Physiology of the pancreas and Insulin

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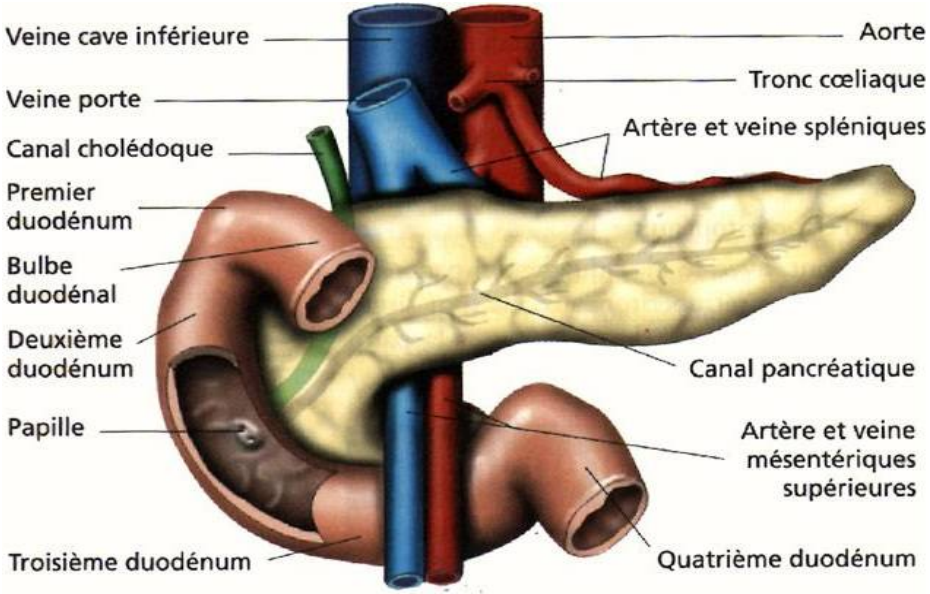
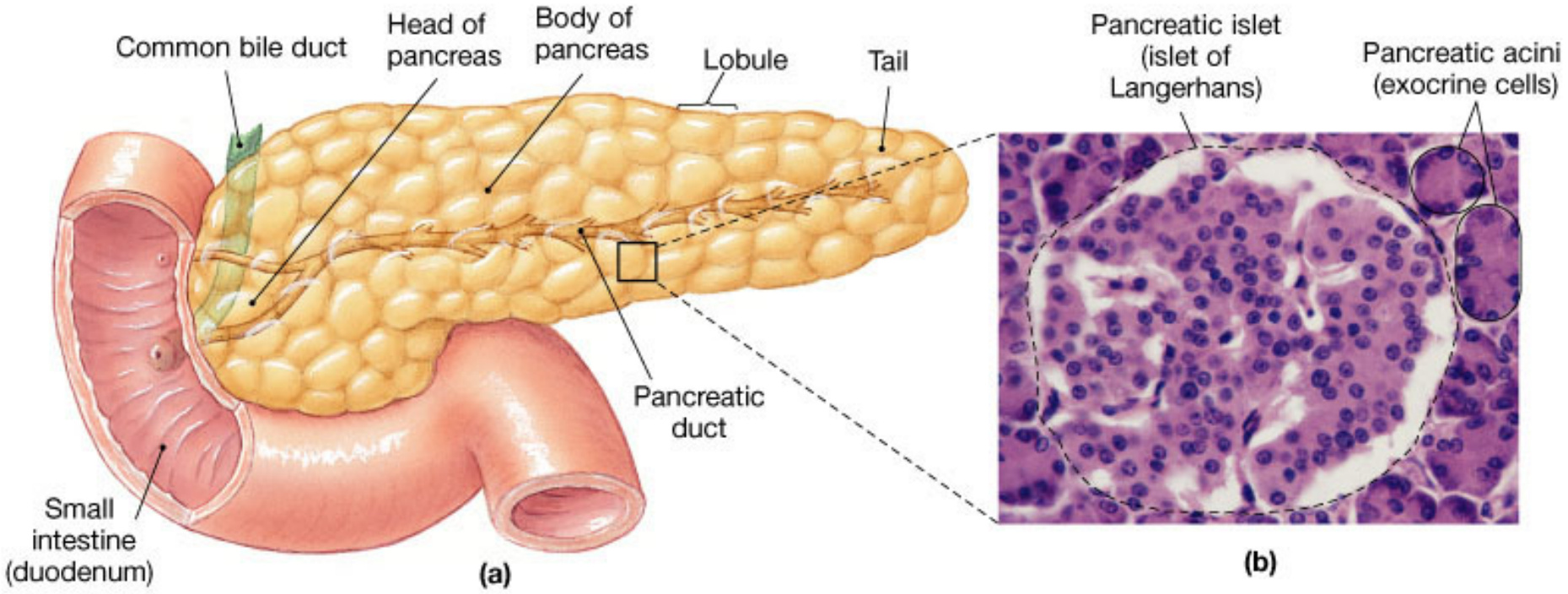


Pancreas

- 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.

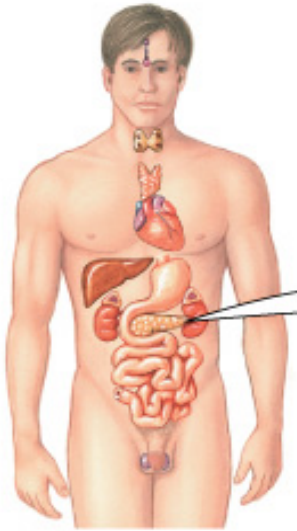
The Endocrine Pancreas



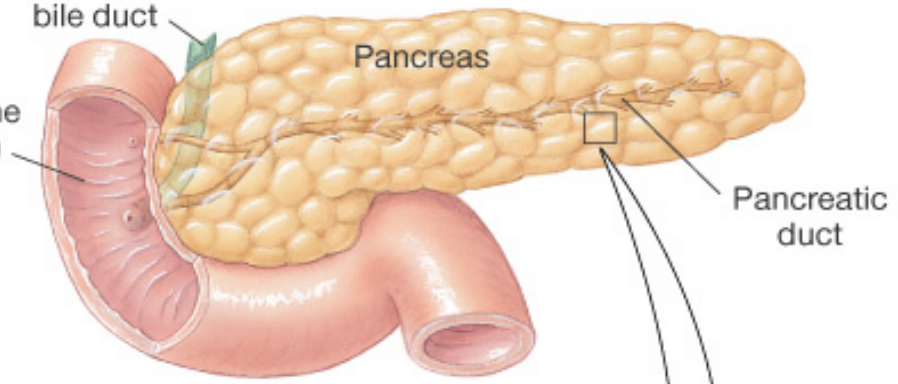
Islets of Langerhans

- 1-2 million islets
- Beta (β) cells produce insulin (70%)
- Alpha (α) cells produce glucagon (20%)
- Delta (δ) cells produce somatostatin (5%)
- F cells produce pancreatic polypeptide (5%)

Islets of Langerhans

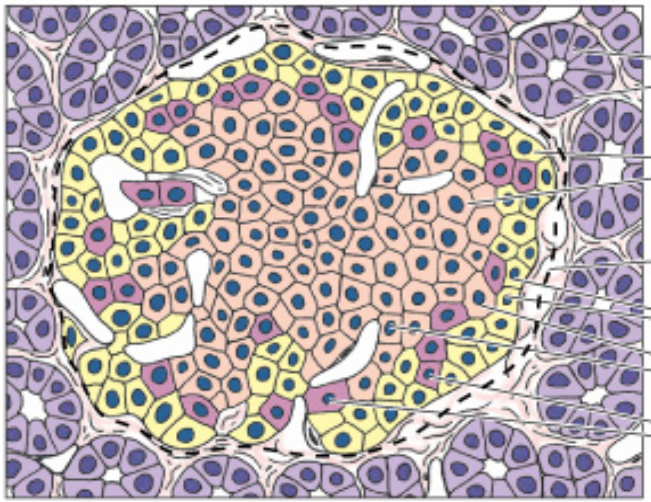


(a)



