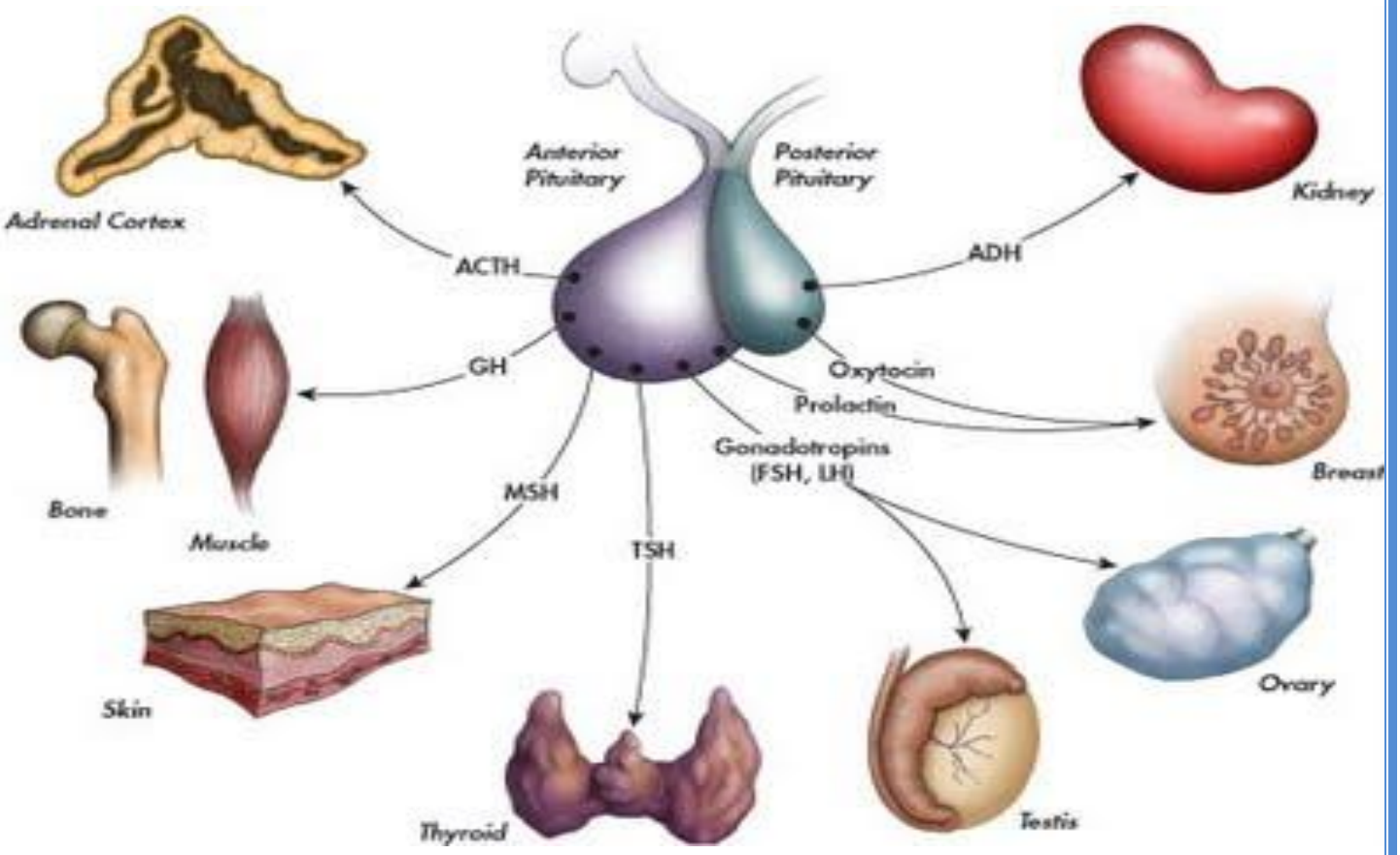
Endocrine Block

14th & 15th Lectures

Pancreas & Insulin



PHYSIOLOGY TEAM – 430

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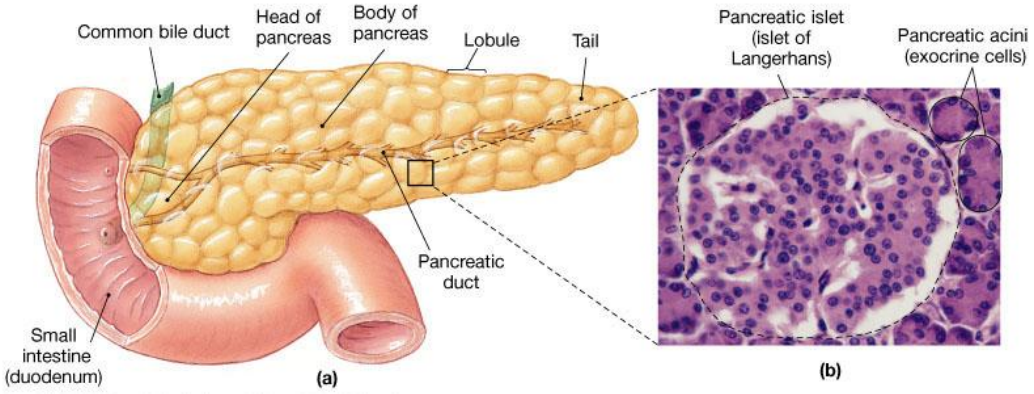
Physiology of Pancreas & Insulin

