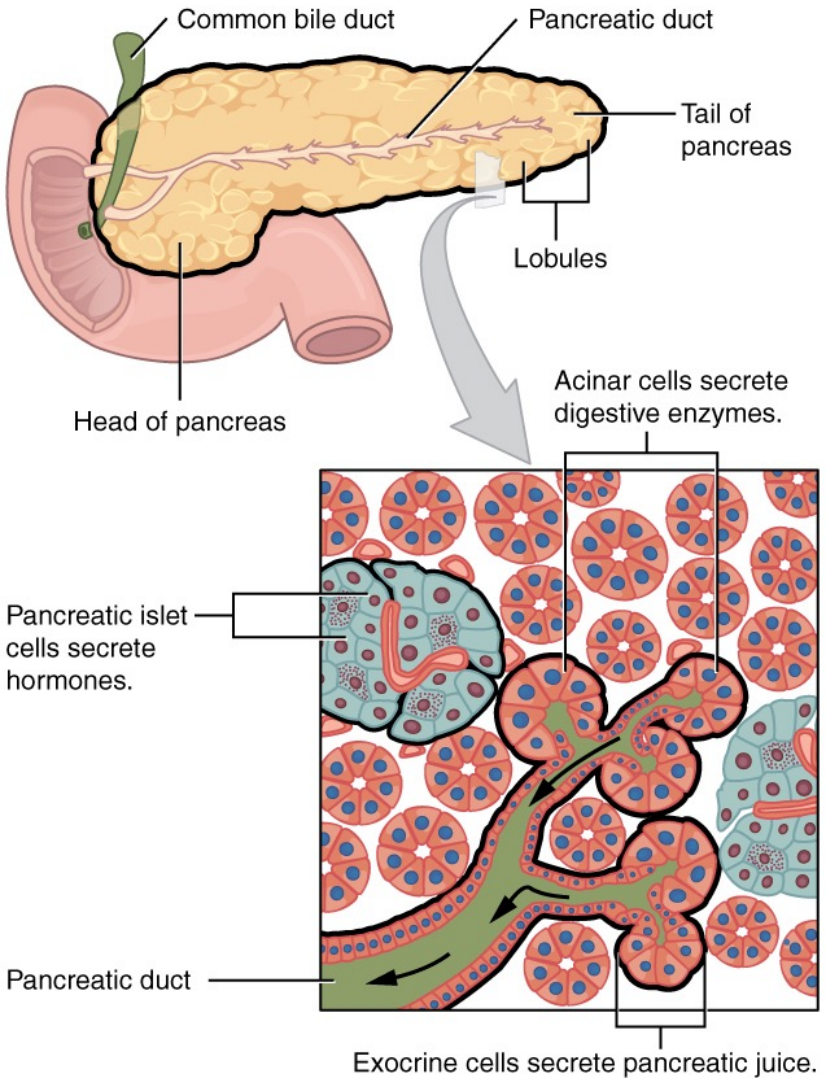
Pancreatic hormones

Anatomy of the pancreas

- Both an exocrine and endocrine organ
- Cells with exocrine function release an alkaline fluid containing sodium bicarbonate and enzymes → pancreatic duct → small intestine
- Pancreatic "juice" aids in breakdown and digestion of food in the small intestine
- Pancreatic exocrine cells = acinar cells



Endocrine Function :

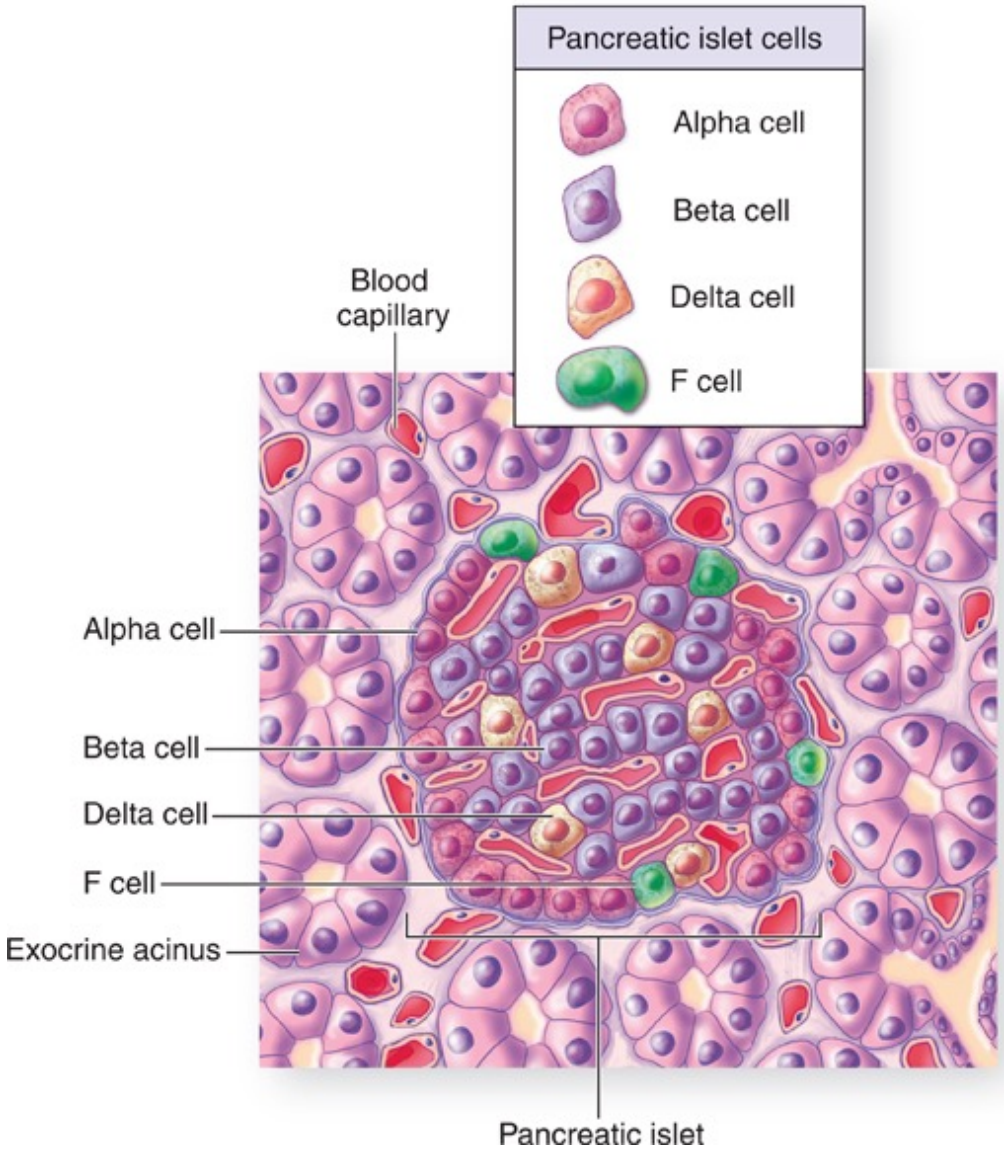
- Cells of the Islet of Langerhans synthesize and release hormones into the circulation.

- **Hormones** travel through the blood stream to target tissues (especially liver and muscle)
- At the target cells, hormones bind **specific receptors** and cause cell changes that control metabolism

Pancreatic Hormones

- Glucagon
- Insulin
- Somatostatin (SS)
- Pancreatic polypeptide (PP)

Pancreas Histology



Pancreatic Hormones, Insulin & Glucagon Regulate carbohydrates, lipids & protein Metabolism

- **Beta cells** produce **insulin** – increases cellular uptake of blood glucose and its utilization → decreases blood glucose level
- **Alpha cells** produce **glucagon** – ↑ blood glucose (from cells)
- **D cells** produce **somatostatin** (SS) – ↓ gastric secretion, inhibits other islets cell hormones secretion, inhibit growth hormone secretion.
- **F cells** produce **pancreatic polypeptide** (PP)- unknown function.

