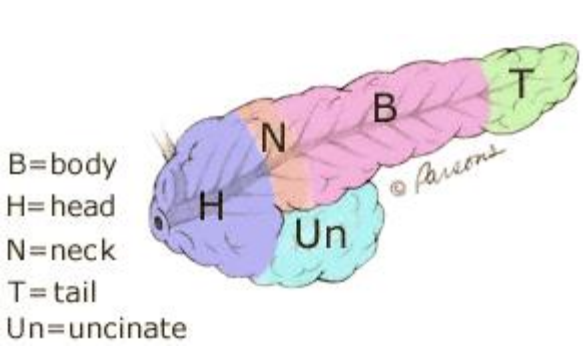
Pancreas



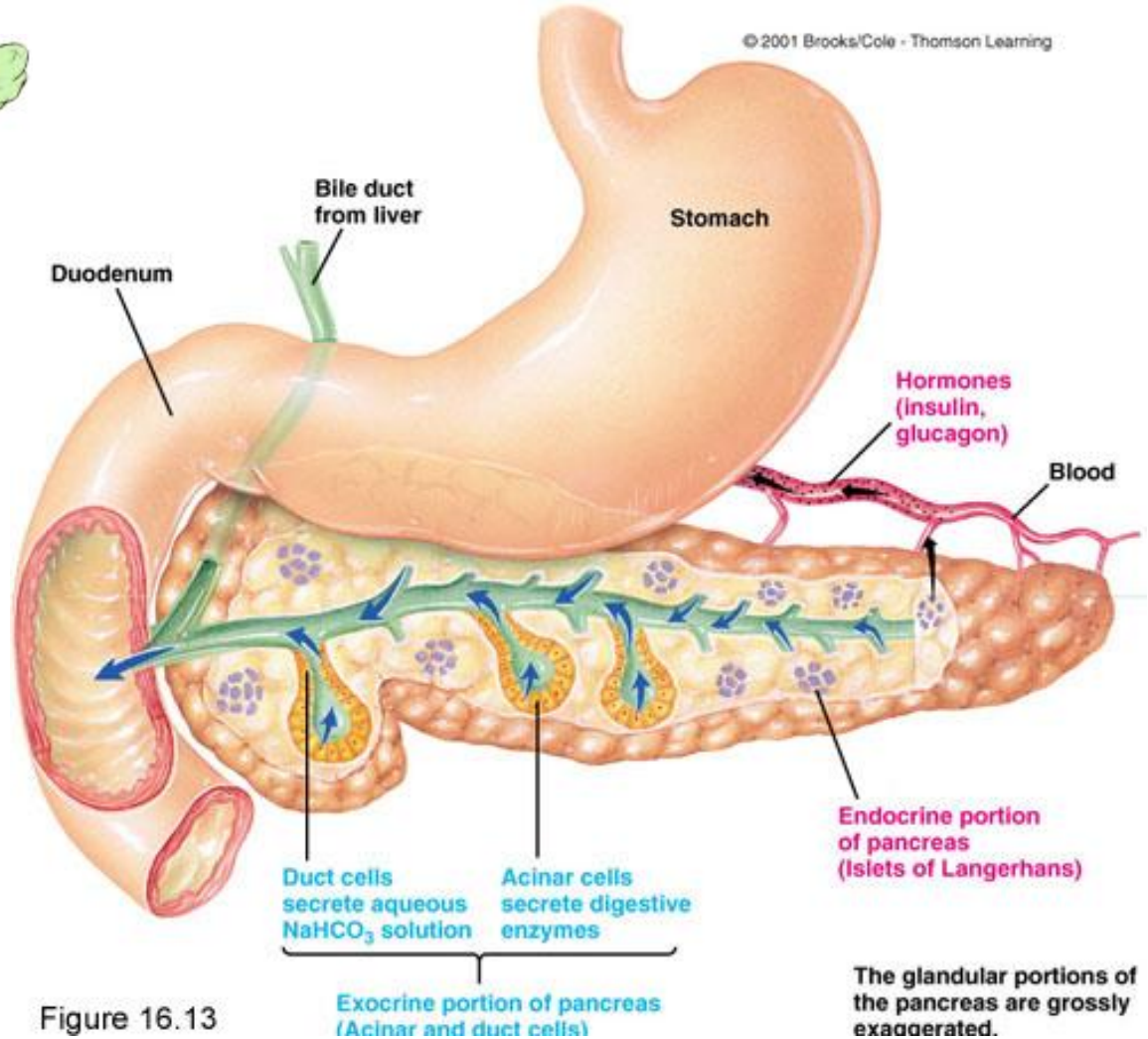
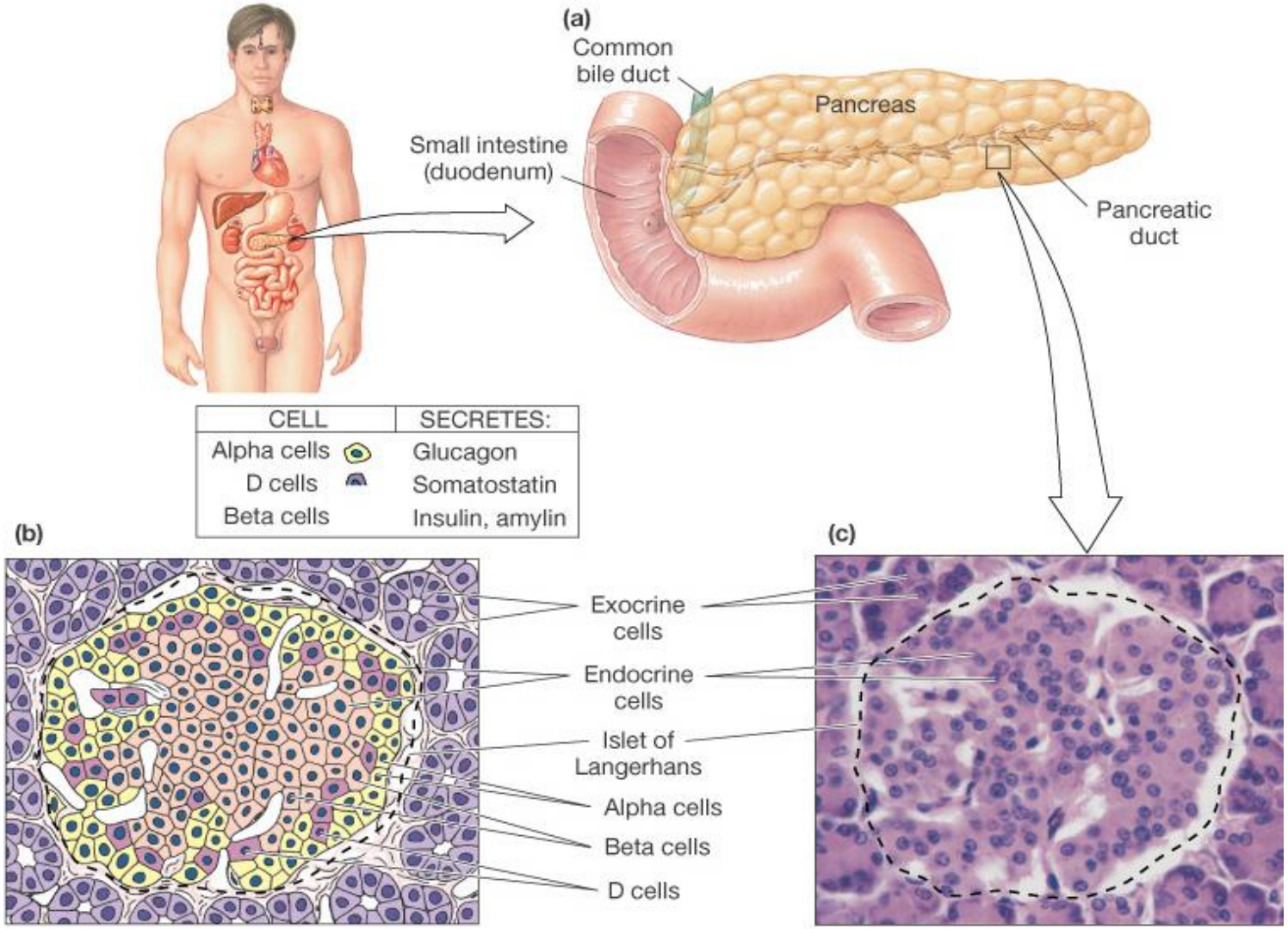