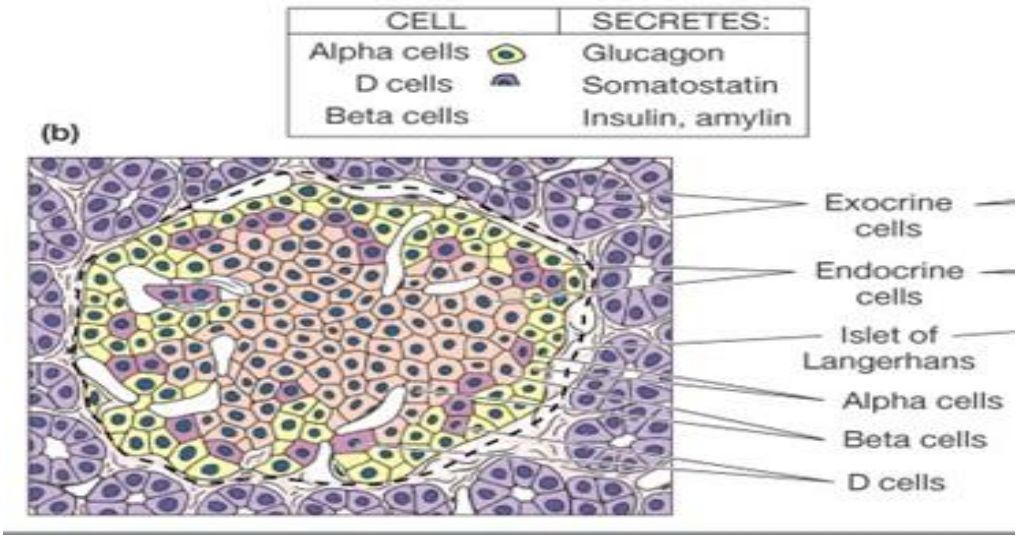
- **Pancreas:**

- 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) (Digestive enzyme)
- Pancreatic islets (**islets of Langerhans**) produce hormones involved in regulating fuel storage and use. (Hormone secretion and production)