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

(b)



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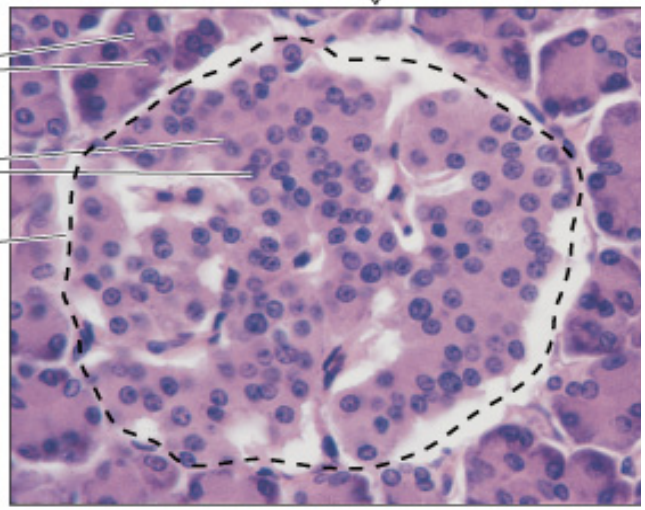
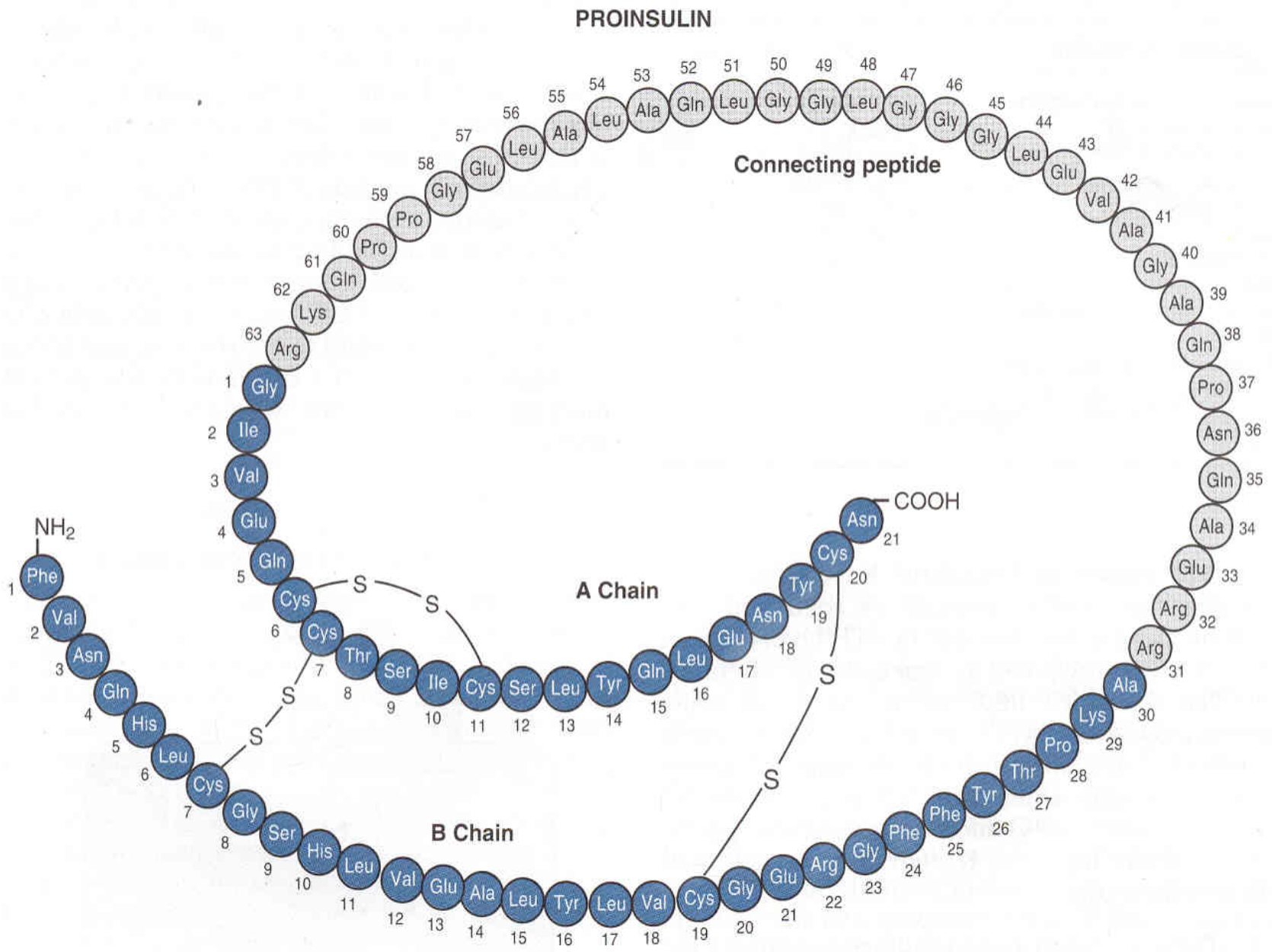


Insulin

- 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).
- Has a plasma half-life of 6 minutes.