Pancreatic Hormones, Insulin & Glucagon Regulate Metabolism

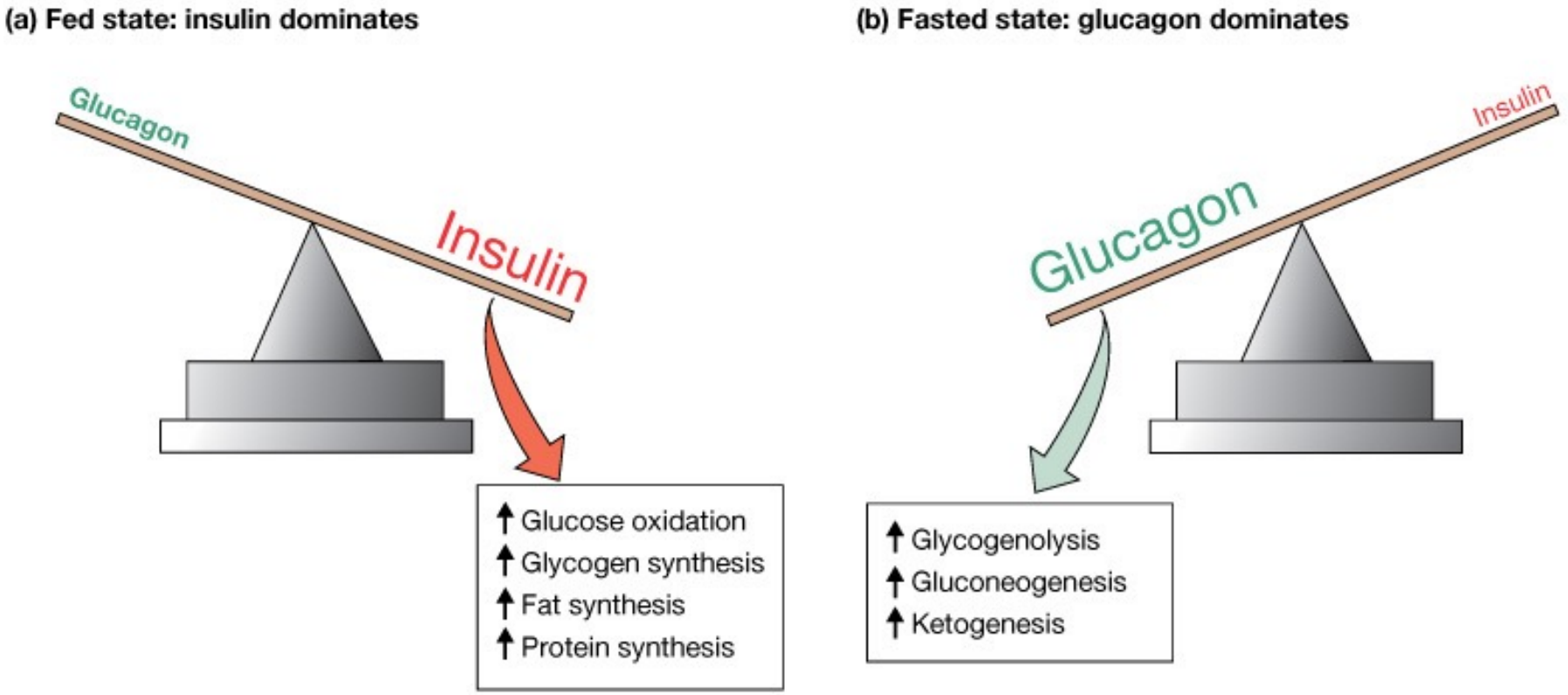


Figure : Metabolism is controlled by insulin and glucagon

INSULIN

Beta cells

Hyperglycemia = insulin secretion

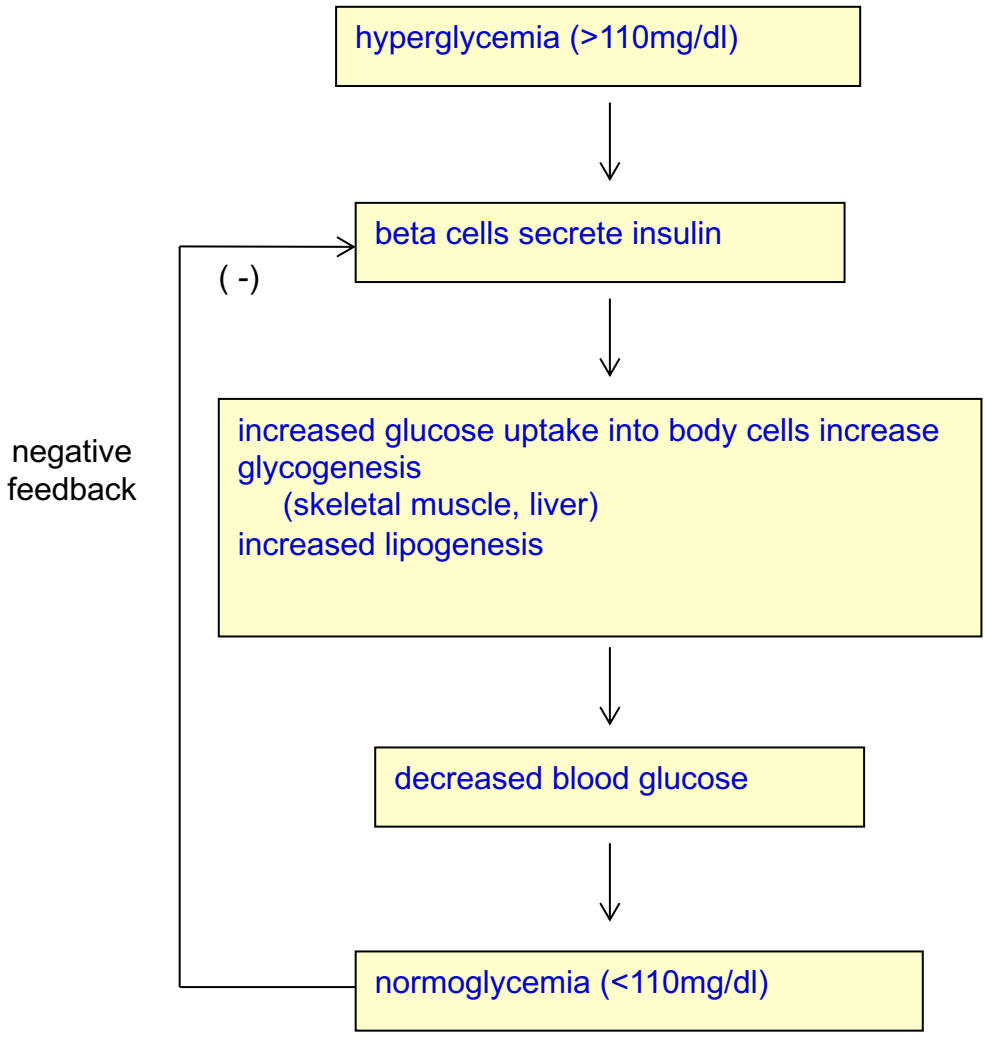
Actions (anabolic);

increased glucose uptake in cells

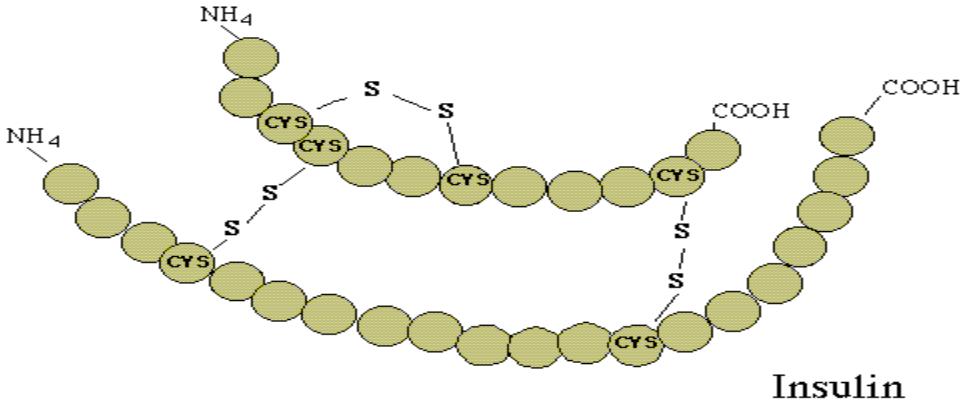
increased glycogenesis

increased lipogenesis

Result = normoglycemia



Insulin Is Synthesized as a Preprohormone & Modified Within the Cell



Insulin

A chain 21AA

B chain 30AA

- It is a hetero-dimeric polypeptide consisting

  of two chains (A, B)

  linked by disulfide bridges.
- one intra-chain disulfide bond (A6–A11)
- and two inter-chain disulfide bridges (A7–B7 and A20–B19)

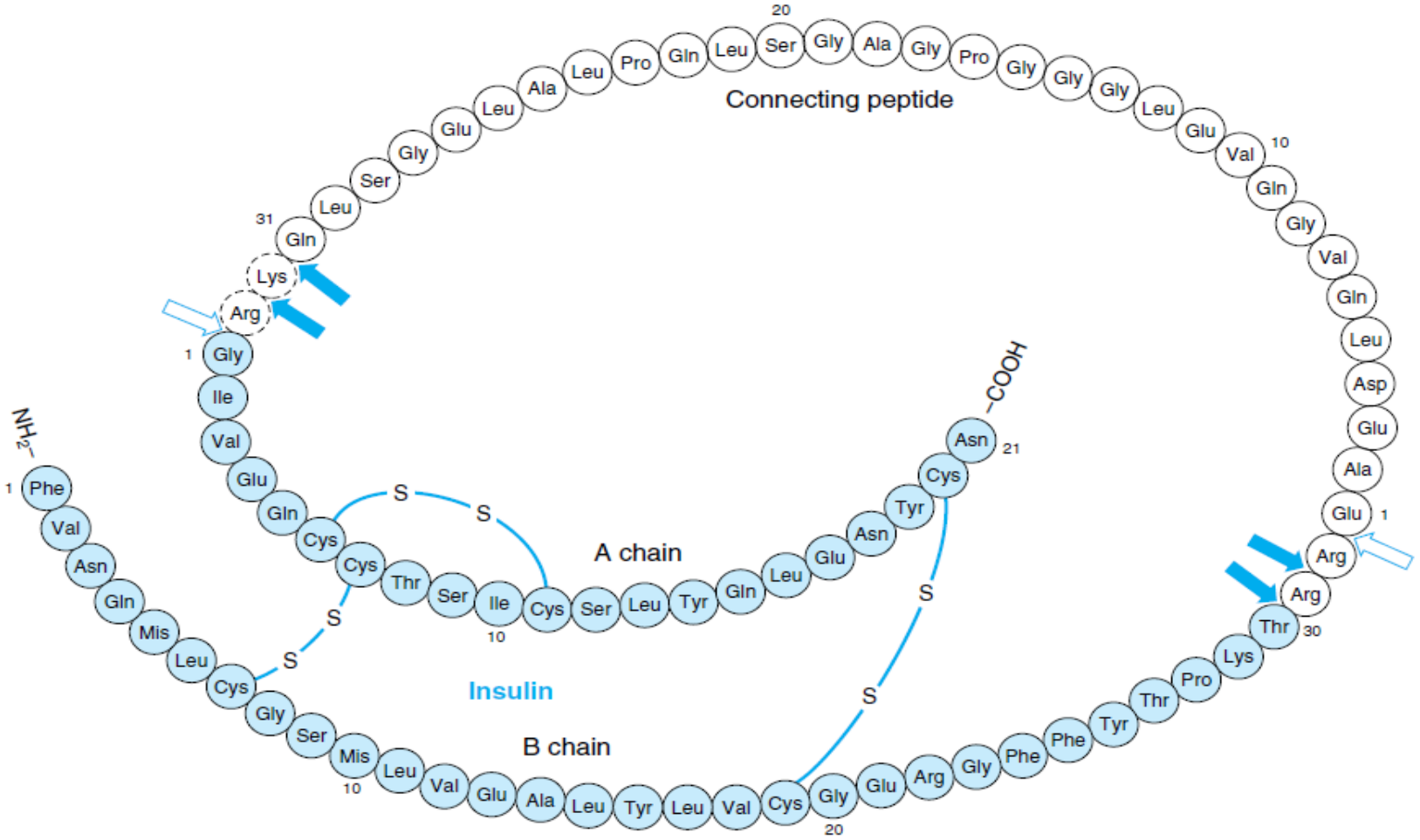


Figure 42–12. Structure of human proinsulin. Insulin and C-peptide molecules are connected at two sites by dipeptide links. An initial cleavage by a trypsin-like enzyme (open arrows) followed by several cleavages by a carboxypeptidase-like enzyme (solid arrows) results in the production of the heterodimeric (AB) insulin molecule (light blue) and the C-peptide.

insulin is synthesized as a **preprohormone** **(molecular weight approximately** 11,500.

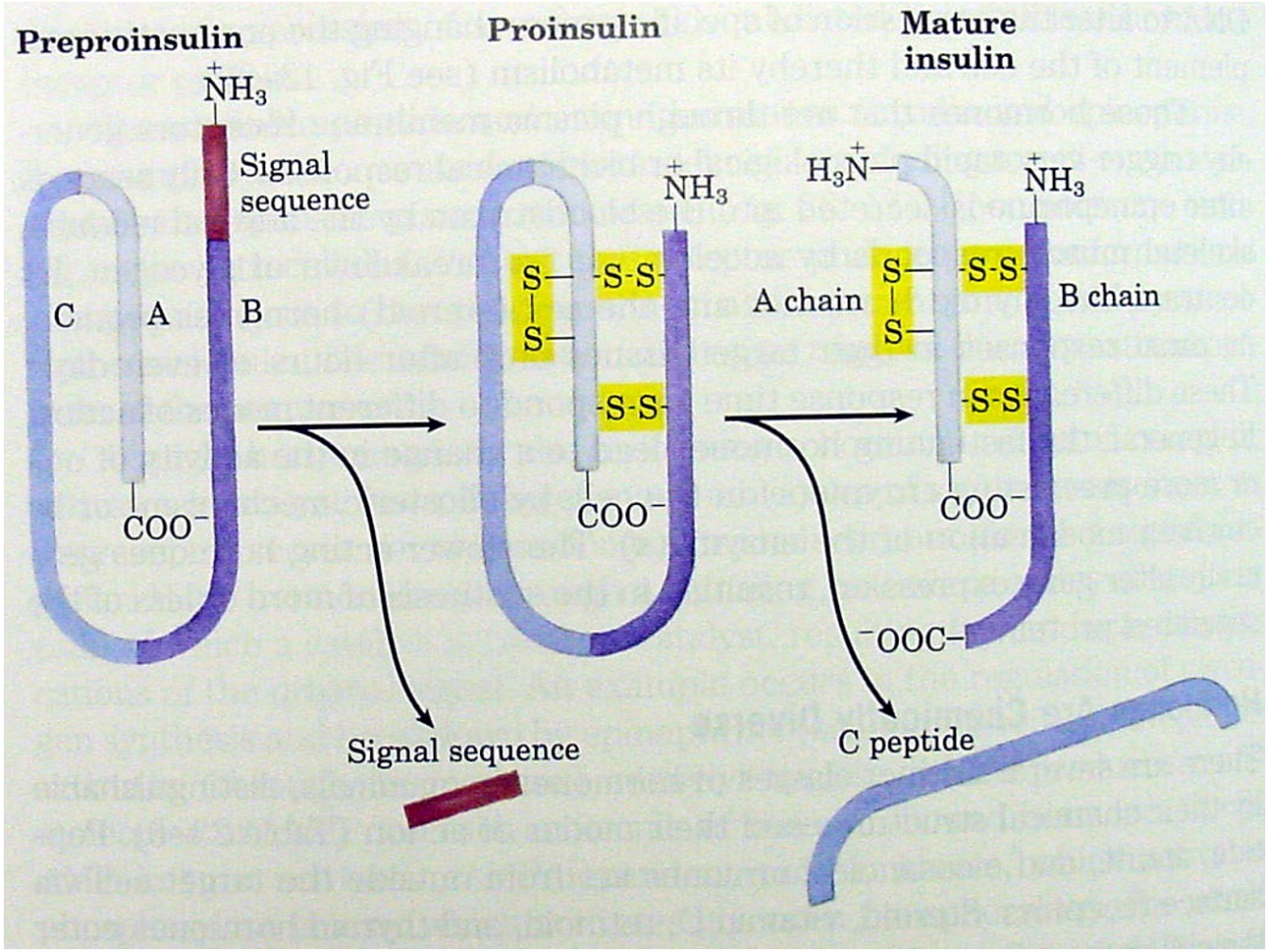
The **hydrophobic 23-amino-acid pre-, or leader**, sequence in the preproinsulin directs the molecule into the endoplasmic reticulum (ER) and then is removed.