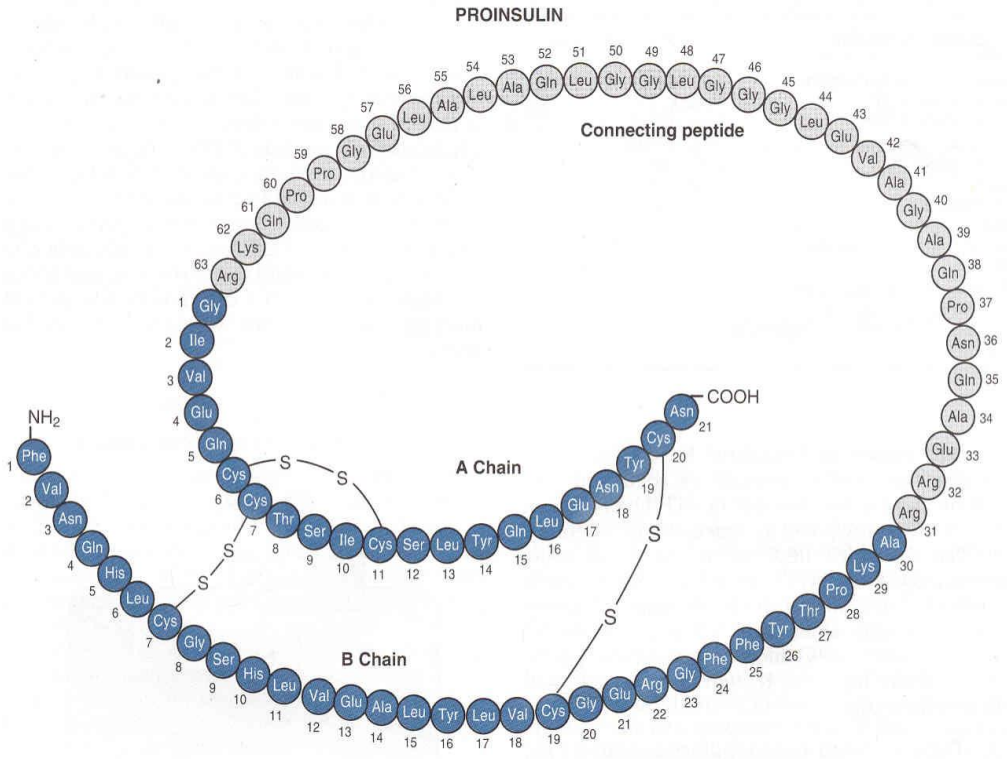
- **Islets of Langerhans**

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



- **Insulin**

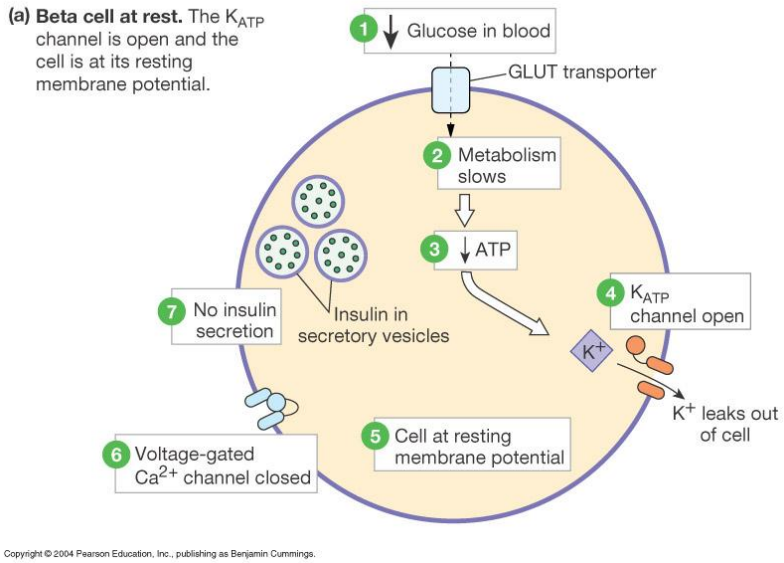
- Hormone of nutrient abundance
- A protein hormone consisting of two amino acid chains linked by disulfide bonds
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA).
- Has a plasma half-life of 6 minutes.

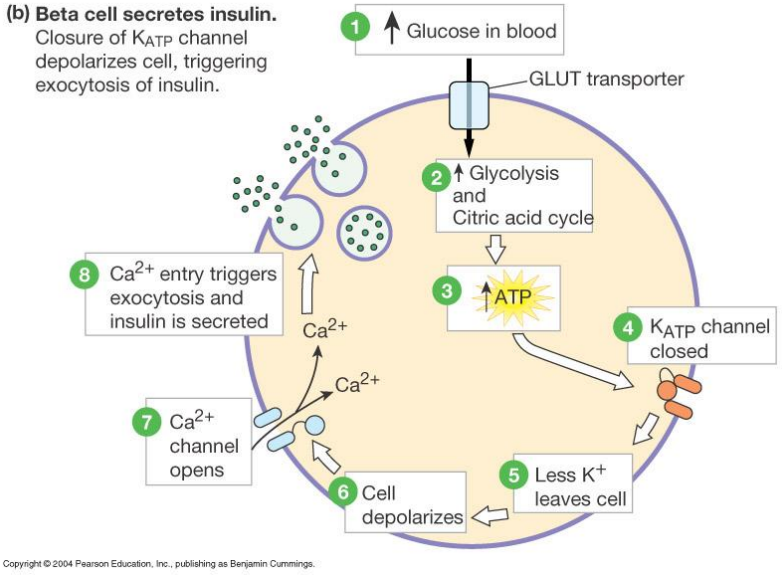


- **Insulin Synthesis**

- DNA (chromosome 11) in β cells → mRNA → Preproinsulin (signal peptide, A chain, B chain, and peptide C) → proinsulin → Insulin.
- 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 secrtion:**





If you didn't understand the diagrams above more details here:

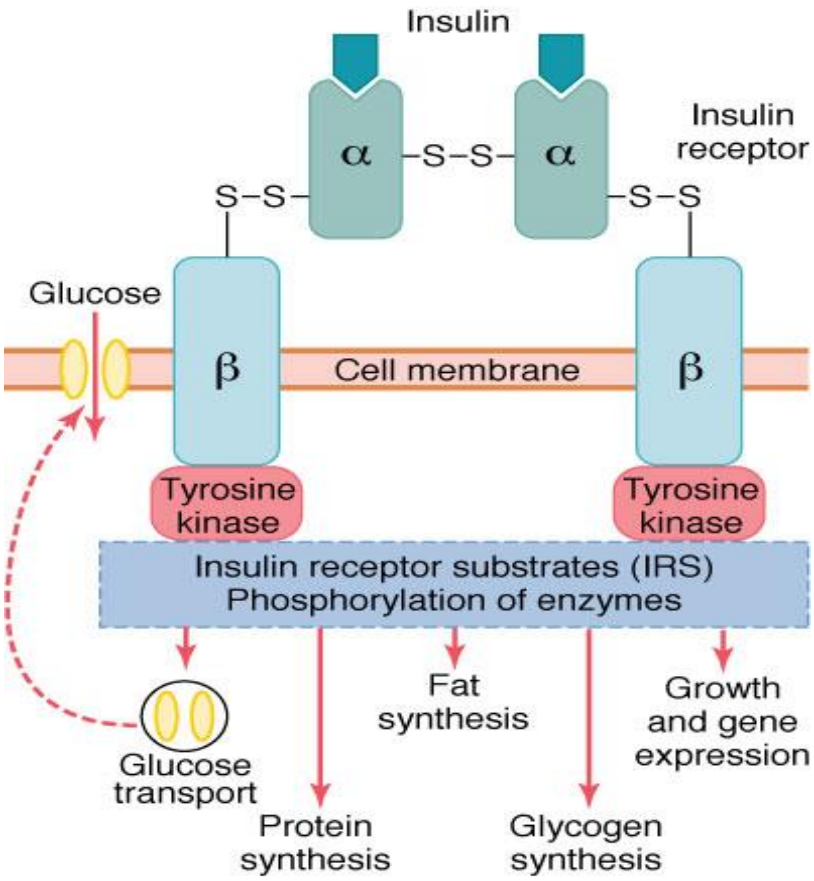
1. Glucose enters ß cells by GLUT 2 transporters.
2. Glucose influx that is proportional to the blood concentration in the physiologic range.
3. Once inside the cells, glucose is phosphorylated to G-6-P by glucokinase.
4. The G-6-P is oxidized to form ATP, which inhibits the ATP-sensitive K+ channels of the cell.
5. Closure of the K+ channels depolarizes the cell membrane, thereby opening voltage-gated Ca++ channels.
6. Influx of Ca++ stimulates fusion of insulin-containing vesicles with the cell membrane and secretion of insulin into the ECF by exocytosis.

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
- Insulin receptor is a combination of four subunits:
- Two α subunits that lie entirely outside the cell membrane
- Two ß subunits that penetrate through the membrane, protruding into the cell cytoplasm.



• Physiology of Insulin

- The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones.
- **Examples:**

✓ Insulin inhibits glucagon secretion.
✓ Amylin inhibits insulin secretion.
✓ Somatostatin inhibits the secretion of both insulin and glucagon.

• Insulin chemistry:

- Insulin is a small protein composed of two amino acid chains connected to each other by disulfide linkages, when the two AA chains are split apart, the functional activity of the insulin molecule is lost.

✓ Alpha chain is composed of 21 AA.
✓ Beta chain is composed of 30 AA.
✓ Alpha-Alpha
✓ Alpha-Beta
✓ Beta-Beta

} The bond between them is called "disulfide linkages"

• Biosynthesis of Insulin

- Insulin RNA is translated to form an insulin pre-pro-hormone → the pre-pro-hormone is cleaved to form a pro-insulin → Pro-insulin is cleaved to form insulin and peptide fragments.
- About 1/6 of the final secreted product is in the form of pro-insulin that has no insulin activity.

• Insulin metabolism

- Insulin circulates in the blood in an <u>unbound</u> form.
- It has a plasma half-life 6 min., so it is mainly cleared from the circulation within 10 to 15 min.
- Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme insulinase mainly in the liver.

Non-suppressible insulin-like activity (NSILA):
Plasma contains a number of substances with insulin-like activity in addition to insulin. Anti-insulin antibodies do not suppress their activity.
Most of this activity persists after (pancreatectomy) and is due to the **insulin-like growth factors IGF-I and IGF-II.**
These IGFs are polypeptides. **In plasma**, IGFs may be:
• Free (small amounts)
• Bound to proteins (large amounts)

NB:
Non-suppressible: they're not suppressed by antibodies,
They only resemble insulin in action,
They're not formed in the pancreas that's why they persist even after pancreactectomy and compensate for the loose of insulin.

- **Principal Actions of Insulin**

- **Rapid (seconds)**

✓ Increased transport of glucose, AA, and K+ into insulin-sensitive cells

- **Intermediate (minutes)**

✓ Stimulation of protein synthesis
✓ Inhibition of protein degradation
✓ Activation of glycolytic enzymes and glycogen synthase
✓ Inhibition of phosphorylase and gluconeogenic enzymes

- **Delayed (hours)**

✓ Increase in mRNAs for lipogenic and other enzymes

Glycolysis:
It is the metabolic pathway that converts glucose C6H12O6, into pyruvate.
Glycogenolysis:
It is the conversion of glycogen polymers to glucose monomers.