Insulin Structure



Insulin Synthesis

DNA (chromosome 11) in β cells

↓

mRNA

↓

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

↓

proinsulin

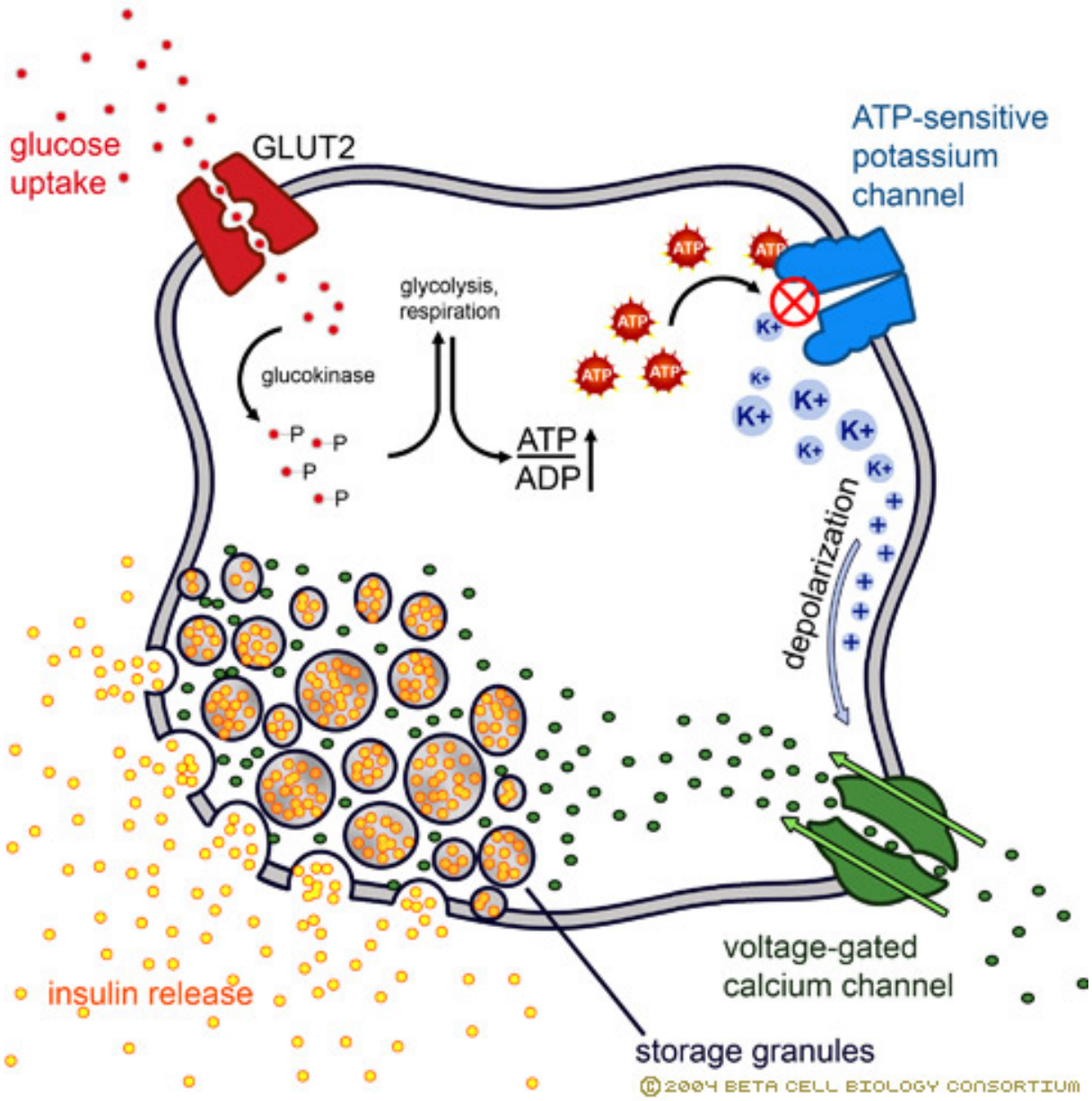
↓

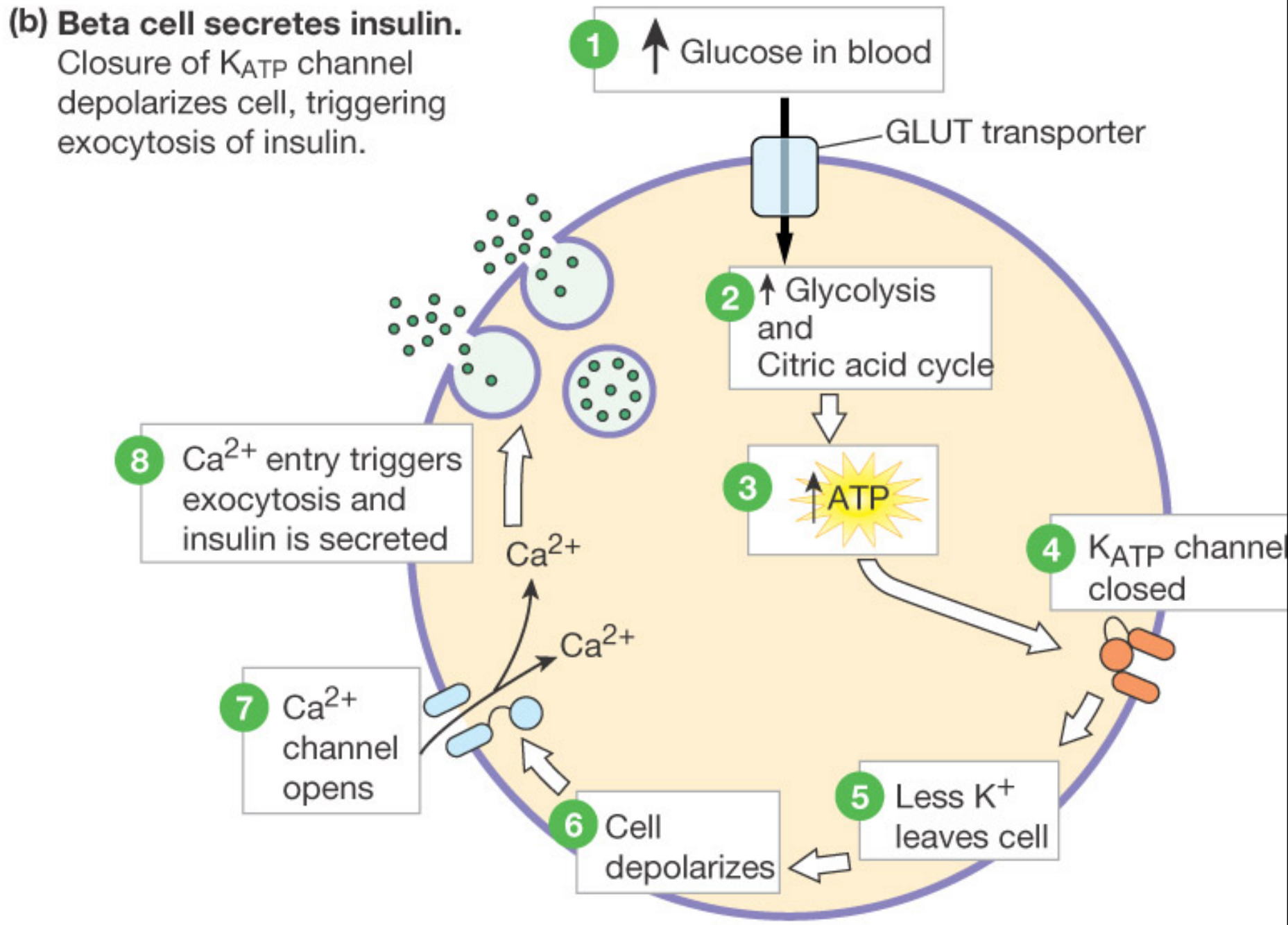
insulin