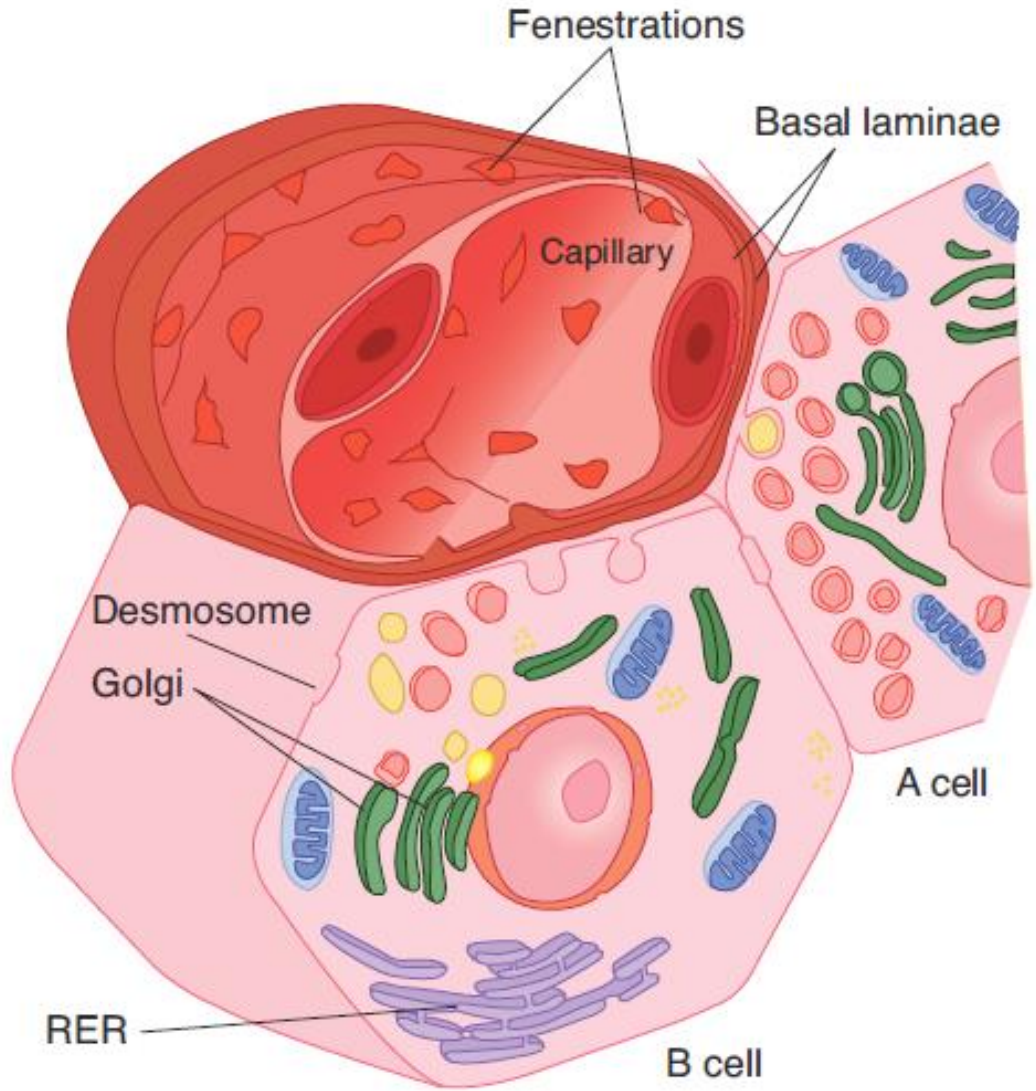