- **Action of insulin on adipose tissue:**

1- Increase glucose entry
2- Increase fatty acid synthesis
3- Increase glycerol phosohate synthesis
4- Increase triglyceride dep0sition
5- Increase lipoprotein lipase
6- Decrease of hormone-sensitive lipase

- **Action of insulin on muscle:**

1- Increase glucose entry
2- Increase glycogen synthesis
3- Increase amino acid uptake
4- Increase protein synthesis in ribosomes
5- Decrease protein catabolism
6- Decrease release of gluconeogenic aminco acids
7- Increase ketone uptake

- **Action of insulin on liver:**

1- Decrease ketogenesis
2- Increase protein synthesis
3- Increase lipid synthesis
4- Decrease gluconeogenesis
5- Increase glycogen synthesis
6- Increase glycolysis

- **Generally, insulin increases cell growth.**

- **Glucose Transport**

- GLUT1 (erythrocytes, brain)
- GLUT2 (liver, pancreas, small intestines)
- GLUT3 (brain)
- **GLUT4**, insulin sensitive transporter (muscle, adipose tissue)

- **Action of insulin on Liver:**

- ↑ Glucose uptake (if blood glucose level is high)
- ↑ Glucose use (↑ Glycogenesis, ↓ Glycogenolysis, ↑ Glycolysis, ↓ Gluconeogensis)
- ↑ Fatty acid synthesis and VLDL formation, ↓ Ketogenesis
- ↓ Urea cycle activity