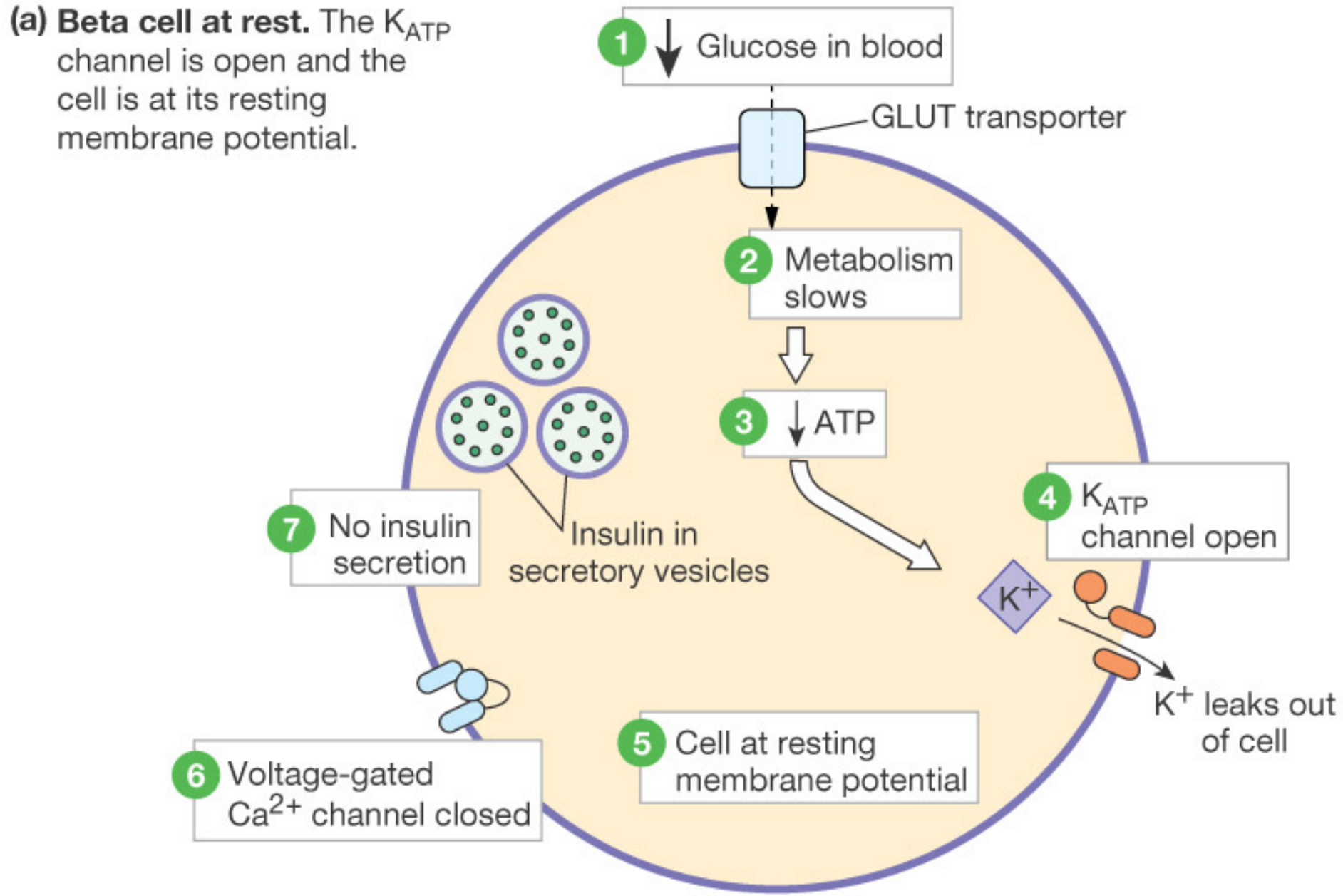
Insulin Synthesis

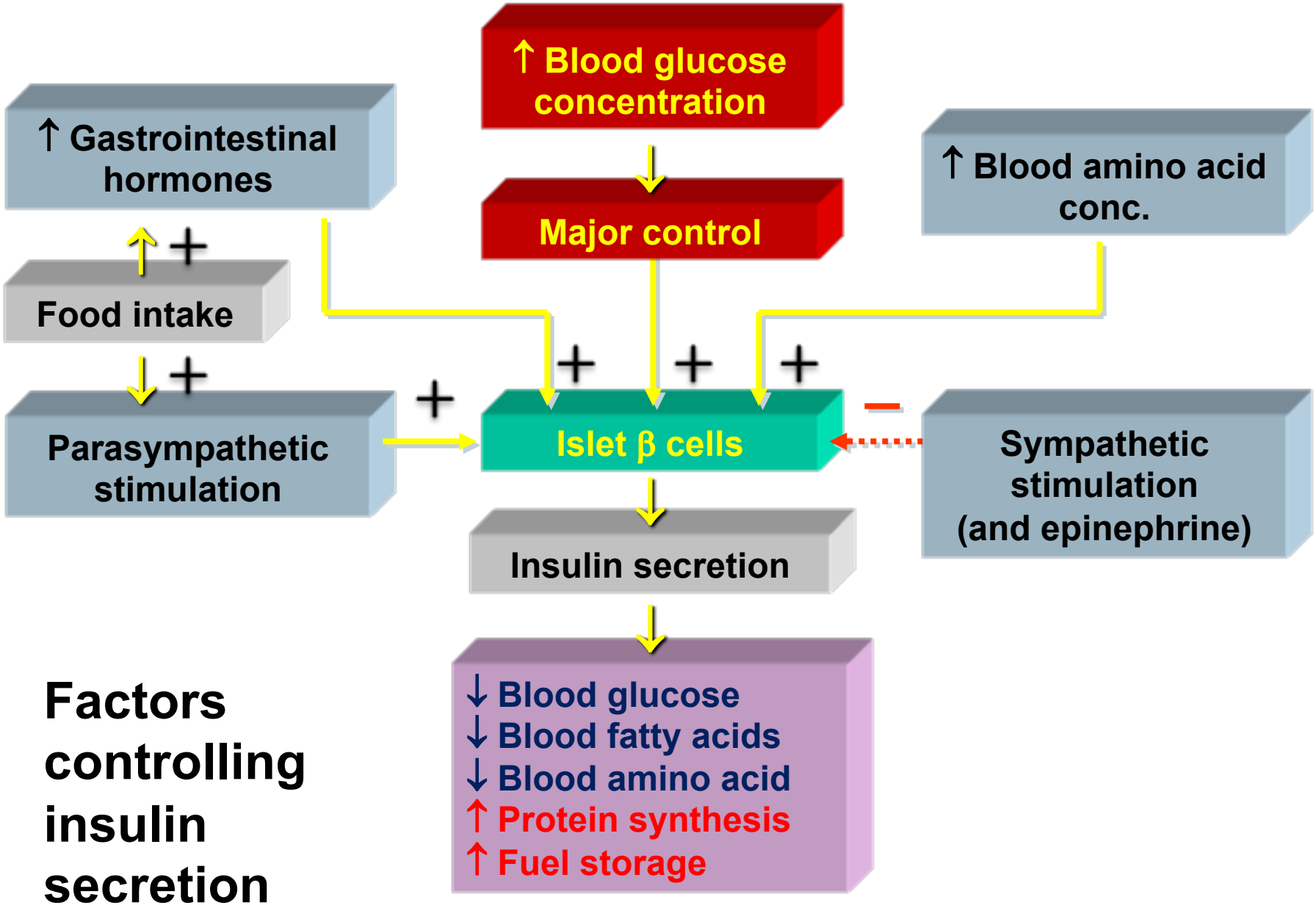
- Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
- Threshold of glucose-stimulated insulin secretion is 100 mg/dl.
- Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene

Glucose is the primary stimulator of insulin secretion









Factors controlling insulin secretion

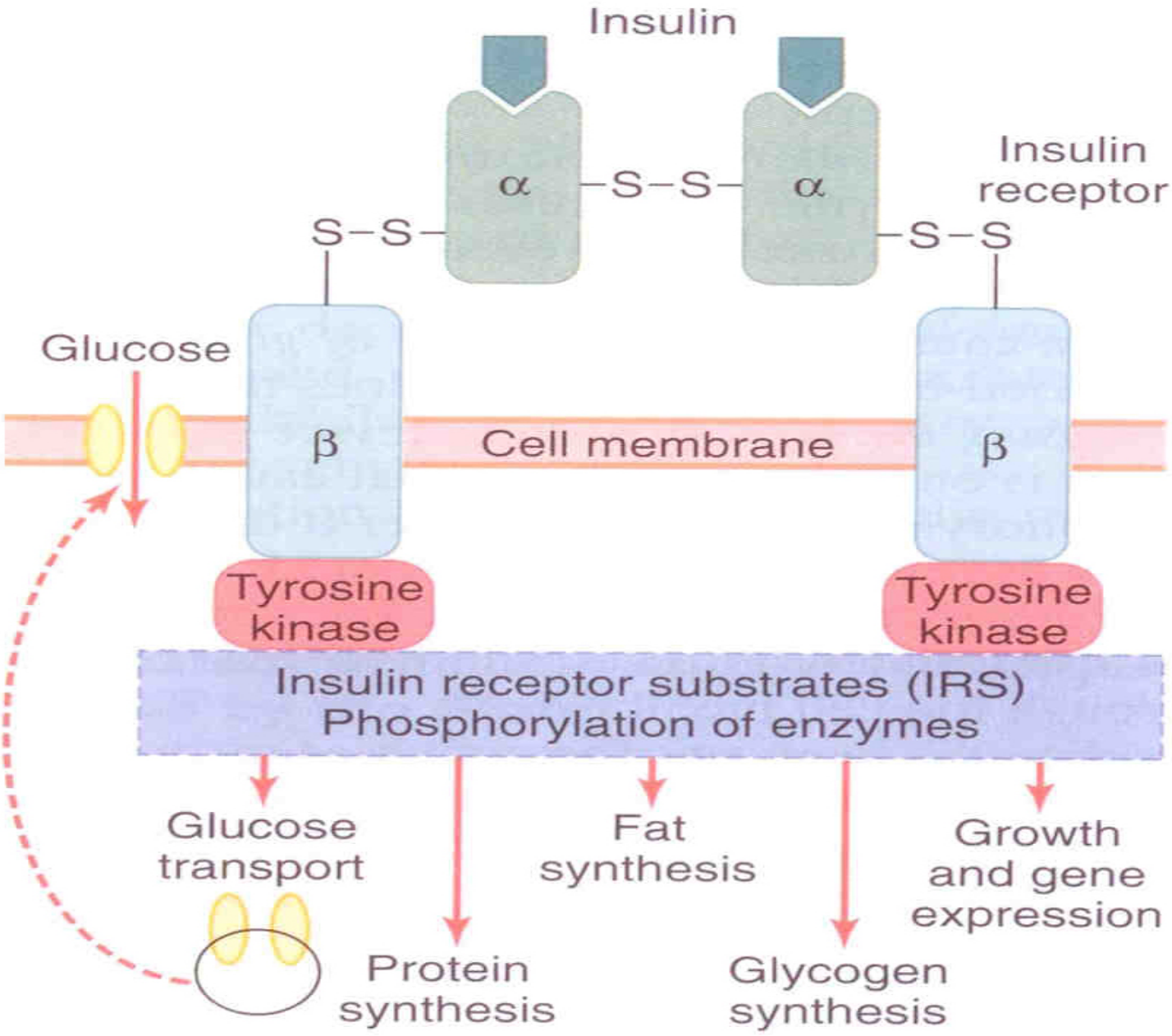
Regulation of Insulin Secretion

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

Insulin Receptor

- 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


Insulin
α
S–S
α
S–S
S–S
Insulin receptor
Glucose
β
Cell membrane
β
Tyrosine kinase
Tyrosine kinase
Insulin receptor substrates (IRS)
Phosphorylation of enzymes
Glucose transport
Protein synthesis
Fat synthesis
Glycogen synthesis
Growth and gene expression

Actions of insulin

Glucose regulation and metabolism terms

- **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+ 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

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

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:

- (+) glucose entry
- (+) glycogen synthesis
- (+) amino acid uptake
- (+) protein synthesis in ribosomes
- (-) protein catabolism
- (-) release of gluconeogenic aminco acids
- (+) ketone uptake
- (+) K uptake

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

Action of insulin on Liver:

- (-) ketogenesis
- (+) protein synthesis
- (+) lipid synthesis
- (-)gluconogenesis, (+) glycogen synthesis, (+) glycolysis.

- **General:**
- (+) cell growth

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

Glucose transporter systems

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

Insulin: Summary

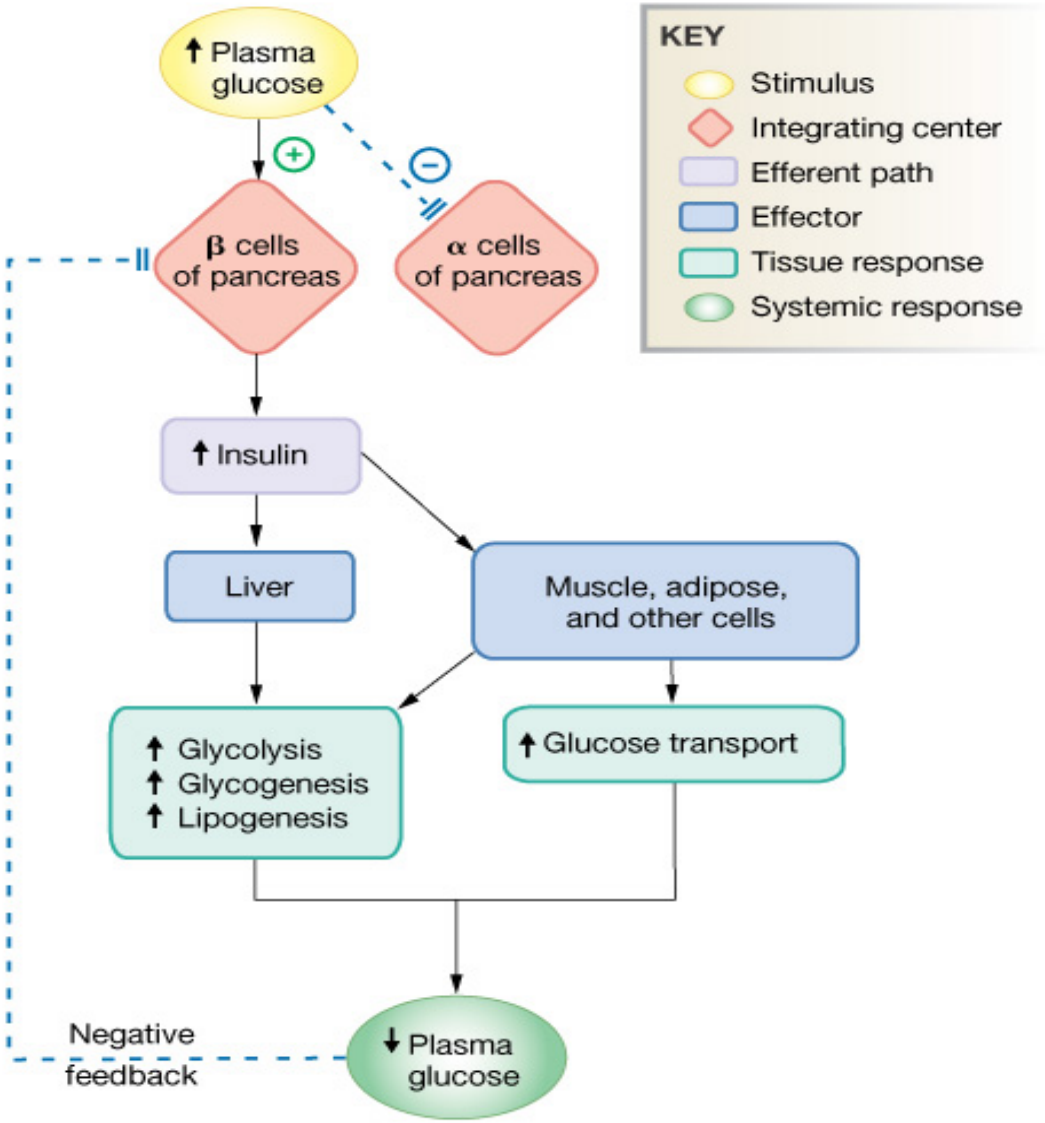


Table 22-3: Insulin

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

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

SYNTHESIS

DNA in α 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

- Its major target is liver:
  - Glycogenolysis
  - Gluconeogenesis
  - Lipid oxidation (fully to CO2 or partially to produce keto acids “ketone bodies”).
  - Release of glucose to the blood from liver cells

Glucagon Action on Cells:

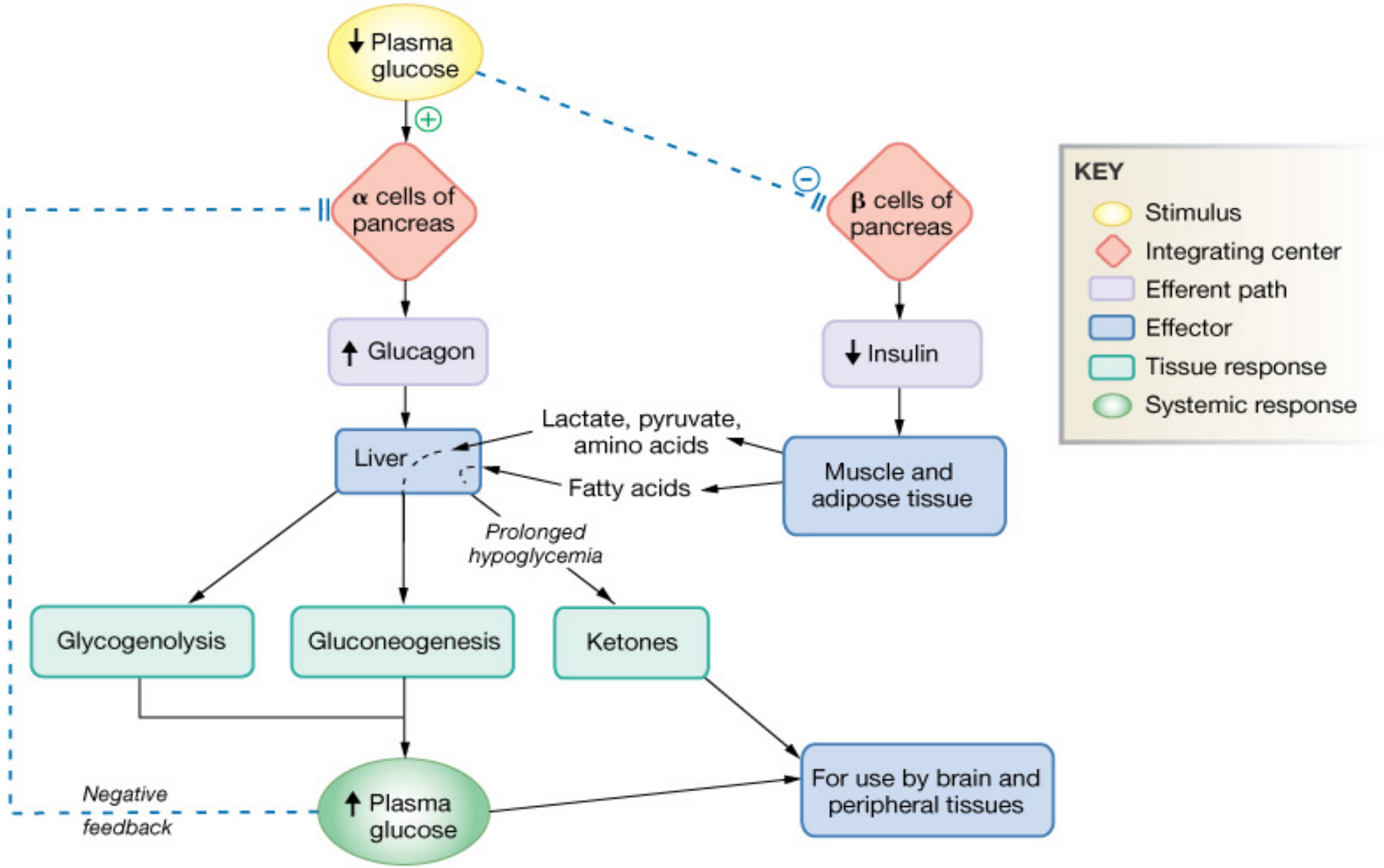
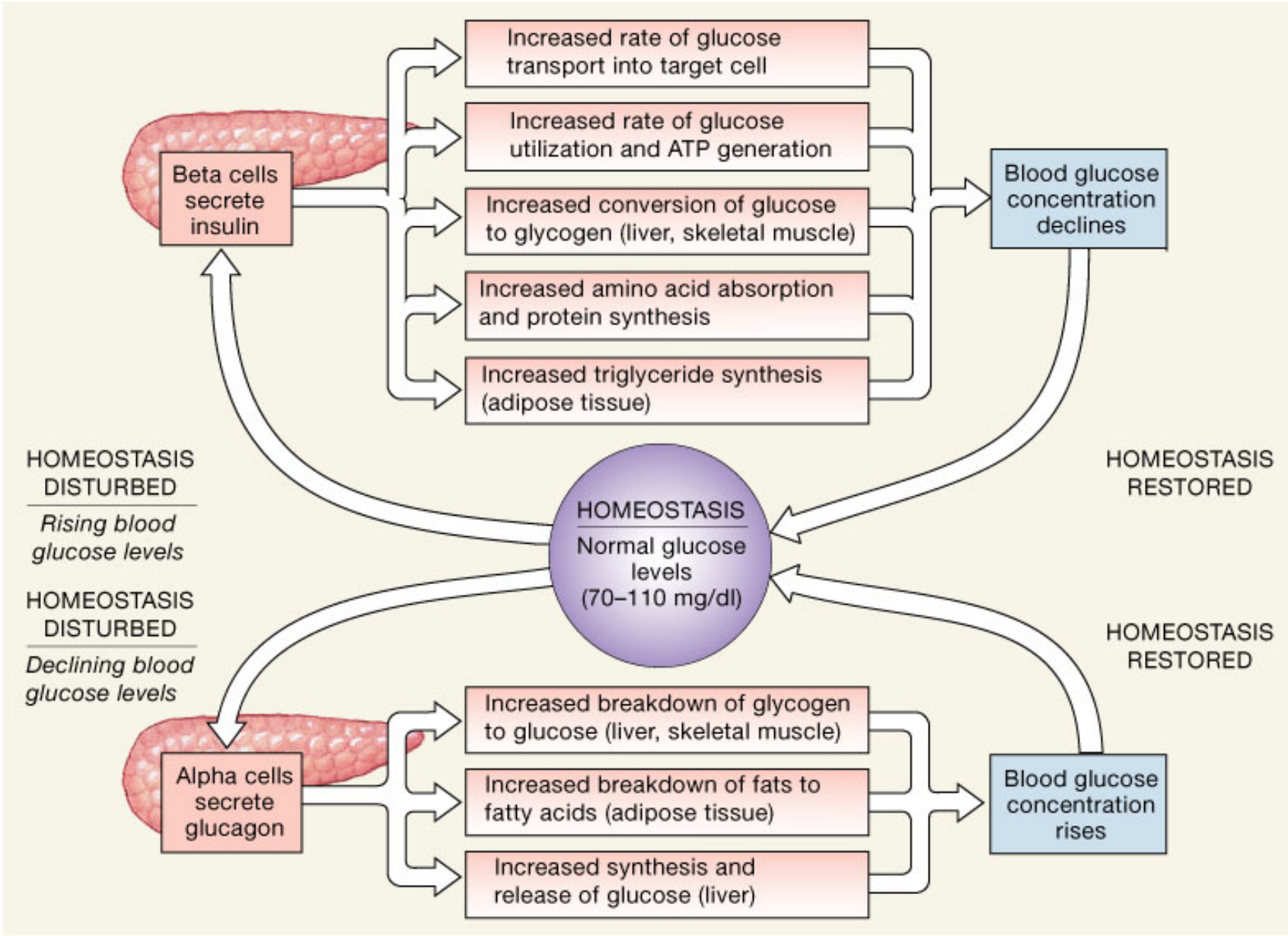