Figure 16.13

Pancreatic Hormones, Insulin and Glucagon, Regulate Metabolism



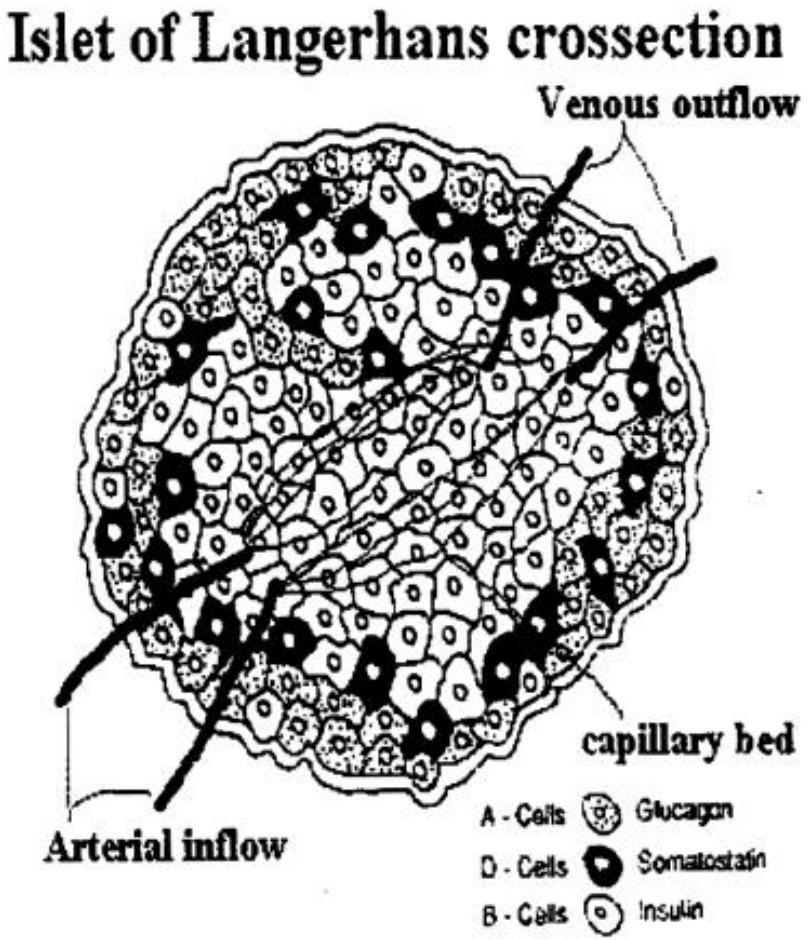

Fenestrations
Basal laminae
Capillary
Desmosome
Golgi
A cell
RER
B cell

Production of Pancreatic Hormones by Three Cell Types

- Alpha cells: 25% of cells, produce glucagon.
- Beta cells : 60% of cells, produce insulin & amylin.
- Delta cells: 10% of cells, produce somatostatin.
- PP cells: produce pancreatic peptide.

Islet of Langerhans Cross-section

- Three cell types are present, A (glucagon secretion), B (Insulin secretion) and D (Somatostatin secretion)
- A and D cells are located around the perimeter while B cells are located in the interior
- Venous return containing insulin flows by the A cells on its way out of the islets



- Close contact between these cells make them to appropriately control each other.
- “Insulin” suppresses “glucagon”secretion.
- “Amylin” suppresses “insulin” secretion.
- “Somatostatin” suppresses both “insulin” & “amylin”.

Insulin

- Discovered by Charles Best &Feredrick Banting in 1922.

Structure

- MW 5808
- A, B & C chains
- Preproinsulin (MW 11500)
- Proinsulin (MW 9000)
- HL 6 min.
- Free in circulation
- Insulinase

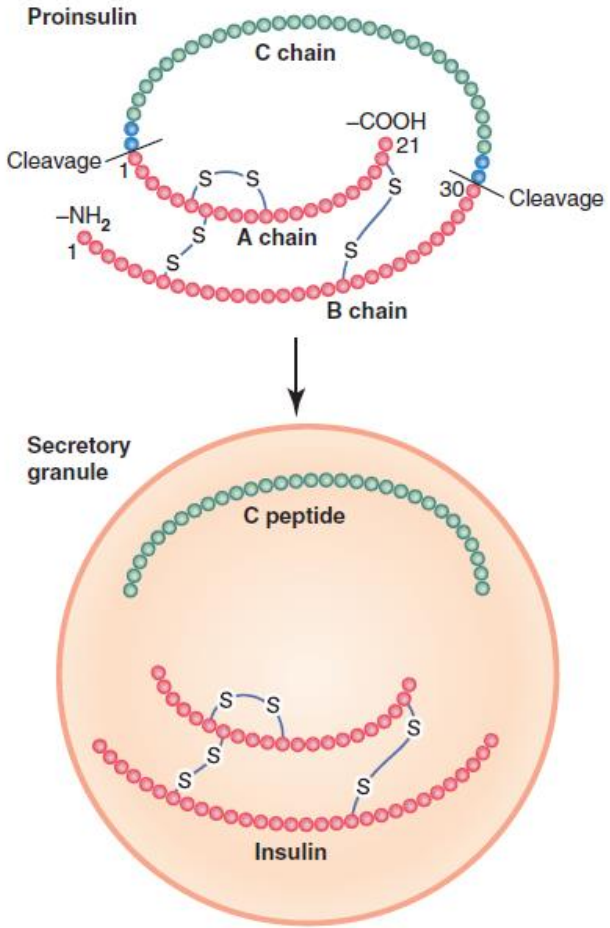
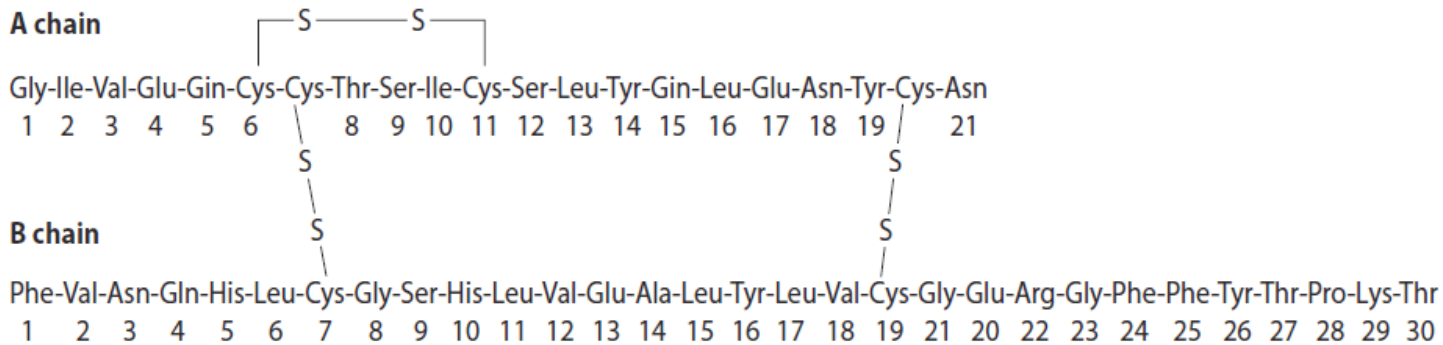