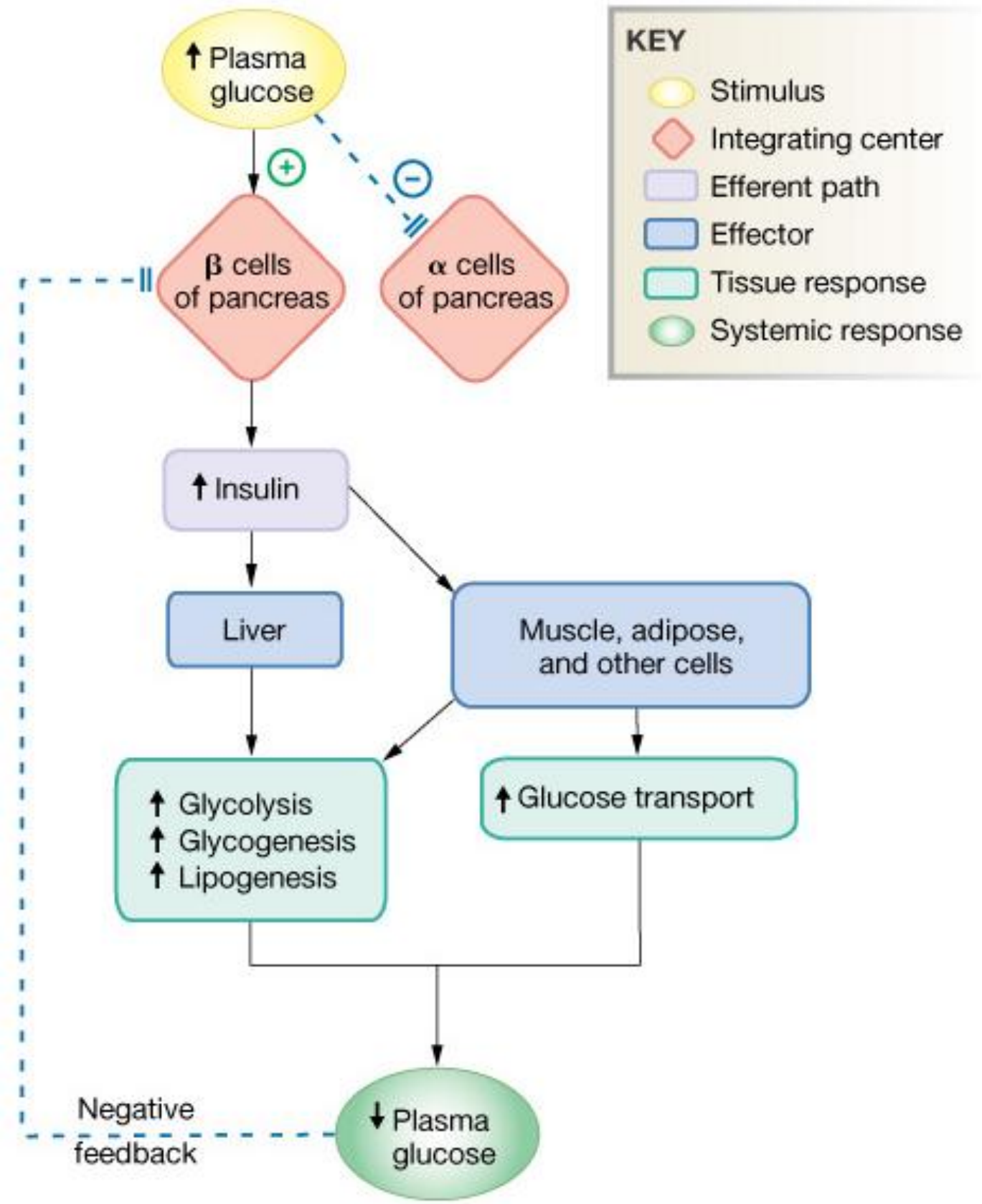
- **Action of insulin on Fat:**

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

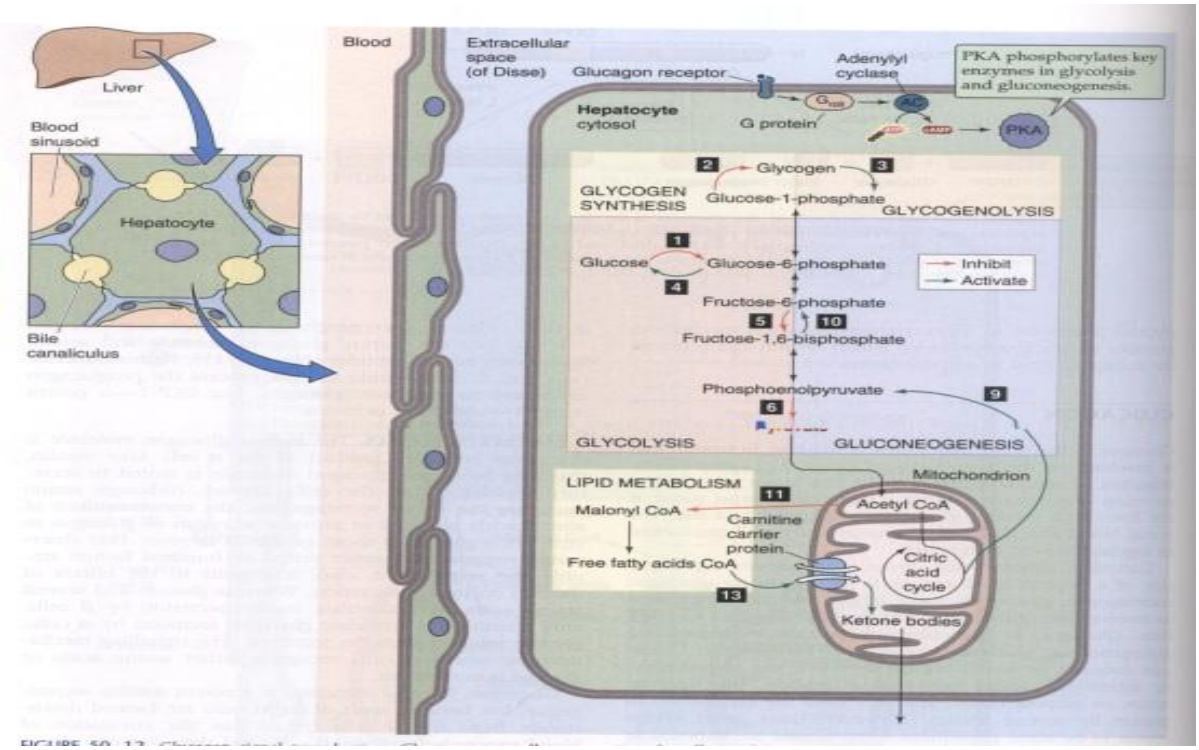
- **Summary**


KEY
Stimulus
Integrating center
Efferent path
Effector
Tissue response
Systemic response
↑ Plasma glucose
+
−
β cells of pancreas
α cells of pancreas
↑ Insulin
Liver
Muscle, adipose, and other cells
↑ Glycolysis
↑ Glycogenesis
↑ Lipogenesis
↑ Glucose transport
Negative feedback
↓ Plasma glucose

- **Glucagon**

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

- **Glucagon Signaling**



- **Synthesis**

- DNA in α cells (chromosome 2) → mRNA → Preproglucagon → proglucagon → glucagon

- **Factors Affecting Glucagon Secretion:**

- **Stimulators:**

✓ ↓ Blood glucose
✓ ↑ Serum amino acids (arginine, alanine)
✓ Sympathetic stimulation
✓ Stress
✓ Exercise