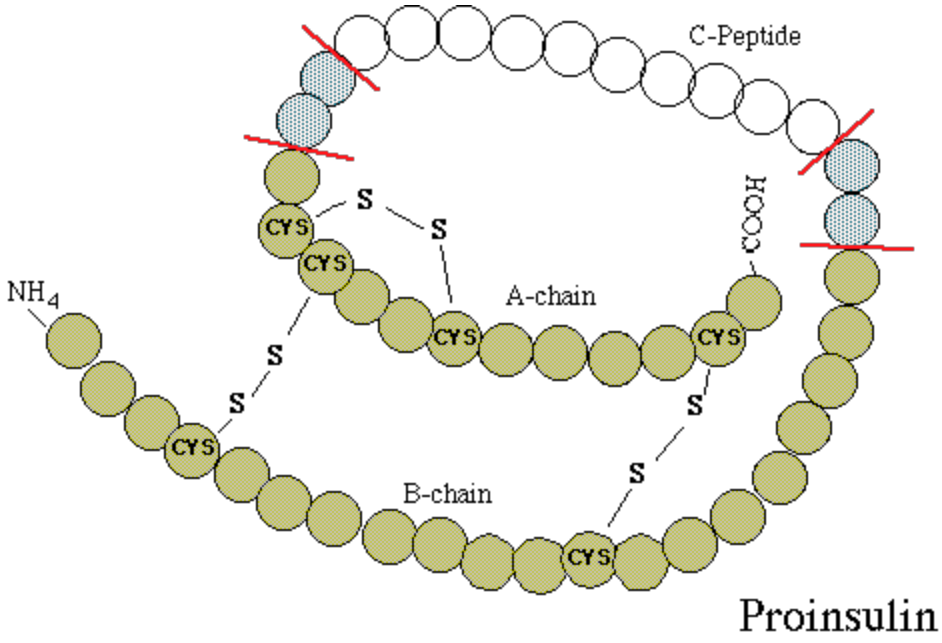
This results molecule is in the 9000- MW **proinsulin** molecule.

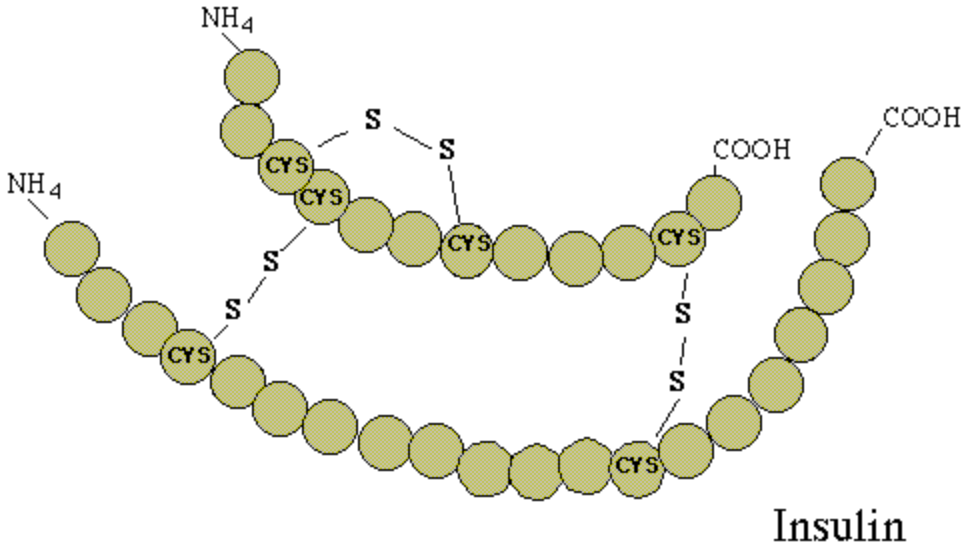
Proinsulin consists of **three domains**: an **amino-terminal B chain (30 amino acids)**, a **carboxy-terminal A chain (21 amino acids)** and a **connecting peptide in the middle known as the C peptide.**

- Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the equimoalr amount of mature form of insulin and C peptide.

- Insulin and free C peptide are packaged in the Golgi into secretory granules.







• Note that with removal of two pairs of basic amino acids (blue), that proinsulin is converted into insulin and C-peptide. "

Beta Cells

Synthesize **pre-proinsulin**, a protein
This is cleaved by enzymes →**proinsulin**, then cleaved again → **insulin**

Insulin is the **biologically active hormone** that is released into the bloodstream

Degradation

Metabolism of insulin is in the liver , kidney and placenta.

Most insulin molecules are degraded by:

1- **insulin specific protease, cleavage insulin proteolytically between amino acids residues 16 & 17 of B chain.**

2- **hepatic glutathione-insulin transhydrogenase that reduce the disulfide bonds then the individual A and B chains are rapidly degraded.**

- Insulin molecule is degraded within approximately one hour after its release into circulation.
- Insulin half-life ~ 4–6 minutes.

Insulin secretion is controlled through several mechanisms:

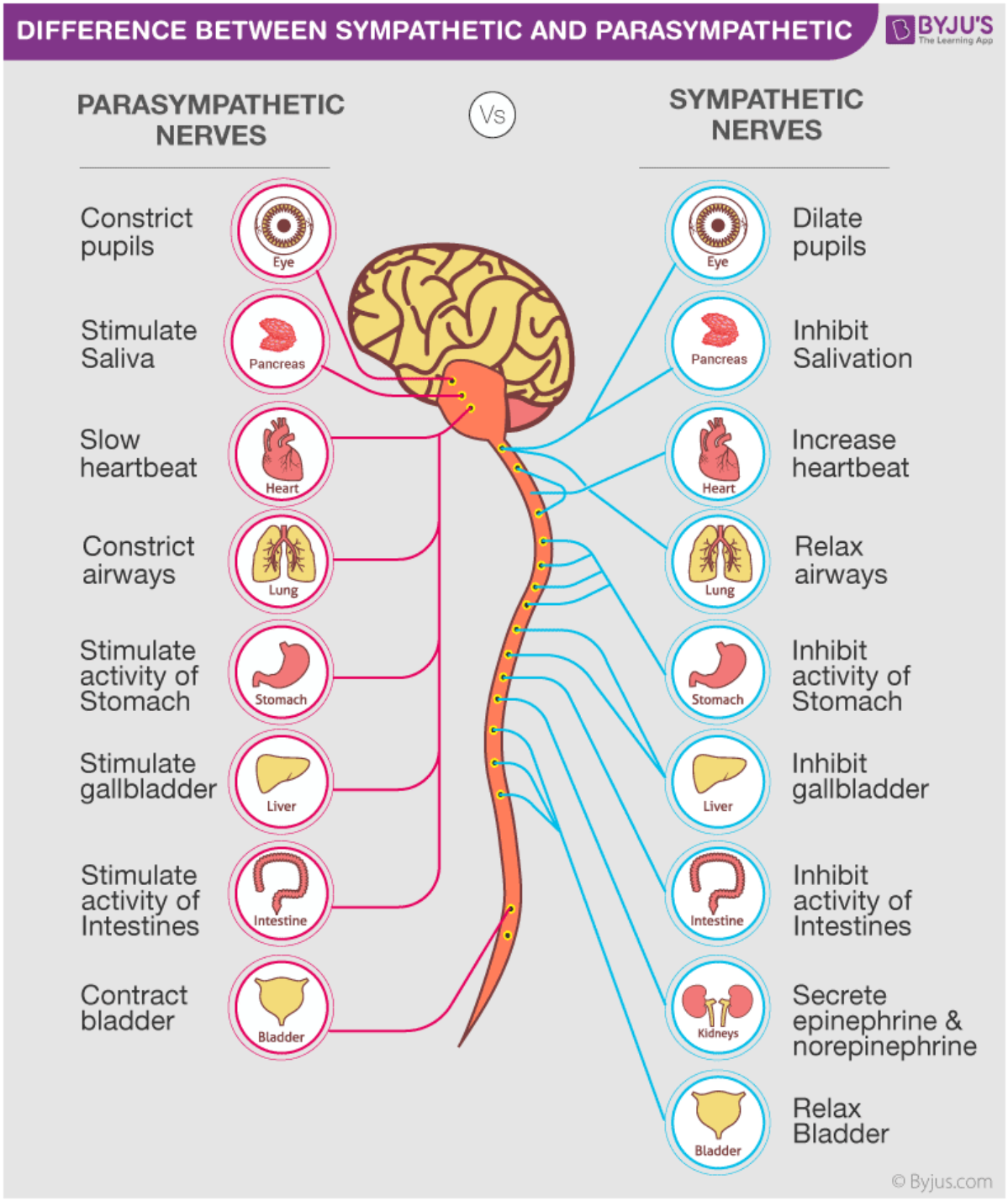
- **Chemically**
- **high levels of glucose** (the most important physiological regulator of insulin secretion).
- **amino acids, free fatty acids, ketoacids and K+** in the blood stimulate insulin secretion.
- **Hormonally**

beta cells are sensitive to several hormones that may inhibit or cause insulin secretion;

- **Exess GH, cortisol, estrogen and placental lactogen stimulate** insulin secretion

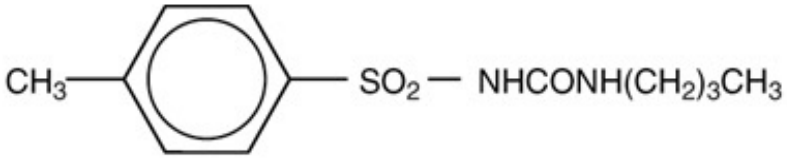
- **Naturally**

stimulation of the **parasympathetic** nervous system causes insulin to be secreted.


DIFFERENCE BETWEEN SYMPATHETIC AND PARASYMPATHETIC
BYJU'S The Learning App
PARASYMPATHETIC NERVES
Vs
SYMPATHETIC NERVES
Constrict pupils
Eye
Stimulate Saliva
Pancreas
Slow heartbeat
Heart
Constrict airways
Lung
Stimulate activity of Stomach
Stomach
Stimulate gallbladder
Liver
Stimulate activity of Intestines
Intestine
Contract bladder
Bladder
Dilate pupils
Eye
Inhibit Salivation
Pancreas
Increase heartbeat
Heart
Relax airways
Lung
Inhibit activity of Stomach
Stomach
Inhibit gallbladder
Liver
Inhibit activity of Intestines
Intestine
Secrete epinephrine & norepinephrine
Kidneys
Relax Bladder
Bladder
© Byjus.com

Pharmacological stimulant for insulin secretion

- **Tolbutamide**



- Used in treatment of diabetes mellitus type II

Insulin secretion is decreased by

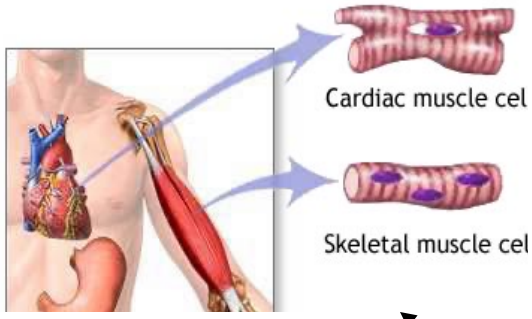
- **Decreased blood glucose** concentration
- **Epinephrine**: inhibits insulin release even in the presence of high blood glucose
- Increased blood insulin concentration
- **Sympathetic** stimulation

Insulin Action on Cells: Dominates in Fed State Metabolism.