Table 22-5: Glucagon

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

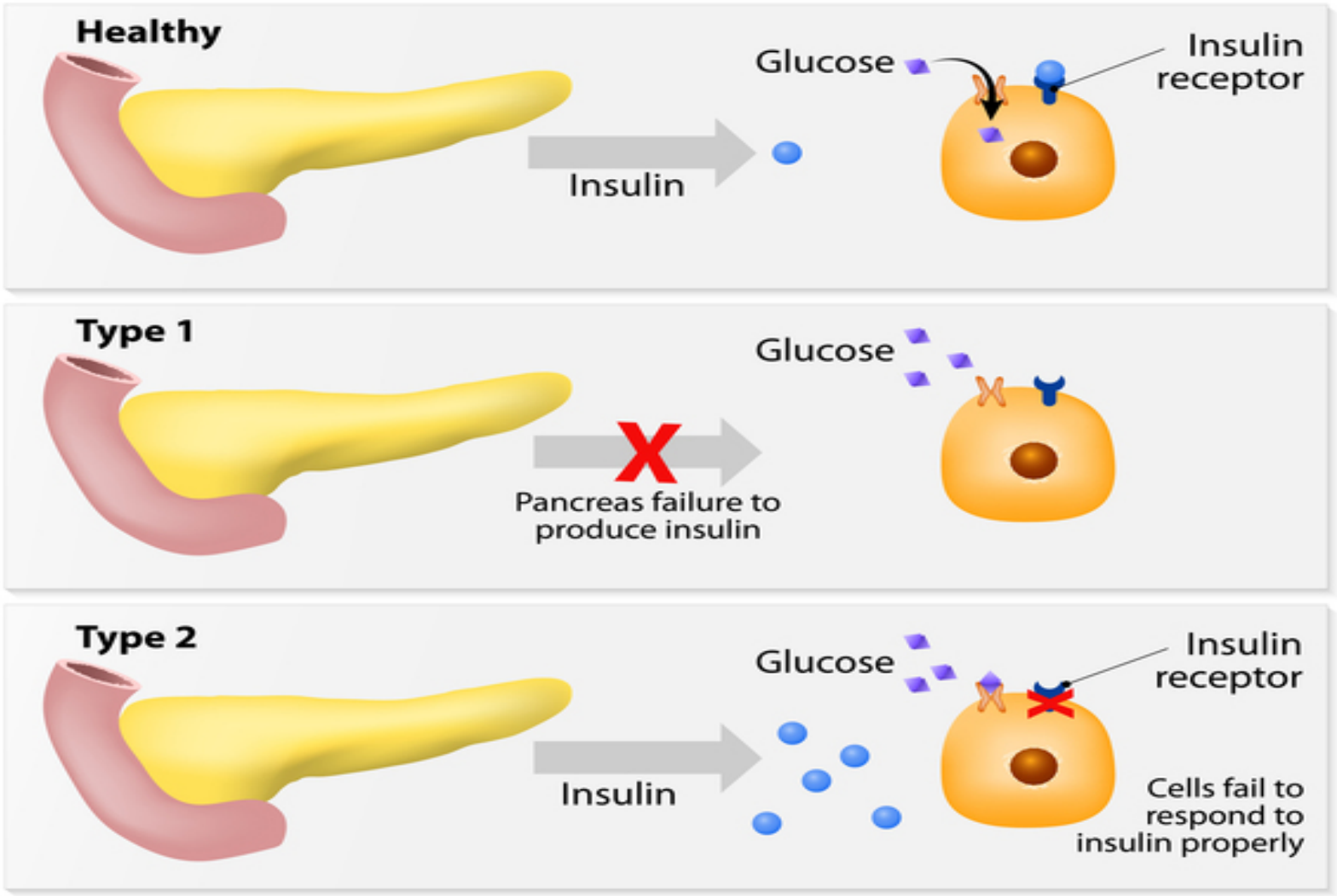
- Diabetes is probably the most important metabolic disease.
- It affects every cell in the body and affects carbohydrate, lipid, and protein metabolism.
- characterized by the polytriad:
  - **Polyuria** (excessive urination)
  - **Polydypsia** (excessive thirst)
  - **Polyphagia** (excessive hunger).

Symptoms of Diabetes Mellitus

Symptoms of Diabetes Mellitus

Hyperglycemia
Polyuria
Polydipsia
Polyphagia
Ketoacidosis (IDDM)
Hyperlipidemia
Muscle wasting
Electrolyte depletion

DIABETES MELLITUS



- **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

Type 1 Diabetes

Affects children

Cause: inadequate insulin secretion

Treatment :

insulin injection

Type 2 diabetes

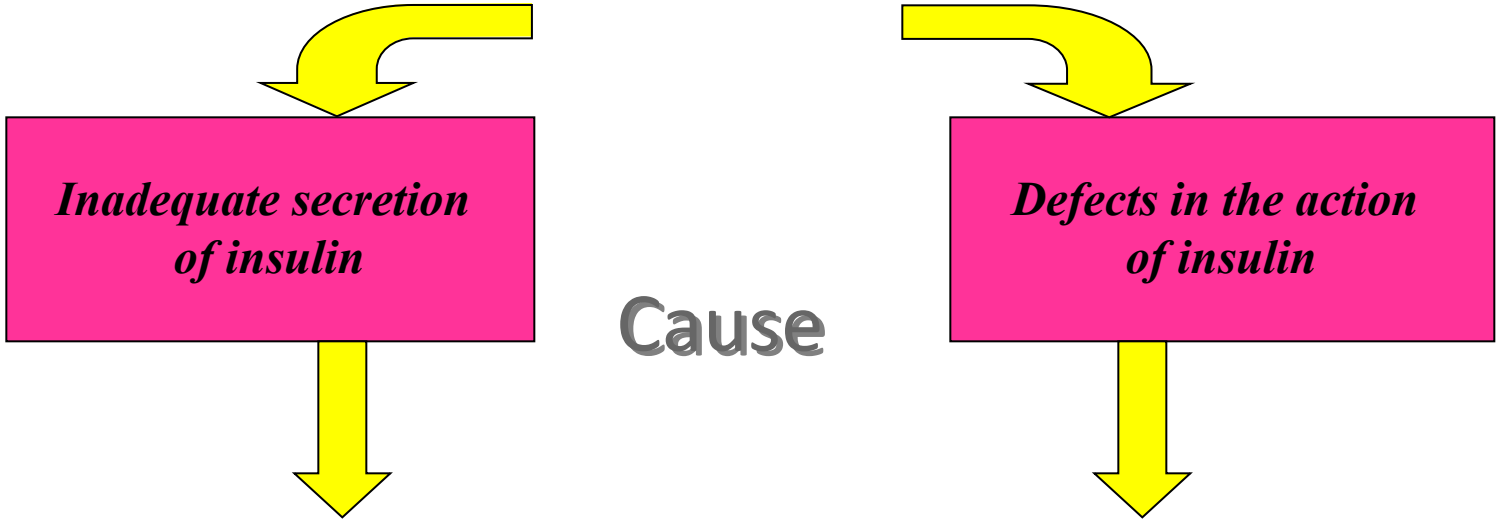
Affects adults

Cause defect in insulin action

Treatment :

diet or OHA (Oral Hypoglycaemic Agents)

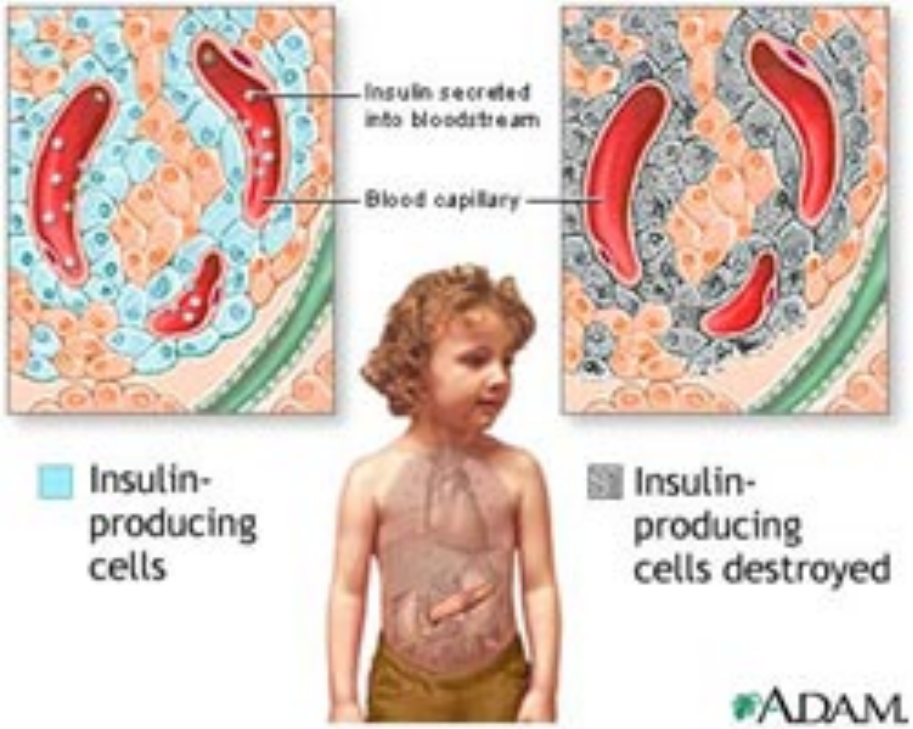
Diabetes Mellitus



Metabolic disturbances

(hyperglycemia and glycosuria)