TABLE 21–1 **Structure of human insulin (molecular weight 5808) and (below) variations in this structure in other mammalian species.**[a]



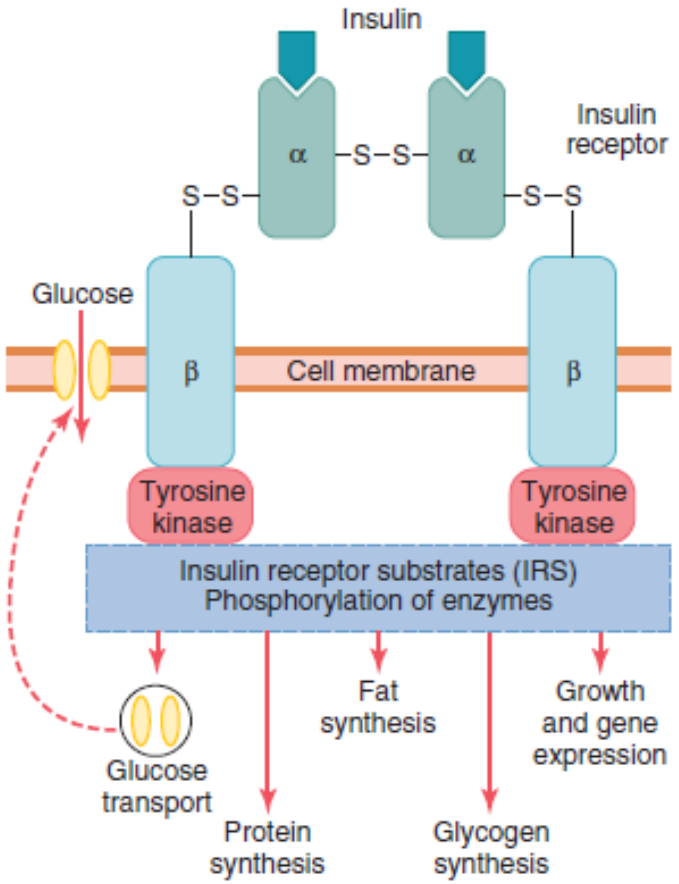
	Variations from Human Amino Acid Sequence	
Species	**A Chain Position 8 9 10**	**B Chain Position 30**
Pig, dog, sperm whale	Thr-Ser-Ile	Ala
Rabbit	Thr-Ser-Ile	Ser
Cattle, goat	Ala-Ser-Val	Ala
Sheep	Ala-Gly-Val	Ala
Horse	Thr-Gly-Ile	Ala
Sei whale	Ala-Ser-Thr	Ala

[a] In the rat, the islet cells secrete two slightly different insulins, and in certain fish four different chains are found.

- Proinsulin & C-peptide have no insulin effect.
- 5-10% of end secretory products is in the form of proinsulin.
- Functions of C-peptide: 1) activation of Na/K ATPase and 2) endothelial nitric oxide synthase.