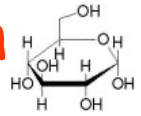
- Insulin transported through the blood to target tissues where it binds to specific receptors.
- The binding of insulin to target cells:
  - Acts as a biochemical signal to the inside of the cell
  - ↑ glucose uptake in most cells (not active muscle)
  - ↑ glucose use & storage
  - ↑ protein synthesis
  - ↑ fat synthesis
- Blood glucose is decreased because insulin causes glucose to leave the bloodstream and enter the metabolizing cells.
- Brain, RBCs, hepatocytes, intestinal mucosa, renal tubules and cornea have insulin independent glucose transporters
- Adipose tissues, cardiac and skeletal muscles contain glucose transporters 4 (GLUT4) which are insulin dependent..

Insulin Stimulates Cellular Glucose Uptake

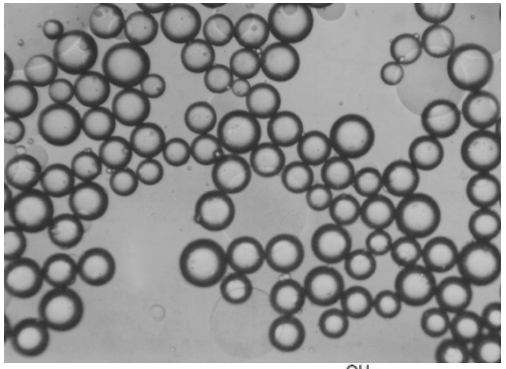
Cardiac Muscles



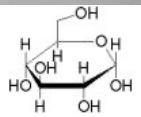
Insulin



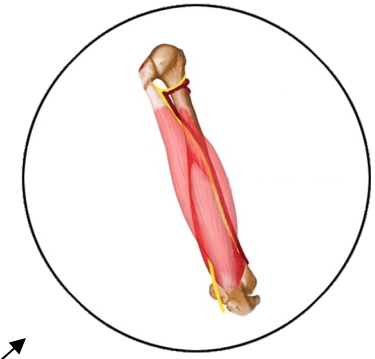
Adipocytes

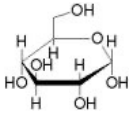


Insulin

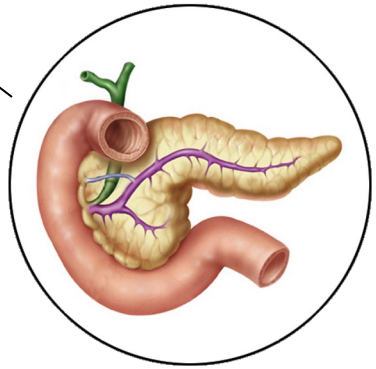


Skeletal Muscle

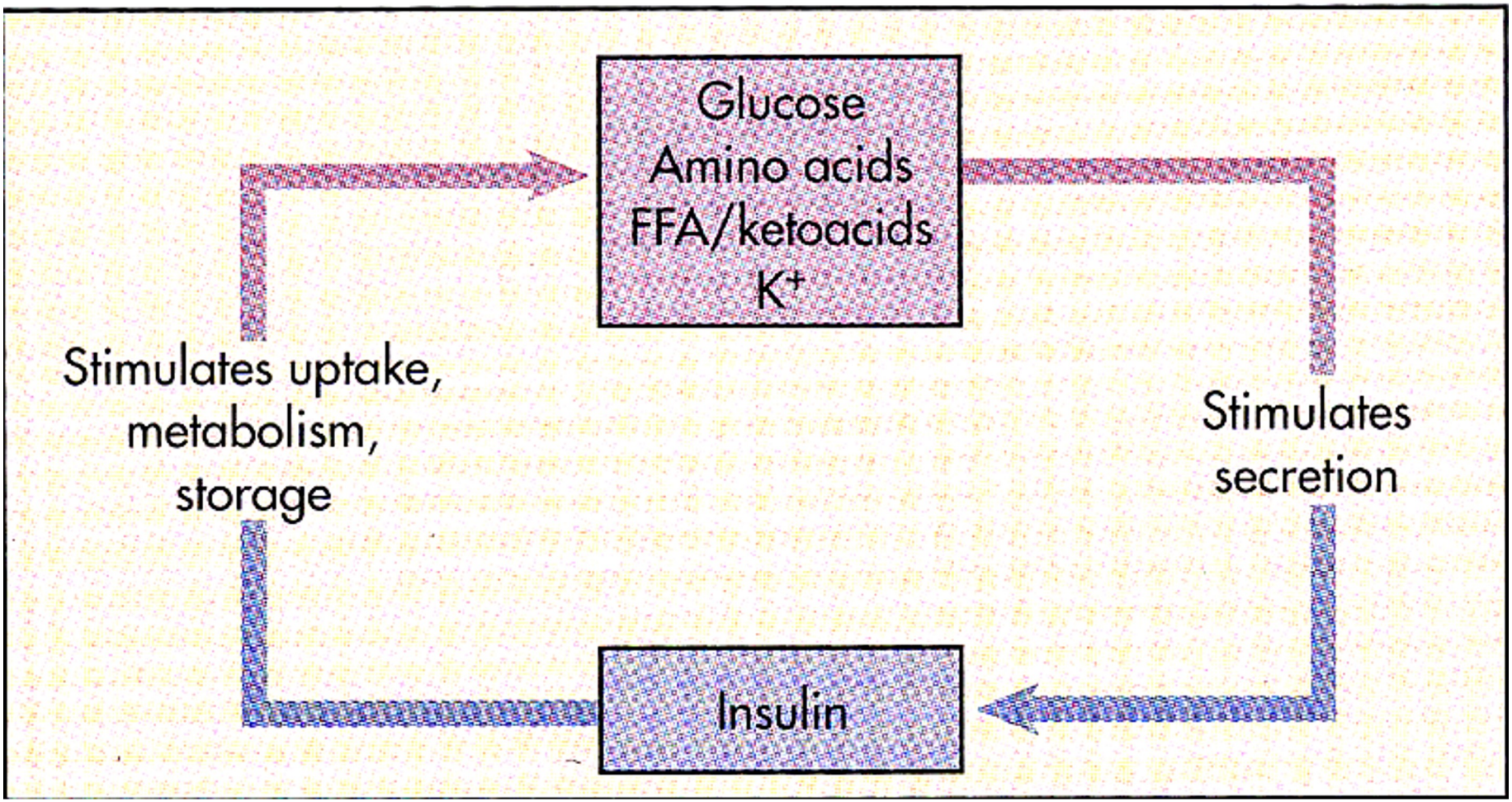




Insulin



Pancreas


Glucose
Amino acids
FFA/ketoacids
K+
Stimulates uptake, metabolism, storage
Stimulates secretion
Insulin

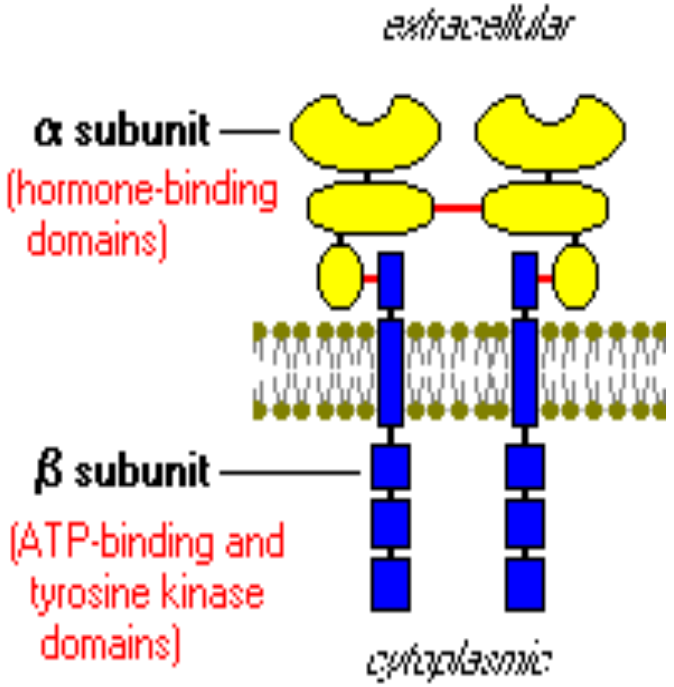
Insulin receptors

❖Insulin receptors are glycoprotein on target cells.

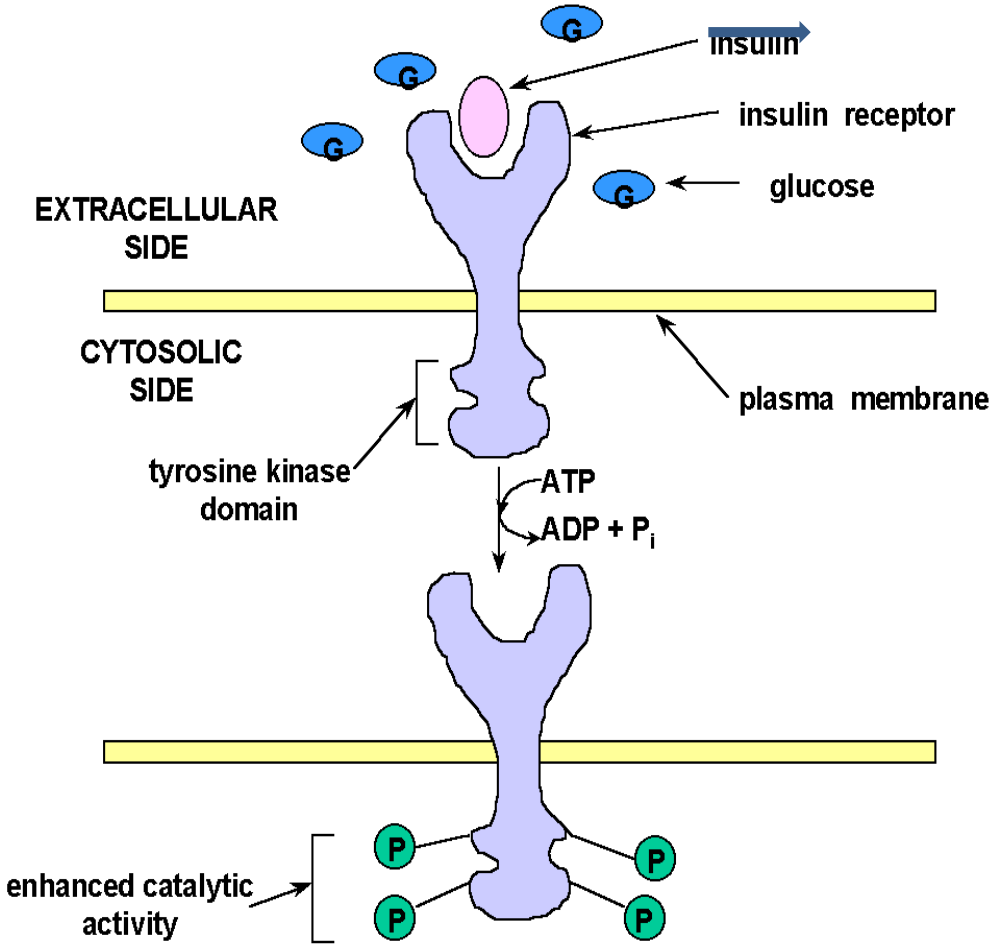
❖ composed of 2 identical α-subunits (extracellualr) and 2 identical β subunits (transmembrane) linked by disulfide bonds (α2β2)

❖ α chains contains insulin binding domains

❖ β chains have tyrosine kinase (TK) and autophosphorylation sites in the cytoplasmic portion