- **Inhibitors:**

✓ 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:**

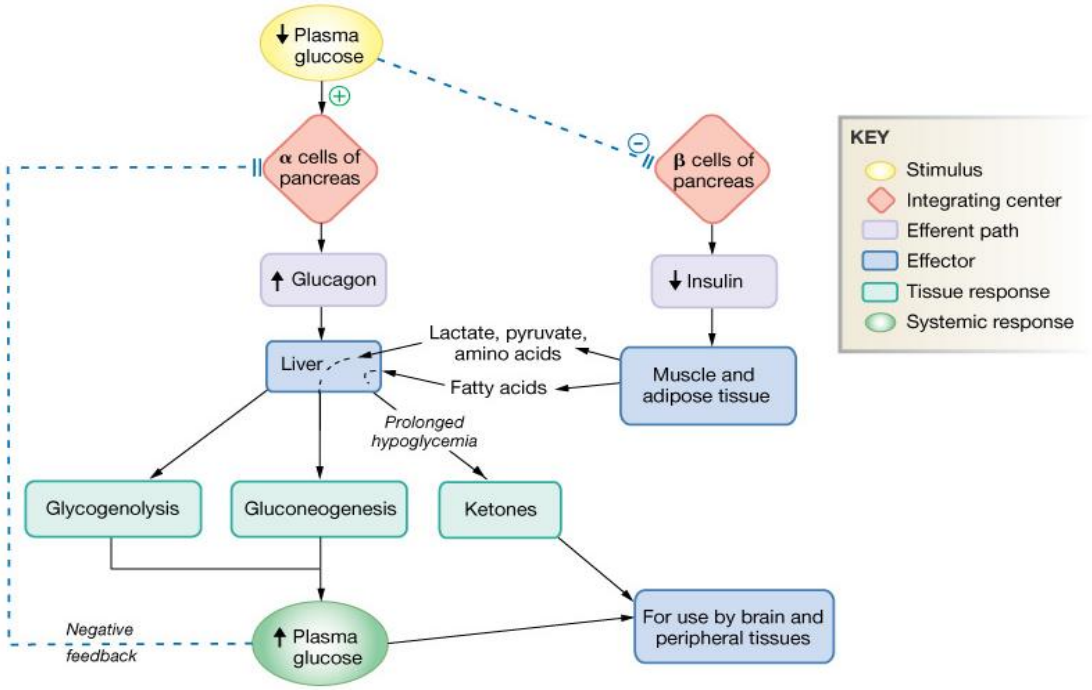
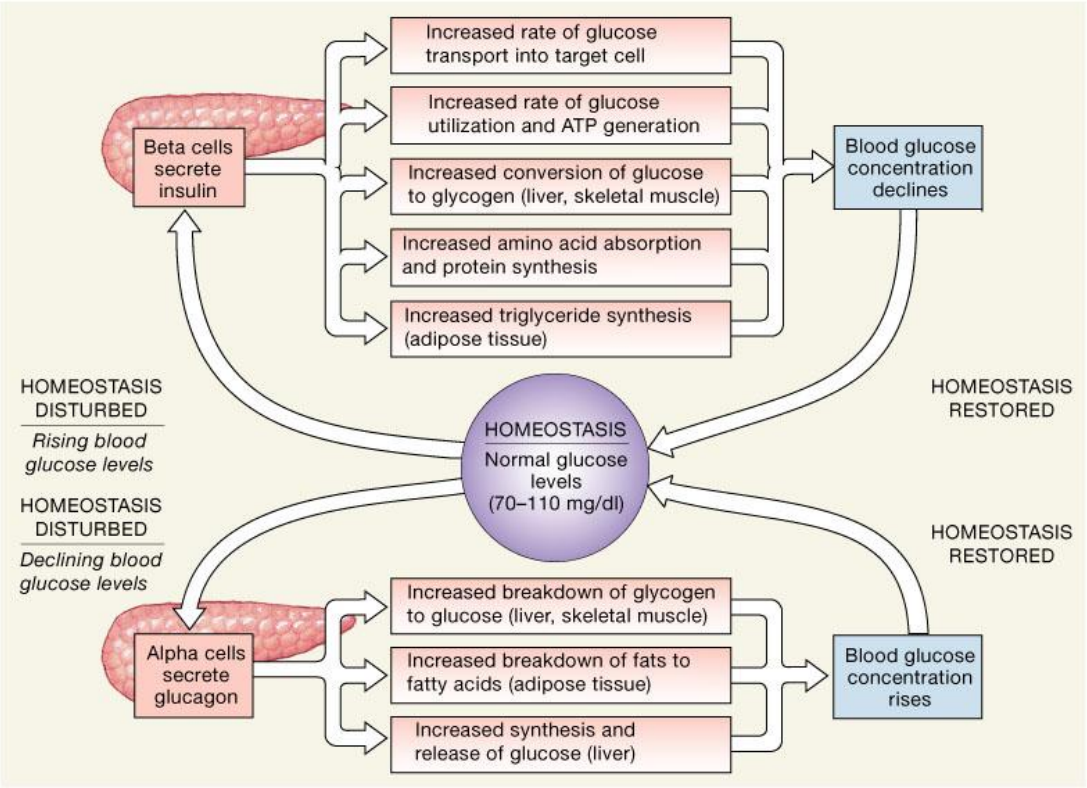