Insulin receptor

1. MW: 300’000 Δ
2. 4 subunits, 2 α & 2 β
3. Tyrosine kinase activation
4. IRSs activation in different tissues.



Changes of enzyme activity

Changes occur in 3 categories:

1. Some changes occur within 10-15 min.
2. Some changes occur within several hours to days (mRNA transcription).
3. Some changes occur within days or weeks (DNA transcription).

Insulin

- Anabolic hormone
- Maintaining the upper limit of blood glucose & FFAs.
- ↑ Glucose uptake & utilization by muscle & adipose tissue.
- ↑ Glycogen storage in liver & muscle.
- ↓ Glucose output by the liver.
- …promotes protein synthesis from AAs & inhibits protein degradation in periphery.
- …promotes TG synthesis in the liver and adipose tissue & represses lipolysis of adipose TG stores.

- Basal insulin secretion: about 1 U/h
- Fivefold to tenfold increase following ingestion of food.

Pancreatic Hormones, Insulin and Glucagon, Regulate Metabolism

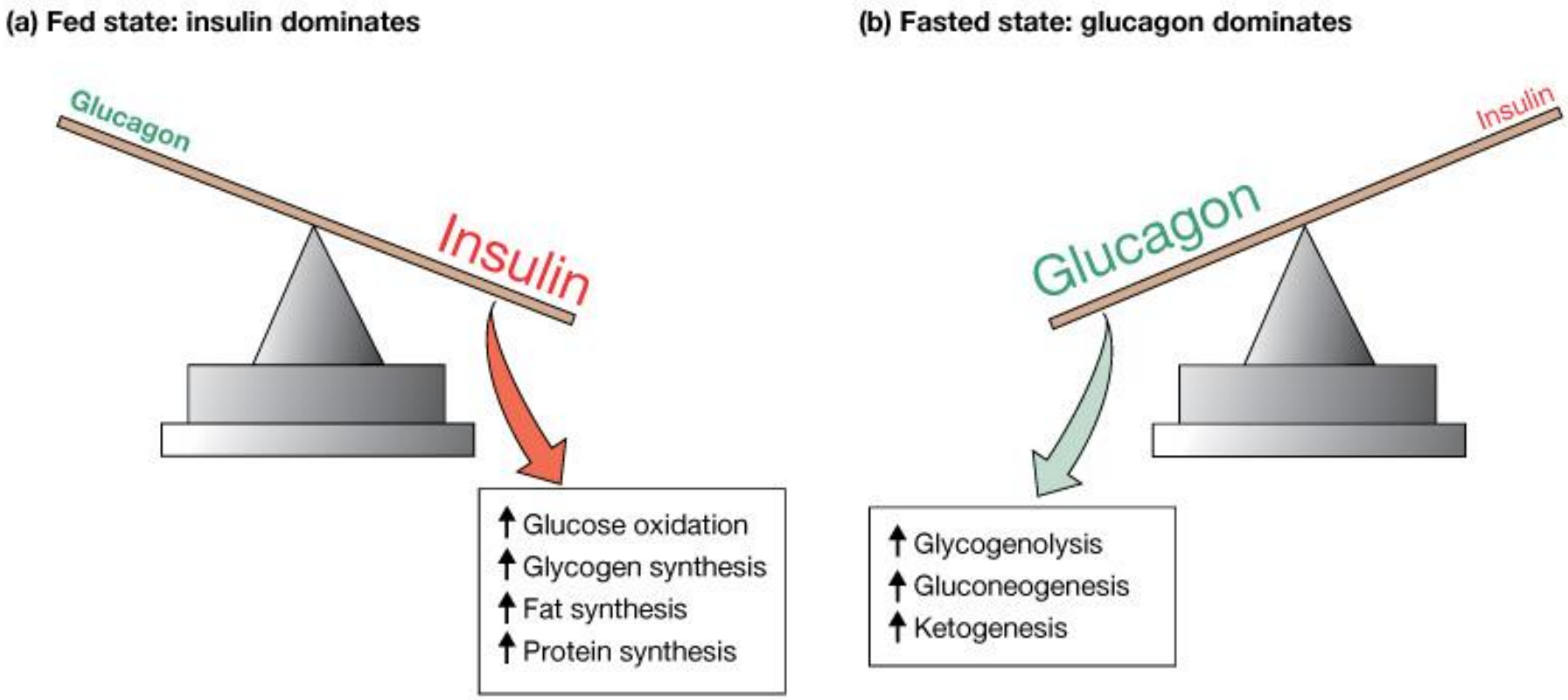


Figure 22-8: Metabolism is controlled by insulin and glucagon

Increased blood level of glucose

1. Activation of “glucokinase”
2. Activation of “glycogen synthase”
3. Inactivation of “glycogen phosphorylase”

Decrease blood level of glucose

All mentioned pathways in reverse:

1. Activation of “glycogen phosphorylase”
2. Activation of “glucose phosphatase”

Insulin effect on CHO metabolism

1. Inactivation of hepatic “Phosphorylase”.
2. Activation of intracellular “Glucokinase”.
3. Activation of “Glycogen synthase”.

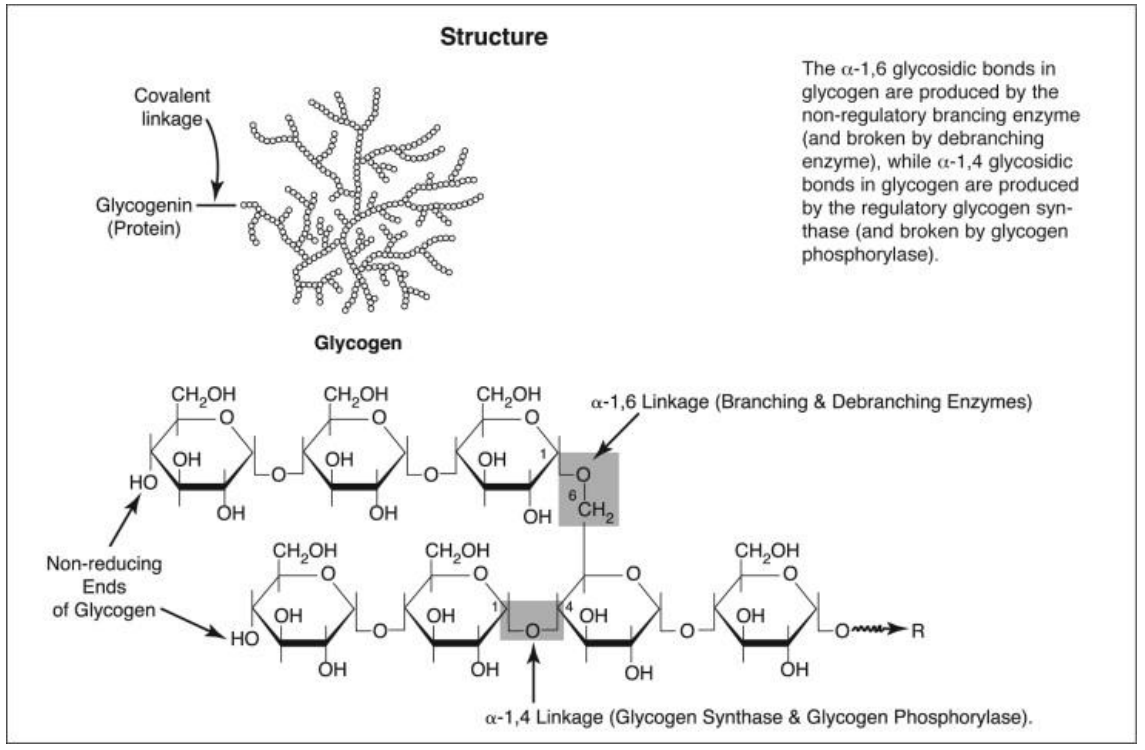


TABLE 21–6 Factors affecting insulin secretion.

Stimulators	Inhibitors
Glucose	Somatostatin
Mannose	2-Deoxyglucose
Amino acids (leucine, arginine, others)	Mannoheptulose
Intestinal hormones (GIP, GLP-1 [7–36], gastrin, secretin, CCK; others?)	α-Adrenergic stimulators (norepinephrine, epinephrine)
β-Keto acids	β-Adrenergic blockers (propranolol)
Acetylcholine	
Glucagon	Galanin
Cyclic AMP and various cAMP-generating substances	Diazoxide
	Thiazide diuretics
β-Adrenergic stimulators	K^+ depletion
Theophylline	Phenytoin
Sulfonylureas	Alloxan
	Microtubule inhibitors
	Insulin