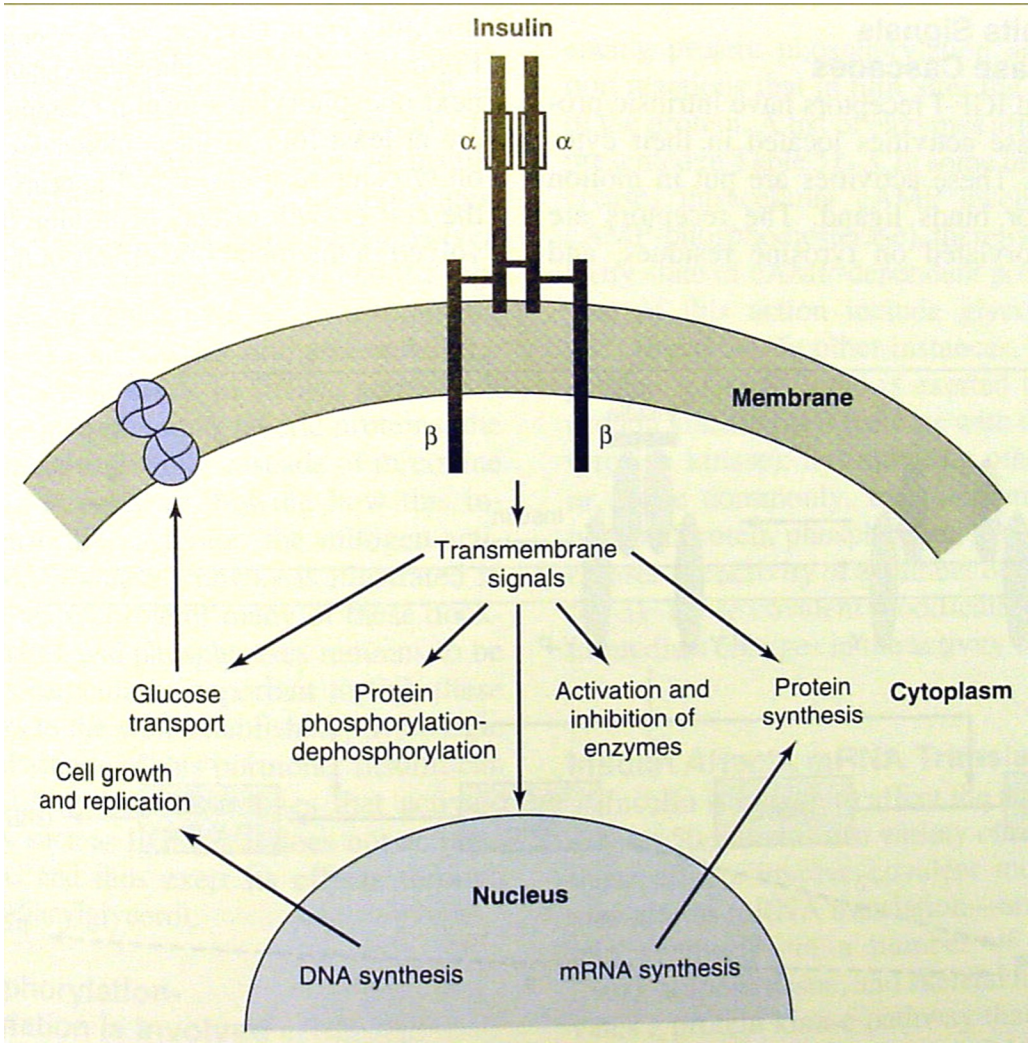


Binding of insulin to its receptors ⇒ activates TK that transfer phosphate group from ATP ⟶ phosphorylate β chain tyrosine residues (autophosphorylation) phosphorylation of number of intracellular proteins [insulin receptor substrates (IRS)] ⟶ insulin effects

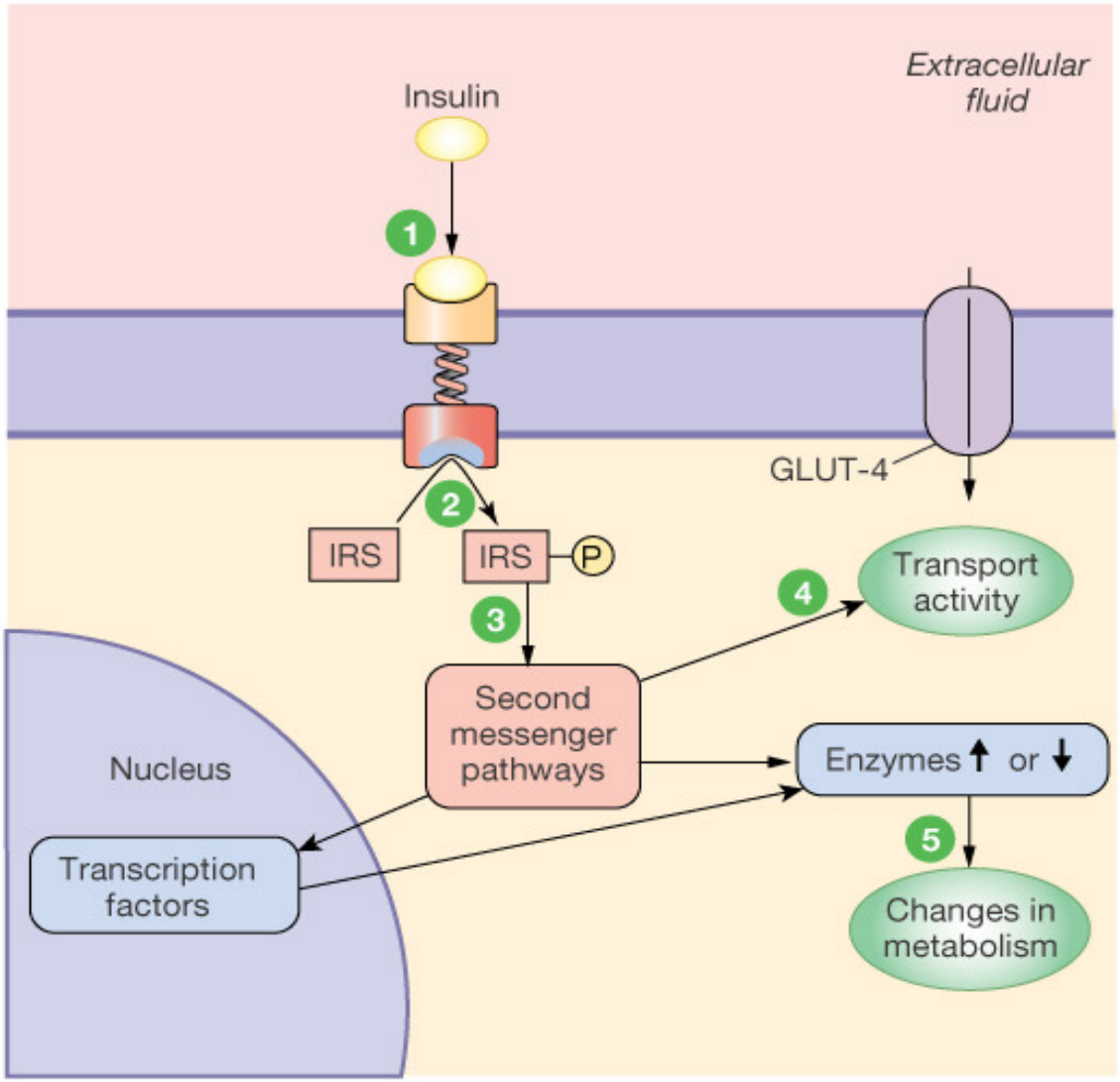


Effects of insulin are mediated by insulin receptor, a transmembrane tyrosine kinase

- Relationship of the insulin receptor to insulin action.
- Insulin binds to its membrane receptor, and this interaction generates one or more transmembrane signals.
- This signal (or signals) modulates a wide variety of intracellular events



Insulin Action on Cells: Dominates in Fed State Metabolism

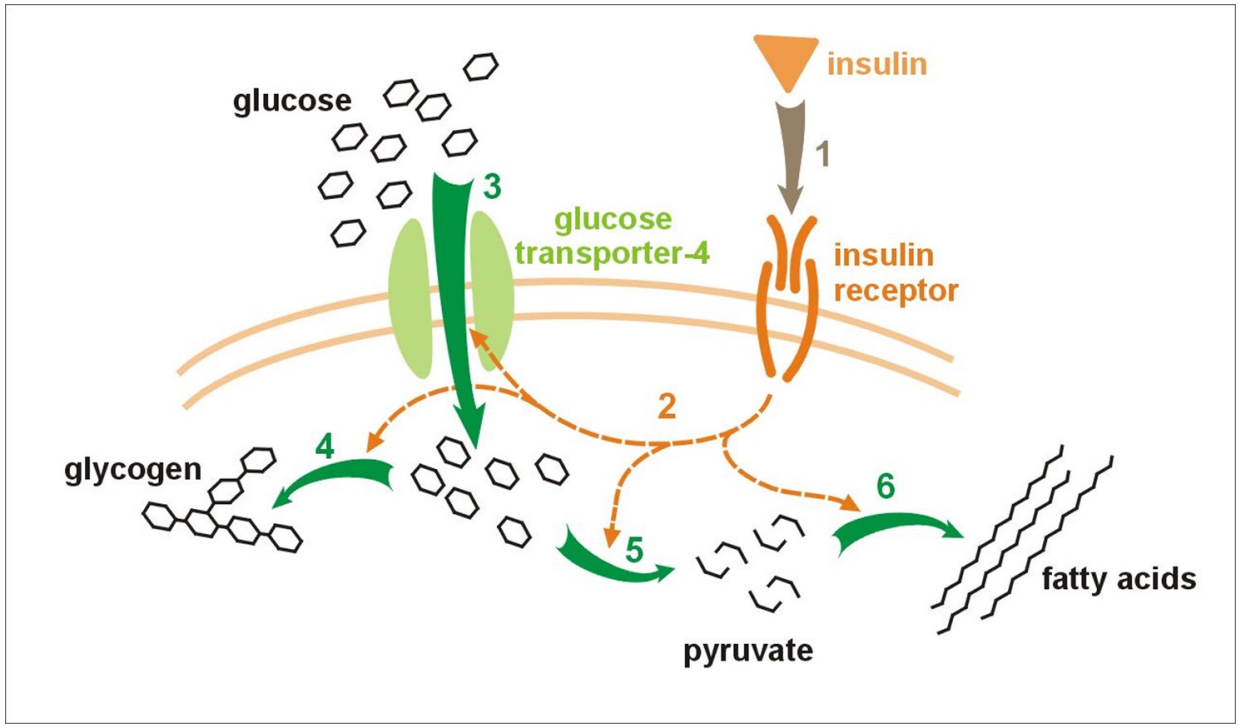


1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
3. Second messenger pathways alter protein synthesis and existing proteins.
4. Membrane transport is modified.
5. Cell metabolism is changed.

Action of Insulin on Adipose Tissue

- **Stimulates glucose uptake** by increasing GLUT- 4 availability
- **Stimulates glycolysis** (increase glucose utilization)
- **Stimulates lipogenesis**
- **Inhibits lipolysis and ketogenesis**

insulin facilitate sugar transporter that mediate glucose transport into adipose cells and skeletal muscles.