Type 1 diabetes



Diabetes Mellitus Type I

- Caused by an immune-mediated selective destruction of β cells
- β cells are destroyed while α cells are preserved:

No insulin :::: high glucagon ⇨ high production of glucose and ketones by liver

glucose & ketones ⇧⟹ osmotic diuresis

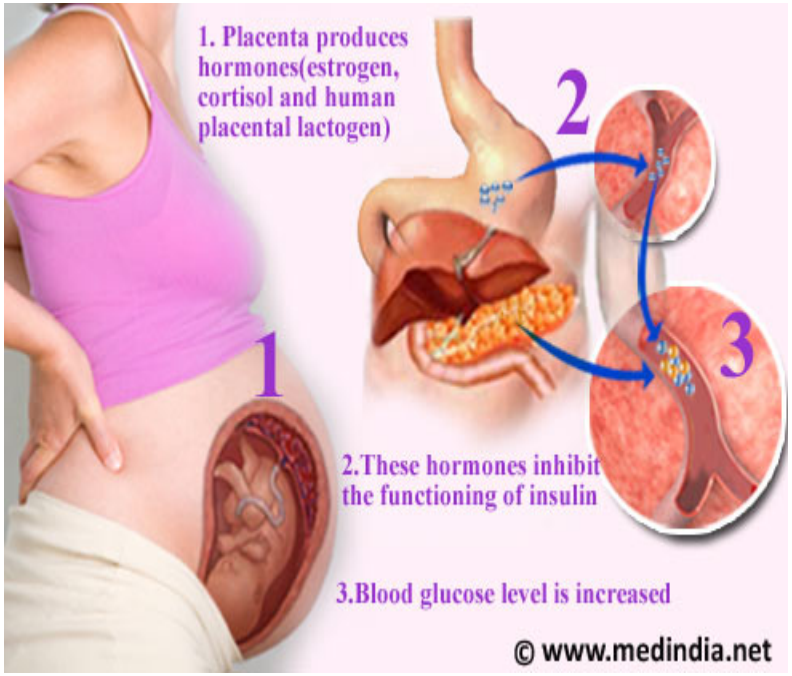
keto acids ⇧⟹ diabetic ketoacidosis

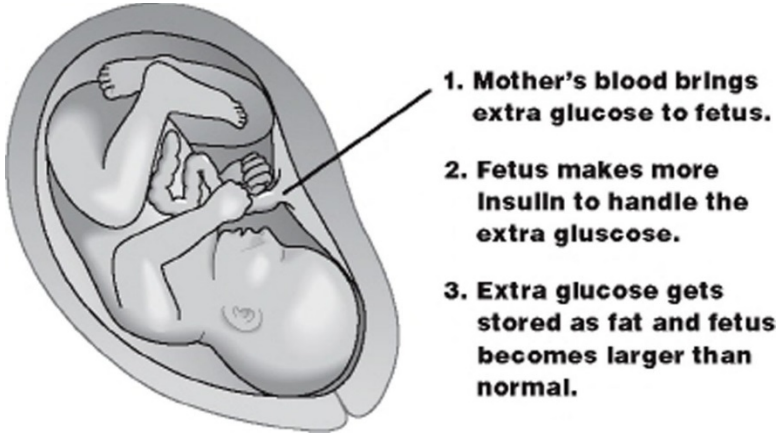
Diabetes Mellitus Type II

- 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.


Avoid sulfites

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

- **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.


JRFC

Glucose Tolerance Test

- Both the FPG and OGTT tests require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.

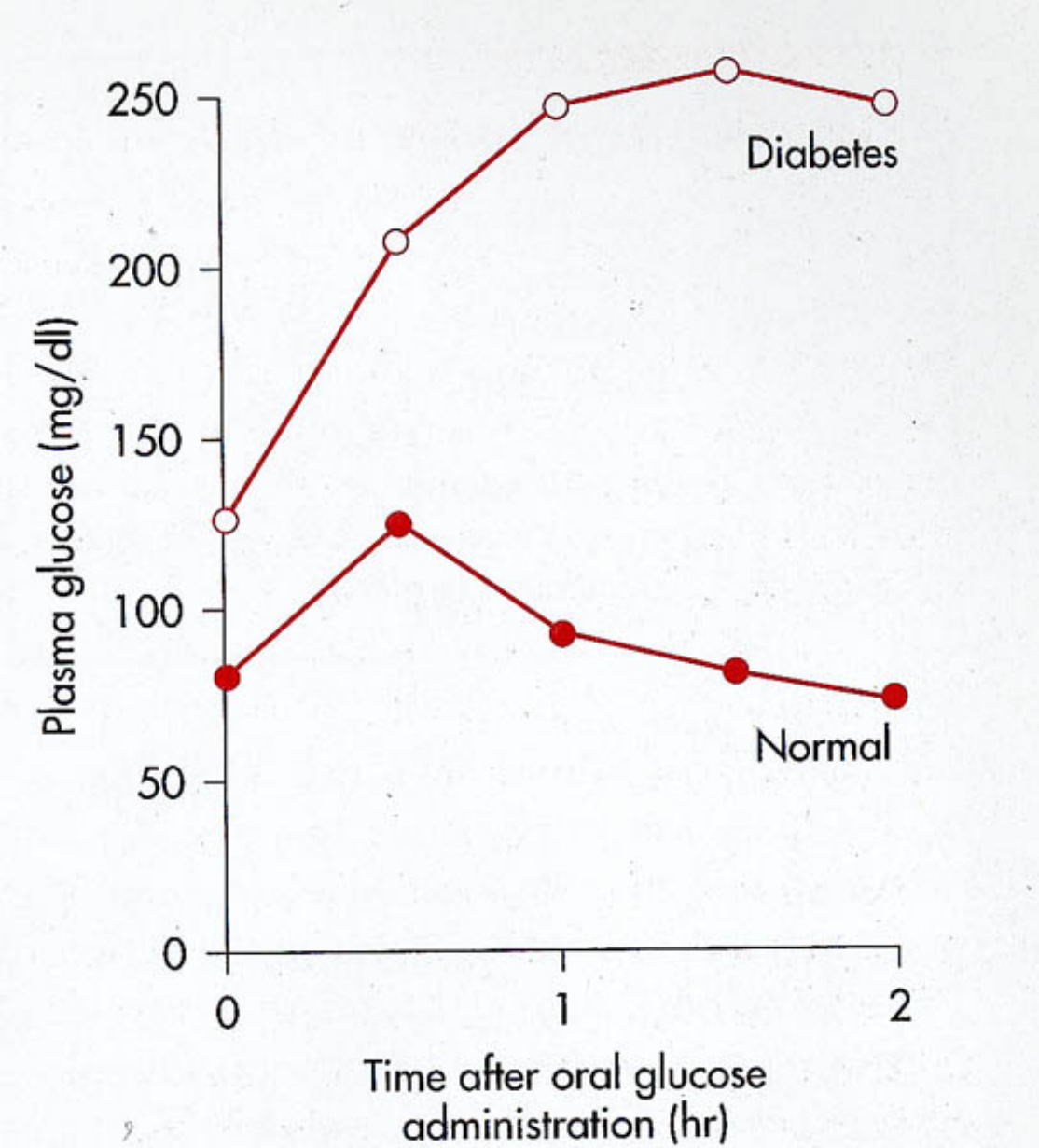
- The oral glucose tolerance test (OGTT):
  - FPG test
  - Blood is then taken 2 hours after drinking a special glucose solution


Oral glucose tolerance test
A.D.A.M.

Glucose Tolerance Test (GTT)

- 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


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

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 ≥ 126 mg/dl
- 2hr PPG levels ≥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	**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