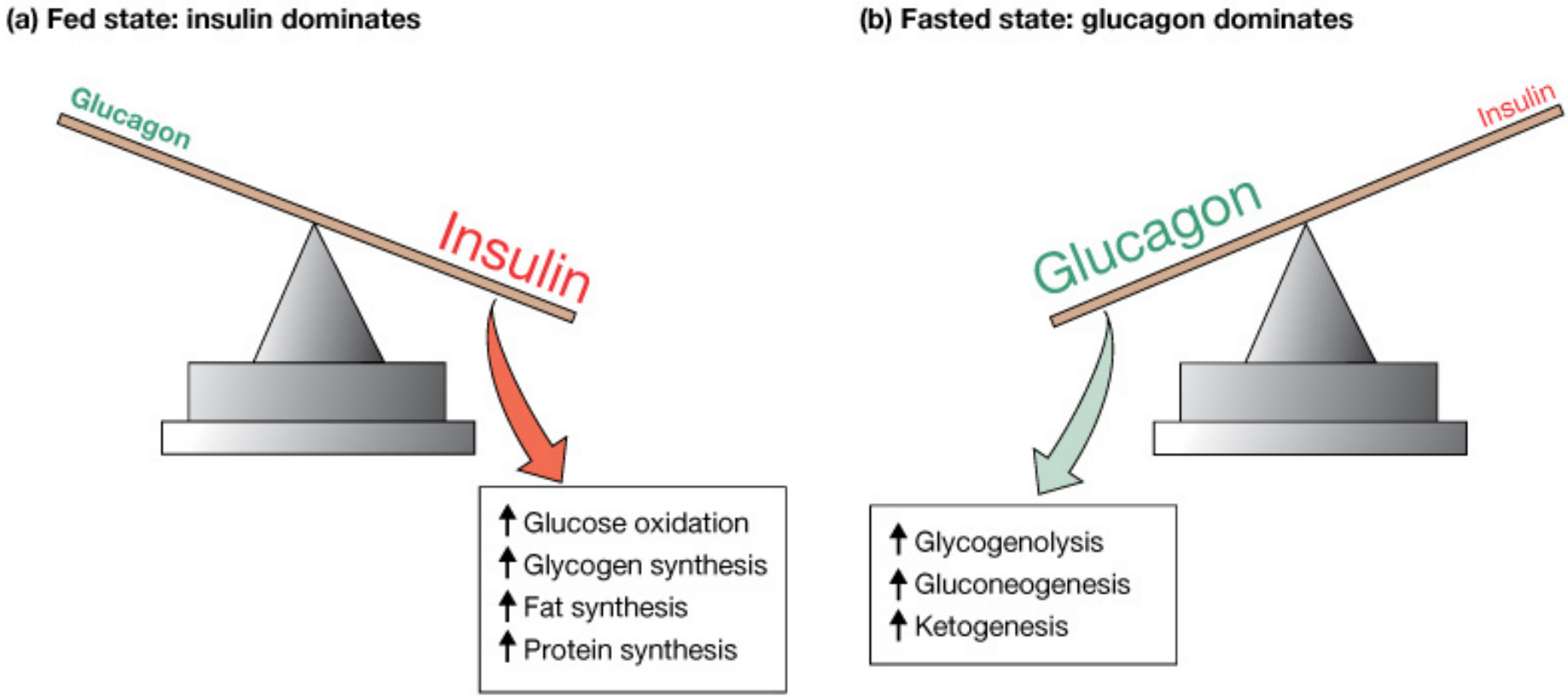


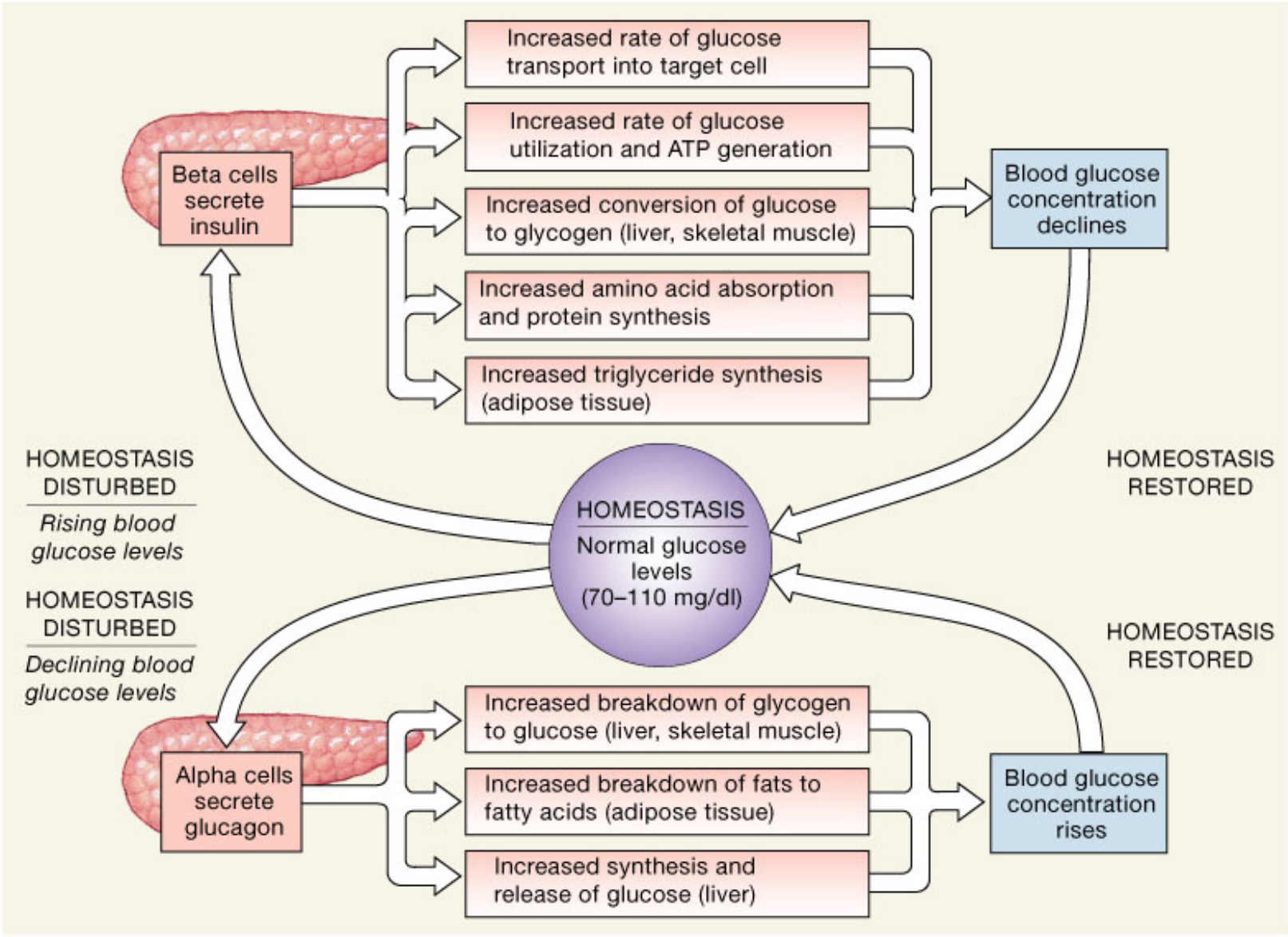
Table 22-5: Glucagon

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

Insulin & Glucagon Regulate Metabolism



The Regulation of Blood Glucose Concentrations



Diabetes Mellitus (DM)

- A serious disorder of carbohydrate metabolism
- Results from hyposecretion or hypoactivity of insulin
- The three cardinal signs of DM are:
  - Polyuria – huge urine output
  - Polydipsia – excessive thirst
  - Polyphagia – excessive hunger and food consumption