Glucose transporters & insulin

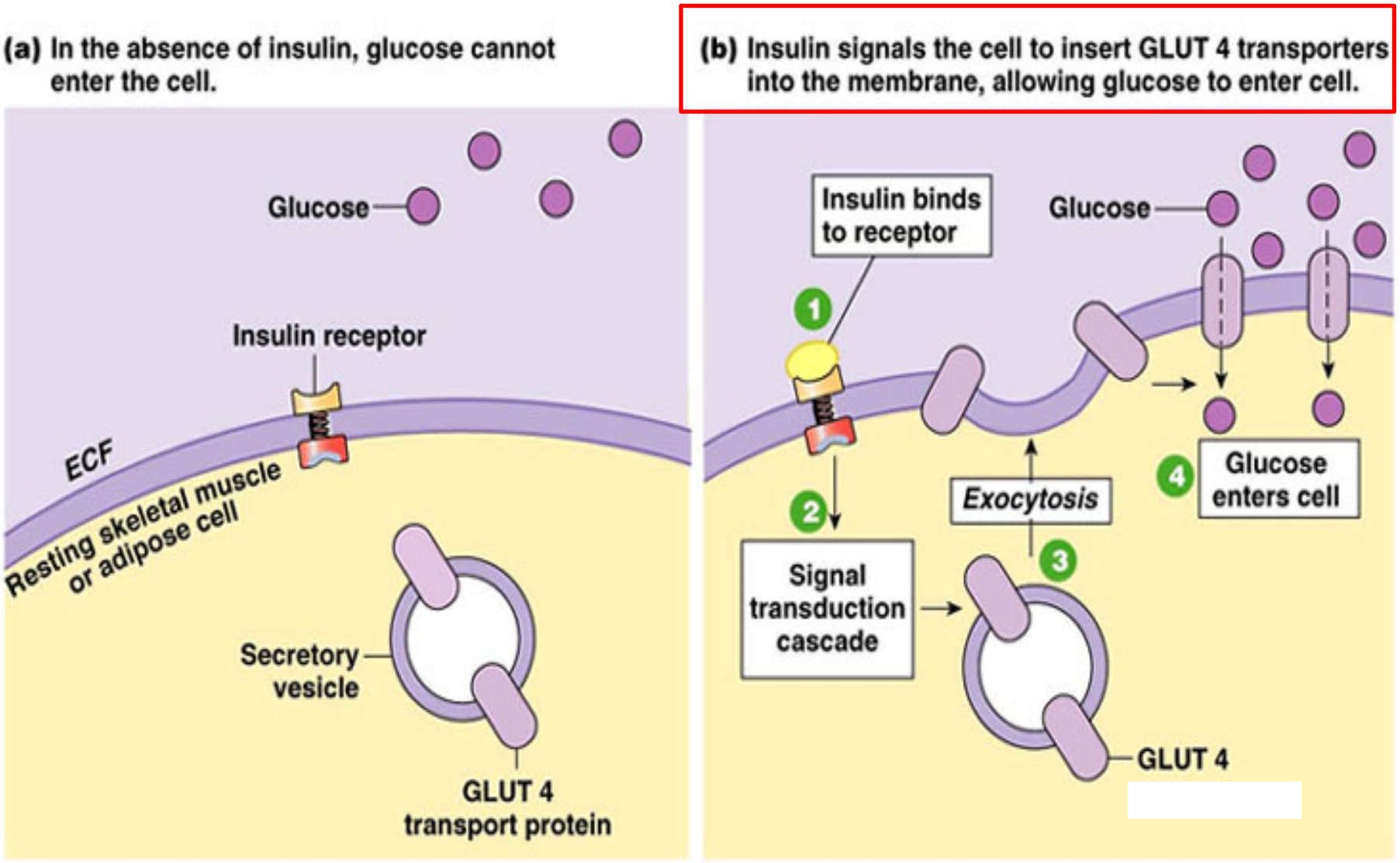


Fig. 22-12

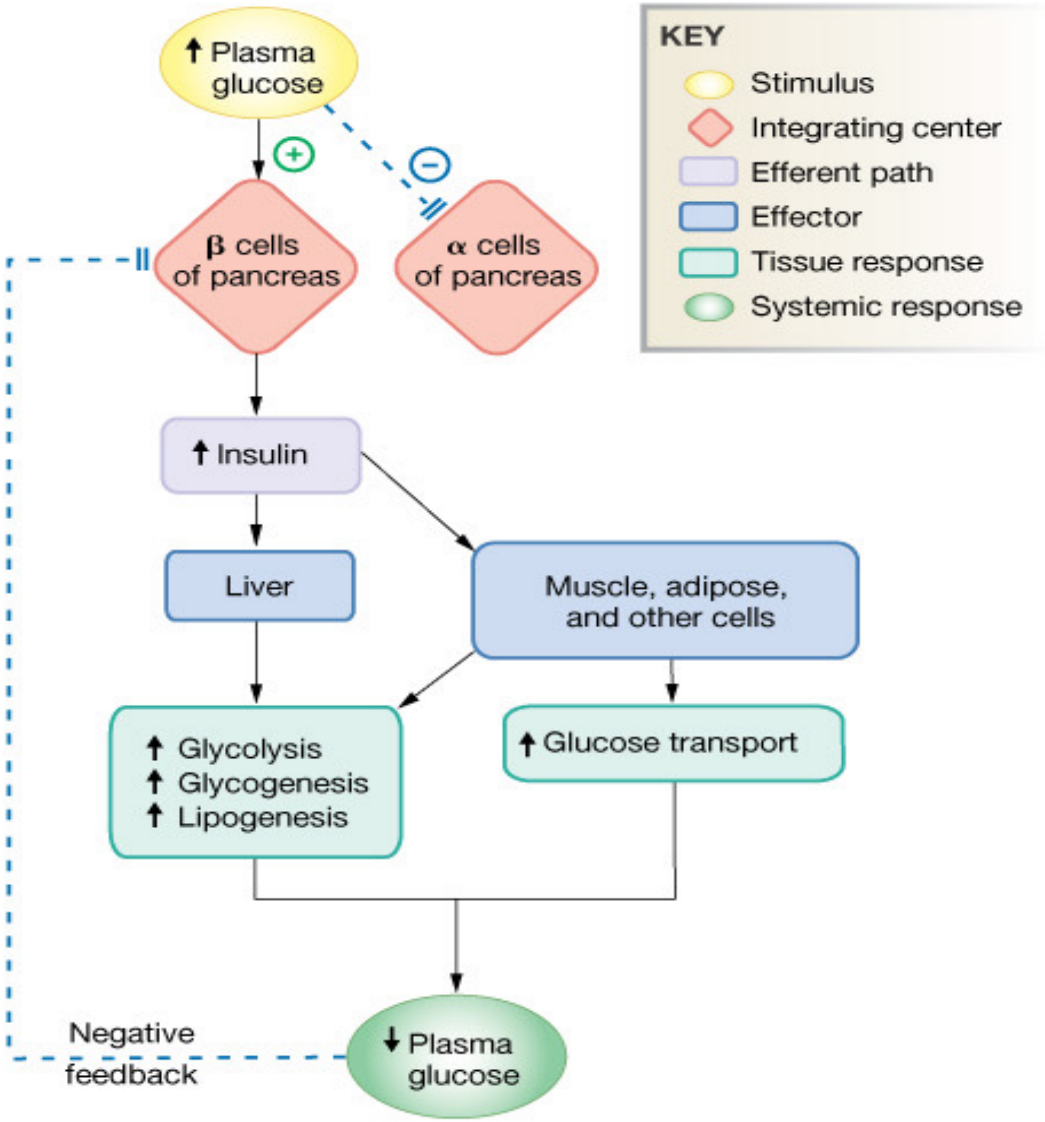
Actions of Insulin on the Liver

- Stimulates glucose uptake (indirect)
- Stimulates glycogenesis
- Stimulates glycolysis (increase glucose utilization)
- Stimulates HMP shunt activity
- Inhibits glycogenolysis
- Inhibits gluconeogenesis
- Stimulates lipogenesis
- Inhibits lipolysis
- Stimulates cholesterol synthesis
- Increases VLDL lipoprotein synthesis
- Decreases ketogenesis
- Increases potassium and phosphate uptake

Actions of Insulin on Muscle

- Stimulates glucose uptake by increasing GLUT-4 availability
- Stimulates glycogenesis
- Stimulates glycolysis (increase glucose utilization)
- Inhibits glycogenolysis
- Inhibits FFA uptake and oxidation
- Increases amino acids uptake (particularly branched chain amino acids)
- Stimulates protein synthesis
- Inhibits proteolysis
- Stimulates uptake of potassium, phosphate and magnesium
- Increases blood flow