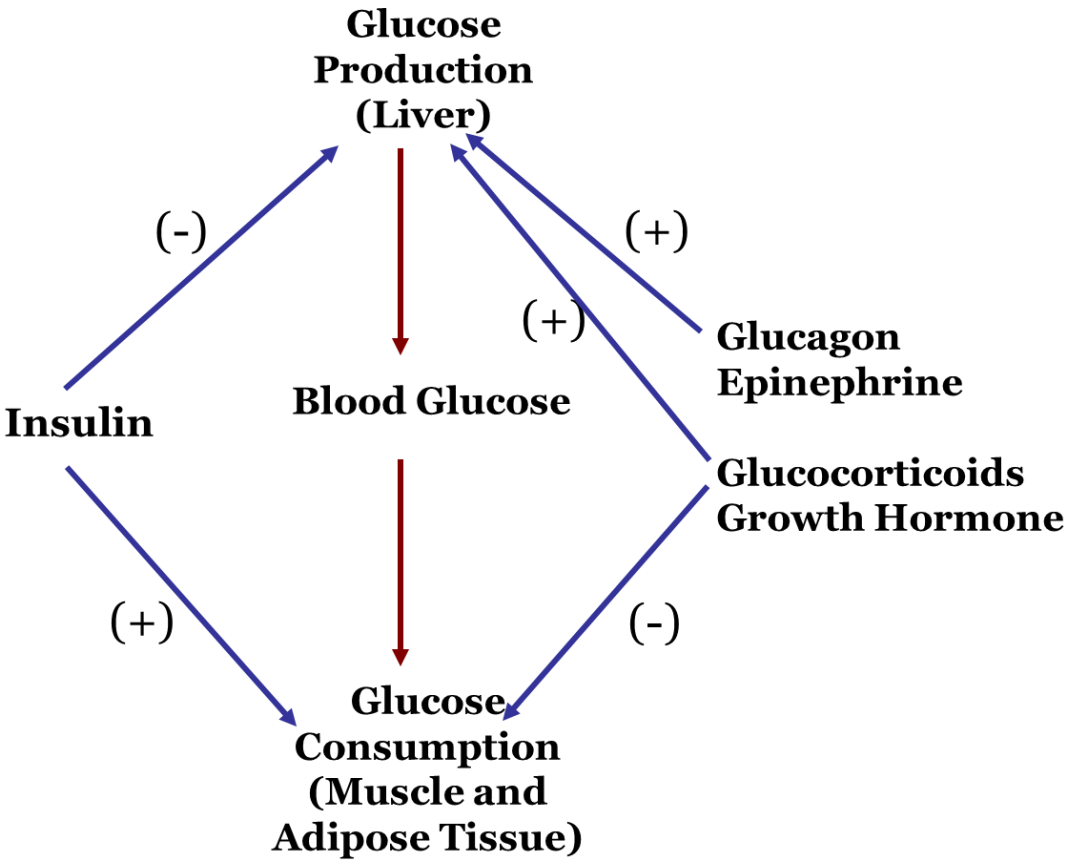
Table 22-5: Glucagon

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:**



- **Hormonal Interactions in the Maintenance of Blood [Glucose]**



- **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)

	Type 1	**Type 2**
Affects	Children, Usually before 20	Adults, Usually after 30
Cause	inadequate insulin secretion	defect in insulin action
weight	Normal	Overweight
Treatment	insulin injection	diet, lifestyle, OHA, or insulin injections
Symptoms	Polyuria - Polydypsia – Polyphagia – Hyperglycemia - Ketoacidosis (IDDM) – Hyperlipidemia - Muscle wasting - Electrolyte depletion	

- **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 :**

- More common in some ethnic groups
- Insulin resistance keeps blood glucose too high
- Chronic complications: atherosclerosis, renal failure & blindness

- **Glucose Tolerance Test:**

- Fasting blood glucose "or sugar" (FBG)
- oral glucose tolerance test (OGTT)
- Both are require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.

- **The oral glucose tolerance test (OGTT):**

- FBG
- Blood is then taken 2 hours after drinking a special glucose solution
- 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.

- **The following results suggest different conditions:**

- **Normal values:**

✓ Fasting <100 mg/dl
✓ 2hr < 140 mg/dL

- **Impaired glucose tolerance**

✓ 2hr PPG = 140 - 199 mg/dL

- **Diabetes**

✓ FPG ≥ 126 mg/dl
✓ 2hr PPG levels ≥200 mg/dL