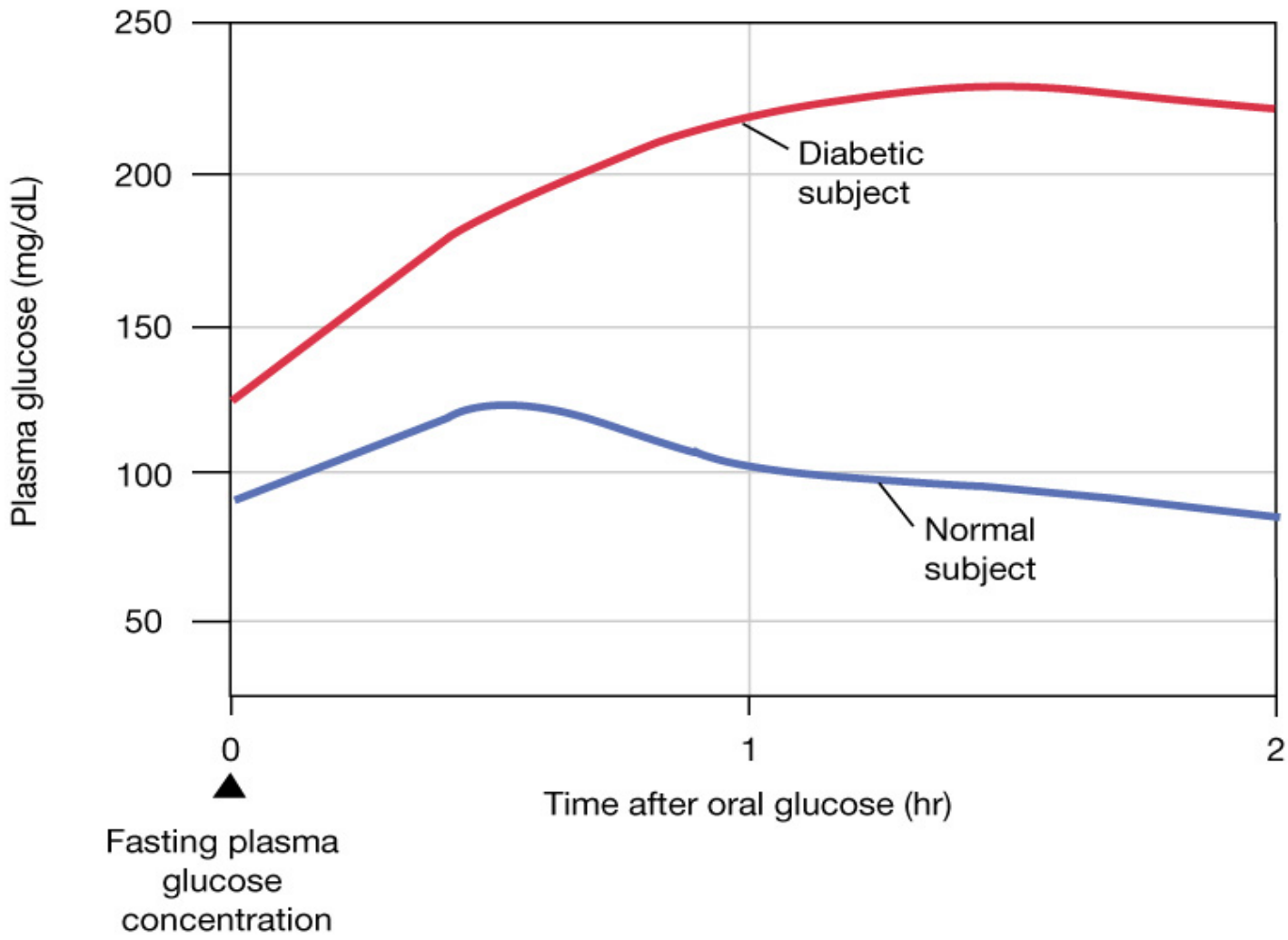
Diabetes Mellitus Type I

- Type 1: beta cells destroyed- no insulin produced→chronic fasted state, "melting flesh", ketosis, acidosis, glucosurea, diuresis & coma