Insulin: Summary and Control Reflex Loop

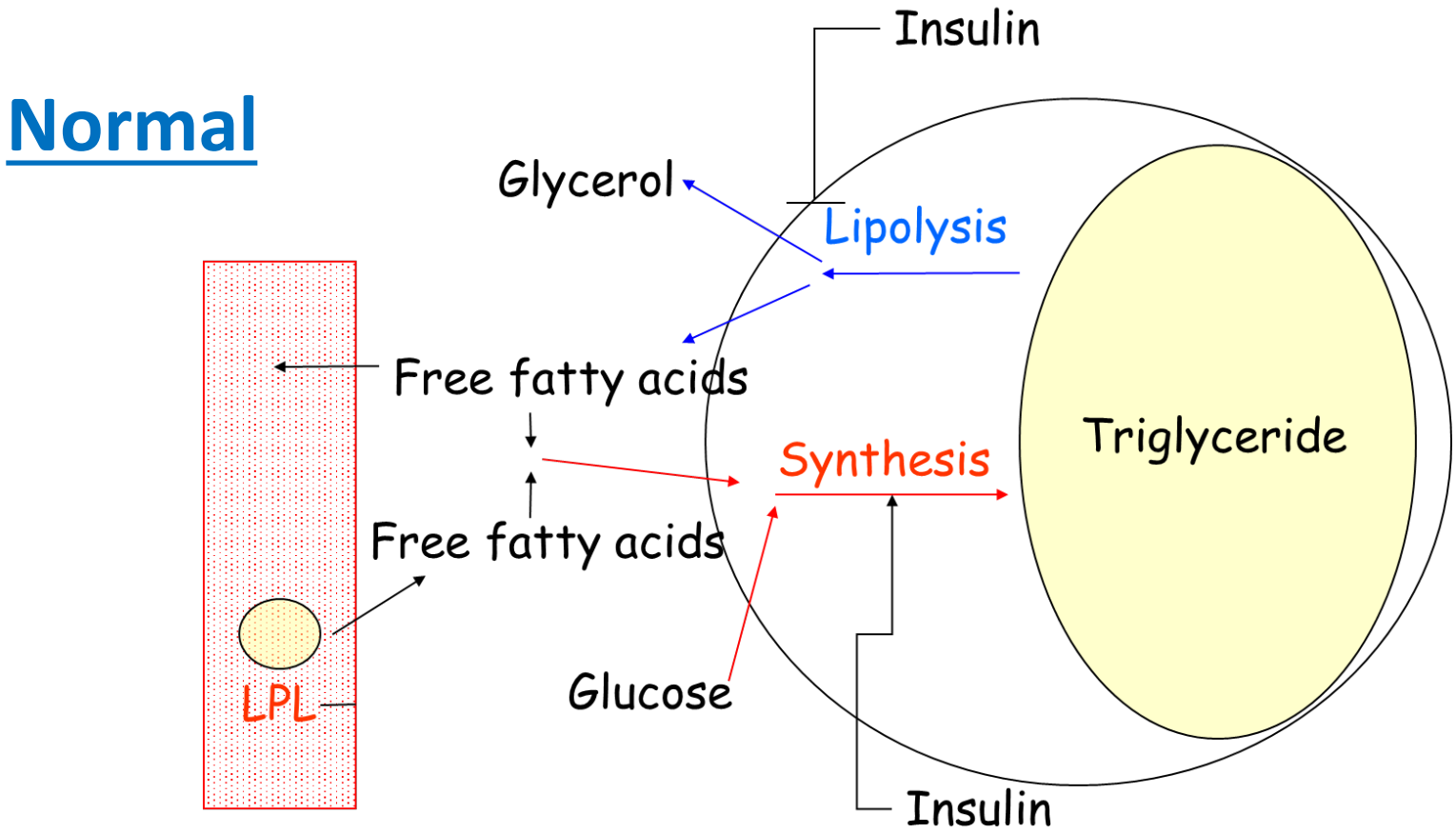


Diabetes Mellitus

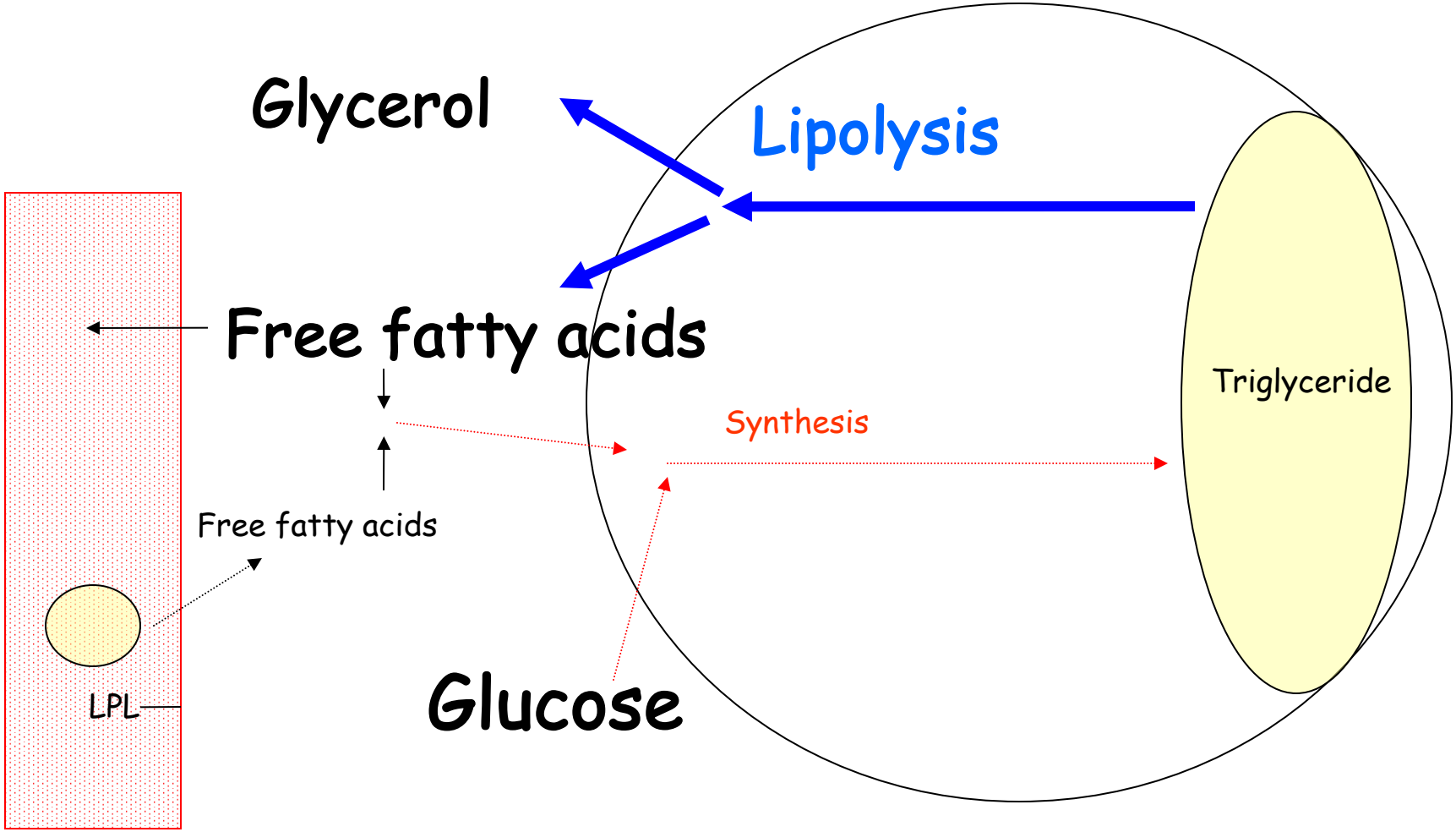
- This is a disease caused by elevated glucose levels (Normal blood glucose 60-110 mg/dl)
- **2 Types of diabetes**:

  Type I diabetes (10% of cases)

  Type II diabetes (90% of cases)



Type 1 Diabetes Mellitus



Type I Diabetes (10% of cases)

- Develops suddenly, usually before age 15
- Caused by **inadequate production of insulin** because T cell-mediated autoimmune response destroys beta cells
- Controlled by **insulin injections**

Type II diabetes (90% of cases)

- Usually occurs after age 40 and in obese individuals
- **Insulin levels are normal or elevated** but there is either a **decrease in number of insulin receptors or the cells cannot take it up.**
- Controlled by **dietary changes and regular exercise or oral hypoglycemic drugs**

Diabetes is a defect of insulin production or action

- Diabetes mellitus - group of metabolic diseases characterized by hyperglycemia due to defective insulin activity

HLA: human leucocytic antigen

Comparison of type 1 and type 2 diabetes mellitus

	Type 1	Type 2
Onset	usually below 20 years of age	usually over 40 years of age
Insulin synthesis	absent: immune destruction of β-cells	preserved: combination of impaired β-cell function and insulin resistance
Plasma insulin concentration	low or absent	low, normal, or high
Genetic susceptibility	yes, inheritance associated with HLA antigens	not associated with HLA, important polygenic inheritance
Islet cell antibodies at diagnosis	yes	no
Obesity	uncommon	common
Ketoacidosis	yes	possible after major stress

Symptoms of Diabetes

- Excessive **thirst**; frequent urination (**polyuria**); large intake of water (**polydipsia**). These changes are due to excretion of large amounts of glucose in the urine (**glucosuria**) that cause **osmotic diuresis**.

- Excessive but incomplete oxidation of fatty acids in the liver, resulting in **overproduction of the ketone bodies acetoacetate and β-hydroxybutyrate**. Acetoacetate can convert to **acetone**, found in the blood of diabetics.

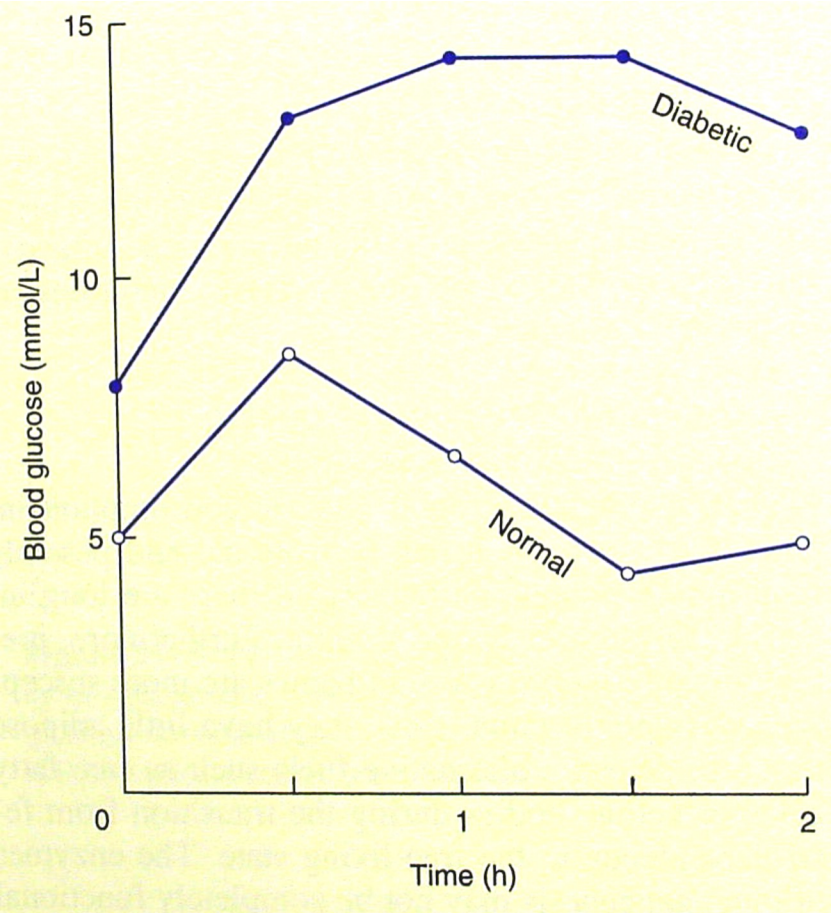
- The overproduction of ketone bodies is called **ketosis**, and their production is accompanied by **decreased blood pH, (acidosis)** or **ketoacidosis**, potentially life-threatening.

Diagnosis of diabetes

- A sensitive diagnostic criterion is provided by the glucose-tolerance test (GTT).
- Glucose tolerance test;

Blood glucose curves of a normal and a diabetic individual after oral administration of 50 g of glucose.

Note the initial raised concentration in the diabetic. A criterion of normality is the return of the curve to the initial value within 2 hours.



Treatment of diabetes

- **Type 1** - **insulin injections** daily

- **Type 2** - do not usually require insulin treatment because insulin synthesis partially preserved. Treatment relies on **diet and oral hypoglycemic agents.**

Glucagon Action on Cells:
Dominates in Fasting State Metabolism

- **Glucagon prevents hypoglycemia** by ↑ cell production of glucose
- **Liver is primary target** to maintain blood glucose levels