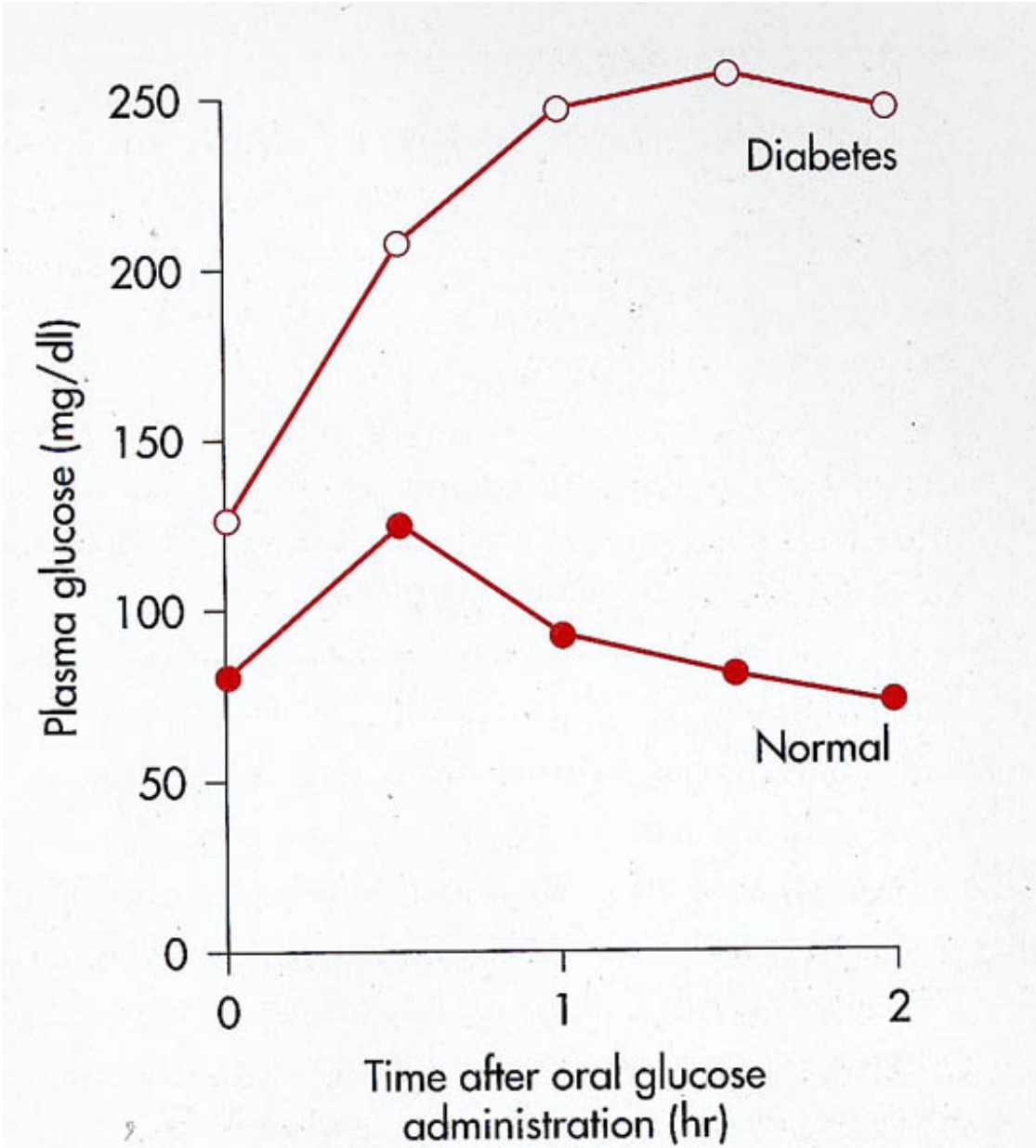
Diabetes Mellitus: Type II a Group of Diseases

- Over 15 million diabetics in USA- 10% type I, 90% type II
- More common is some ethnic groups
- Insulin resistance keeps blood glucose too high
- Chronic complications: atherosclerosis, renal failure& blindness