GLUCAGON

Alpha cells

Hypoglycemia =

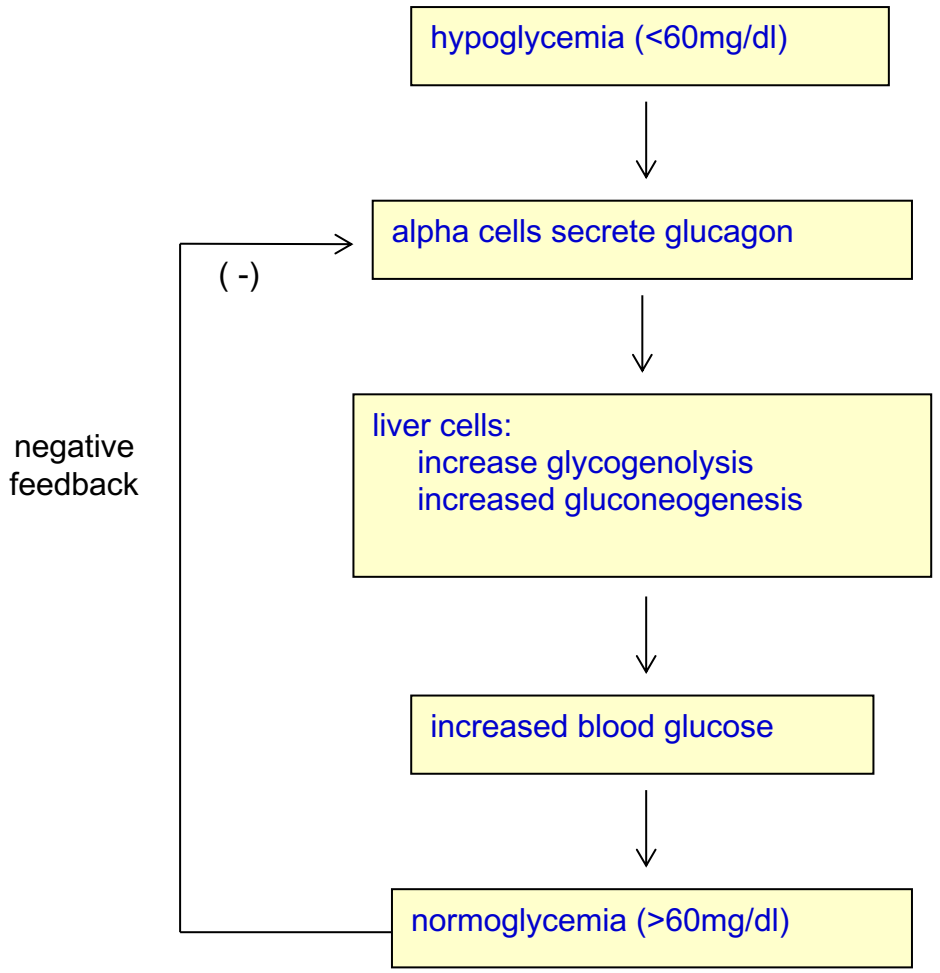
glucagon secretion

Actions

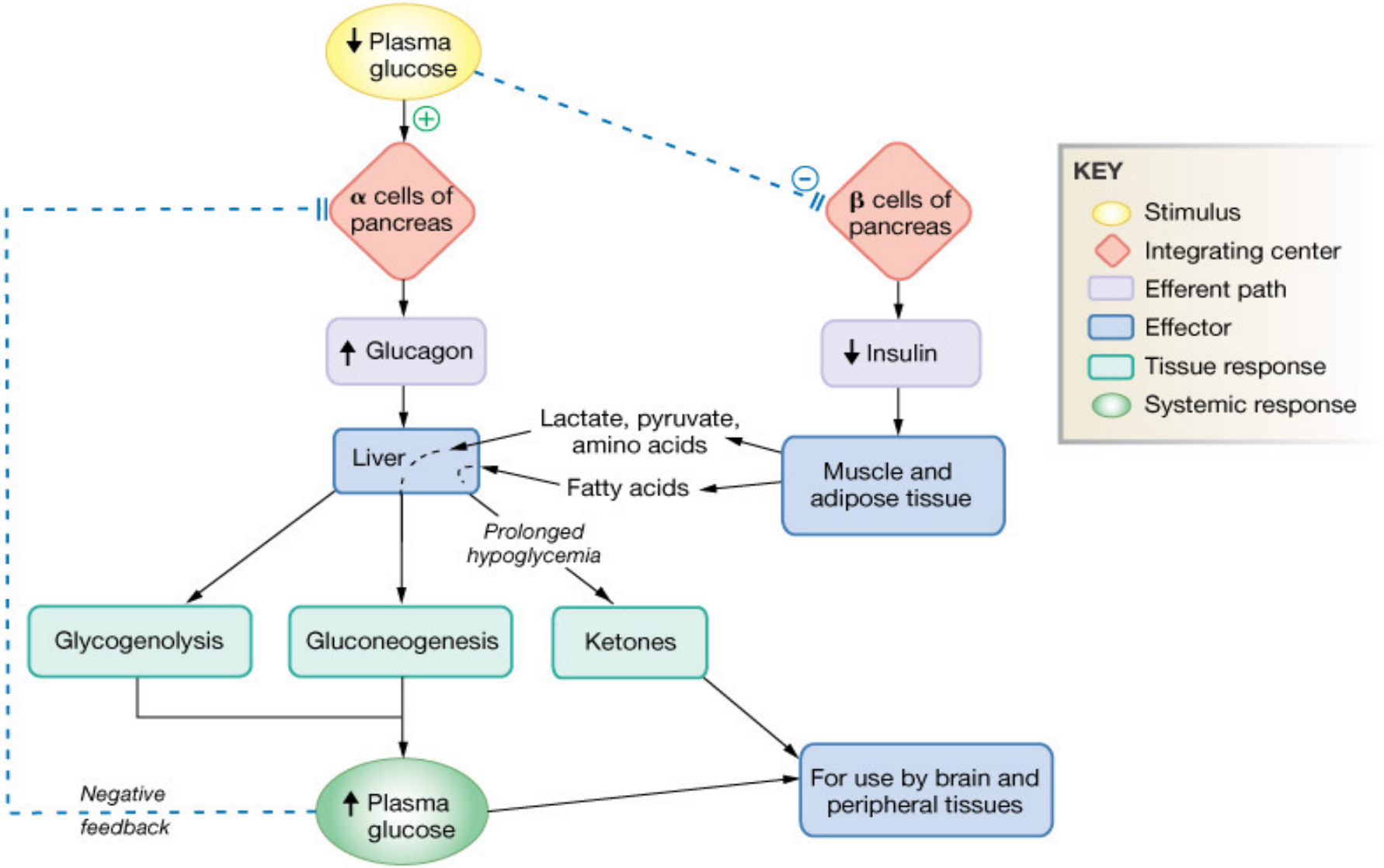
increased glycogenolysis

increased gluconeogenesis

Result = normoglycemia



Glucagon Action on Cells: Dominates in Fasting State Metabolism



Effects on Glucagon Secretion

Stimuli for Glucagon Secretion

↓ Blood glucose

↑ Serum amino acids (arginine, alanine)

Sympathetic nervous system stimulation

Stress

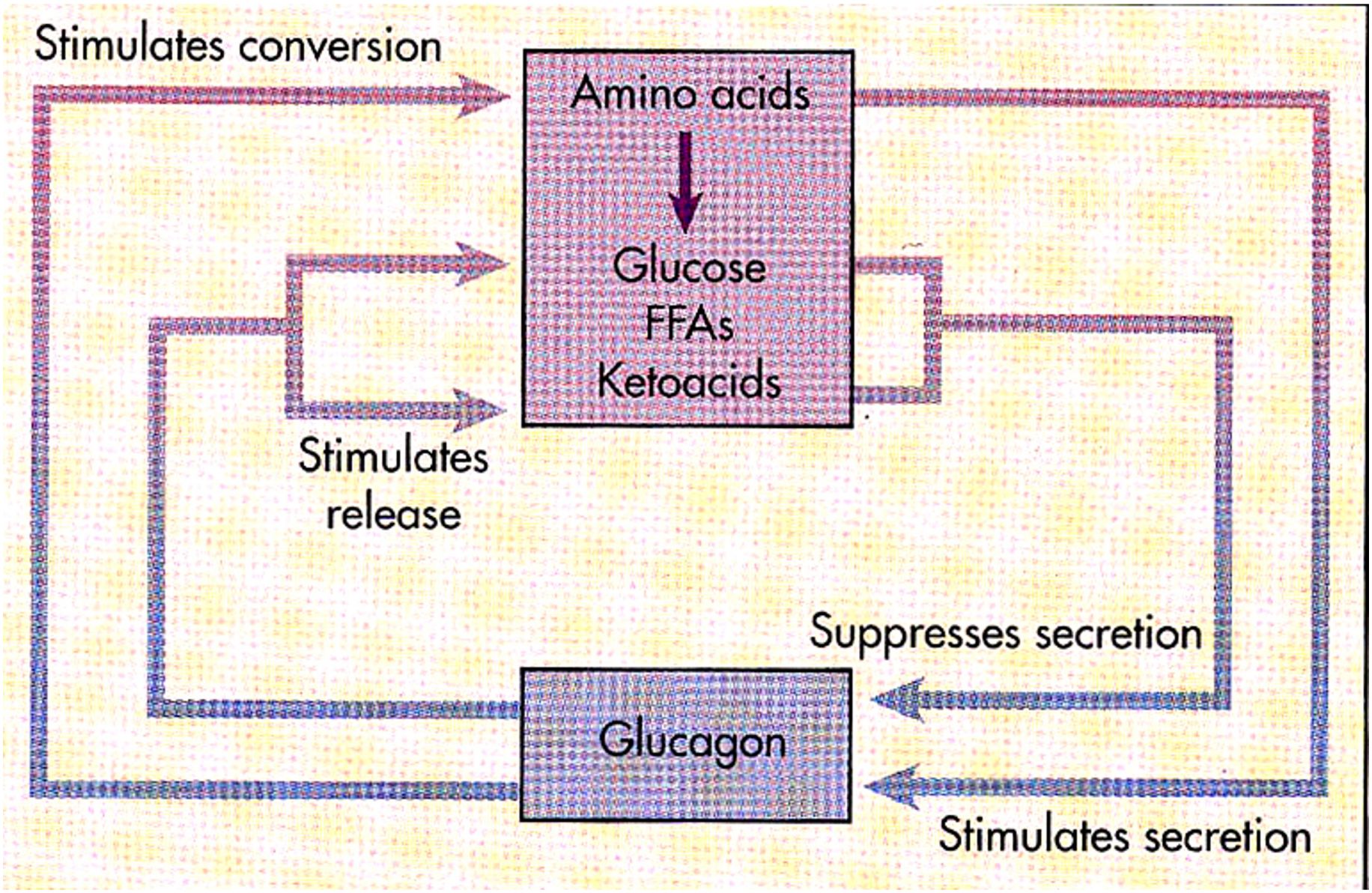
Exercise

Inhibitors of Glucagon Secretion

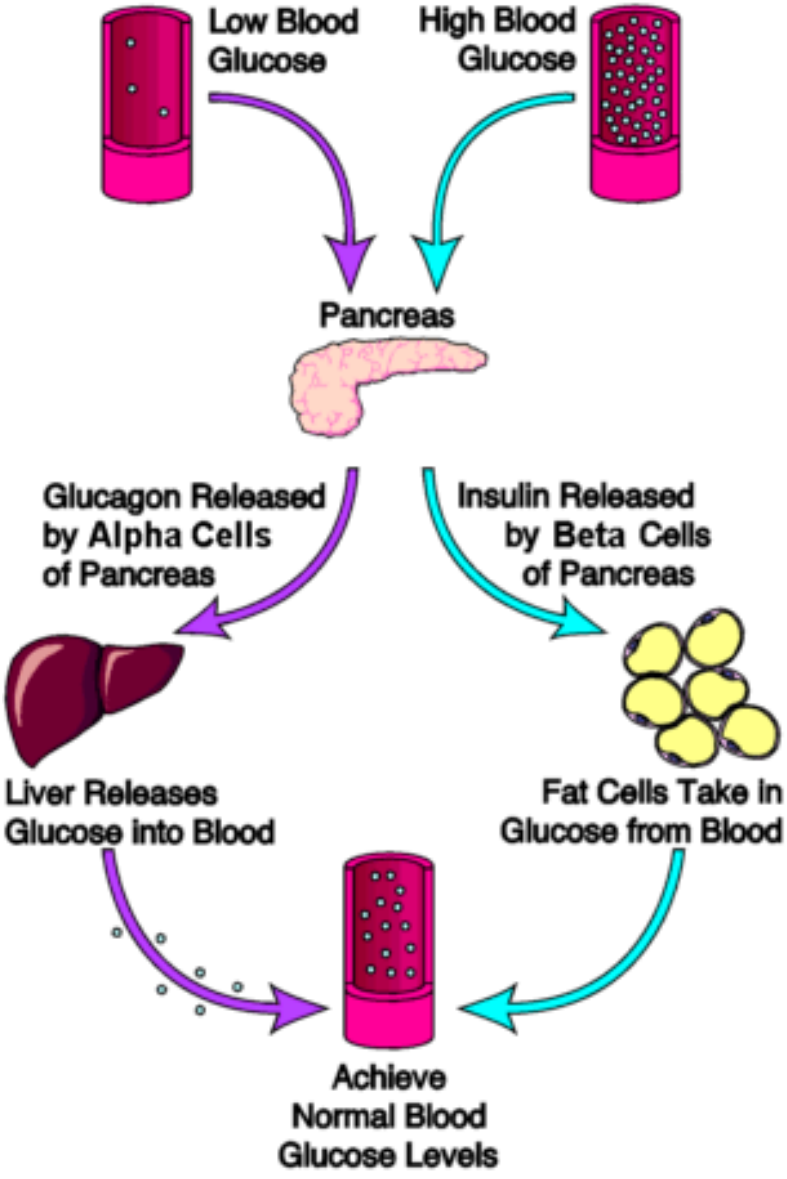
Somatostatin

Insulin

↑ Blood glucose


Stimulates conversion
Amino acids
Glucose
FFAs
Ketoacids
Stimulates release
Suppresses secretion
Glucagon
Stimulates secretion

Glucagon and Insulin



Actions of Glucagon on the Liver

- Stimulates glycogenolysis (breakdown of liver glycogen)
- Stimulates gluconeogenesis
- Inhibits glycolysis (glucose breakdown in liver)
- Stimulates lipolysis and ketogenesis

Together, these lead to accumulation of liver glucose, allowing its export to blood

Actions of Glucagon on adipose tissue

- Glucagon stimulates fatty acid mobilization in adipose tissue, liberating an alternate fuel for tissues (other than brain)