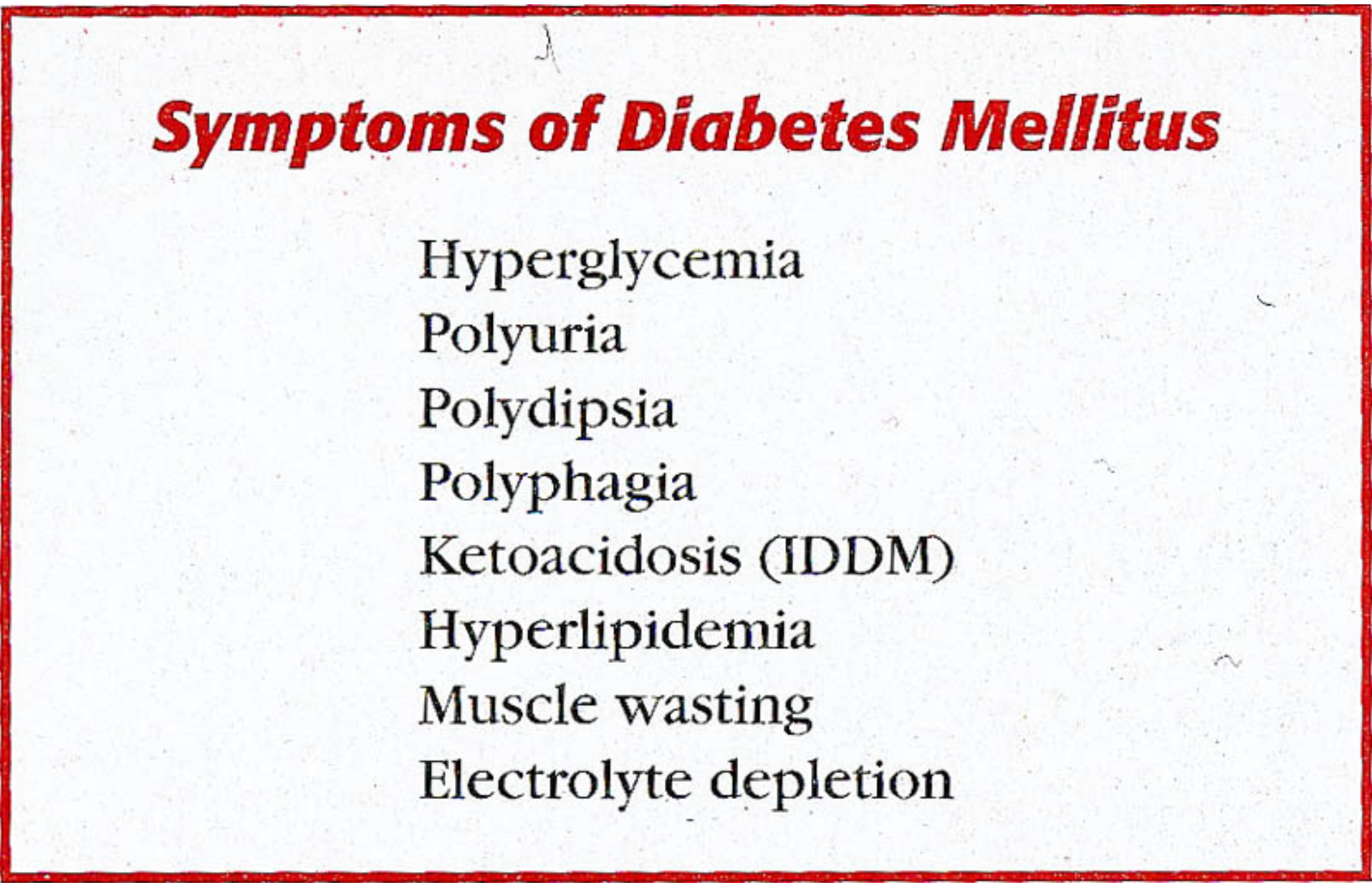
Diabetes Mellitus: Type II a Group of Diseases



GTT


250
200
150
100
50
0
Plasma glucose (mg/dl)
Diabetes
Normal
0
1
2
Time after oral glucose administration (hr)

Symptoms of Diabetes Mellitus



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	**Polyuria** - dehydration - soft eyeballs
	Glycogenolysis		Osmotic diuresis	**Polydipsia** Fatigue Weight loss **Polyphagia**
	Protein catabolism and gluconeogenesis			
	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