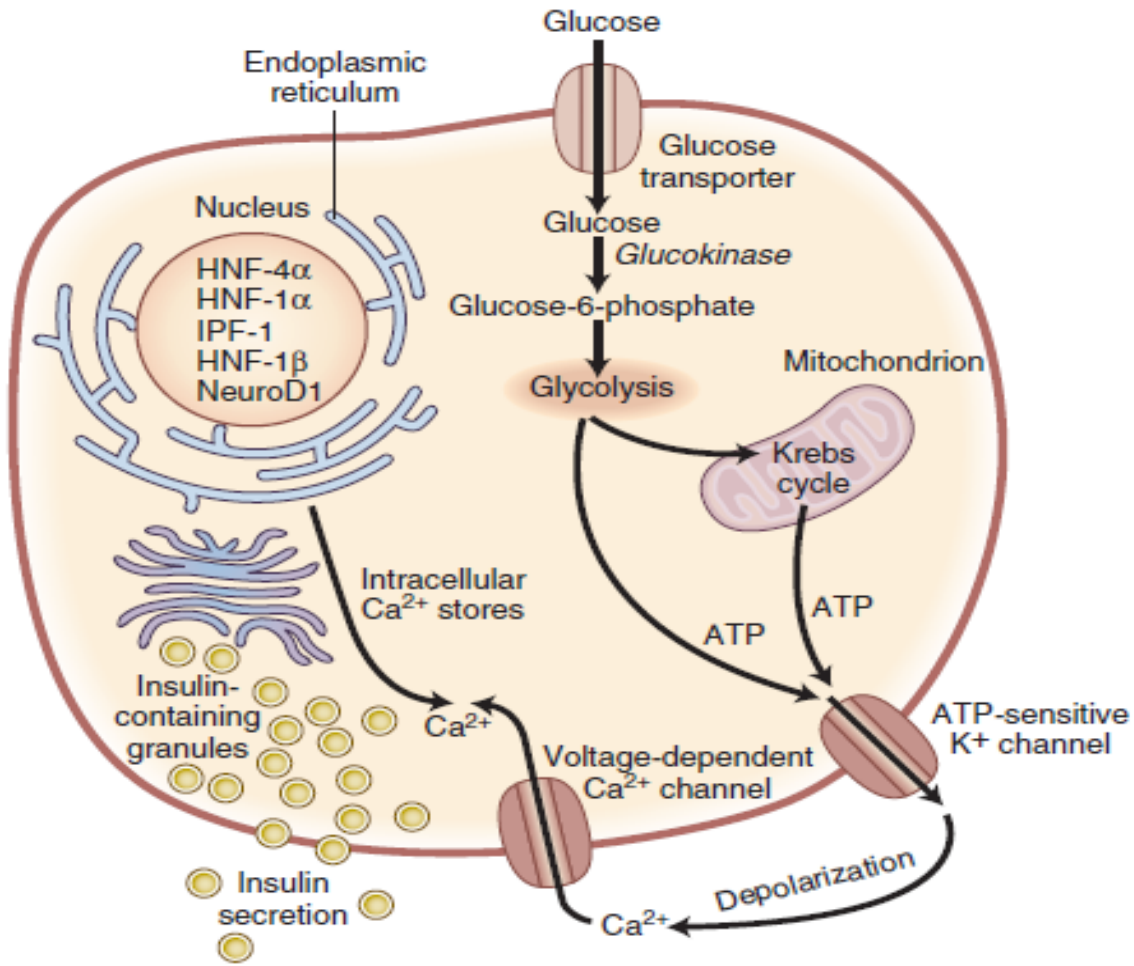


Figure 31-2 **Model of a pancreatic beta cell and the proteins implicated in maturity-onset diabetes of the young. ATP, adenosine triphosphate; HNF, hepatocyte nuclear factor; IPF, insulin promoter factor; NeuroD1, neurogenic differentiation 1.** (From Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med.* 2001;345:973.)

Other Factors That Stimulate Insulin Secretion

1) Amino acids

1. The most potent are “arginine” & “lysine”.
2. The effect differs from glucose stimulation:

a) Amino acids administered in the absence of a rise in blood glucose cause only a small increase in insulin secretion.

a) amino acids strongly potentiate the glucose stimulus for insulin secretion (as much as doubled)

2) Gastrointestinal Hormones

1. Gastrin, secretin, cholecystokinin, glucagonlike peptide–1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP).
2. GLP-1 & GIP are most potent (incretins).
3. GI hormones act the same way as AAs to increase Insulin.

3) Other Hormones

1. Glucagon, growth hormone, cortisol, and to a lesser extent, progesterone and estrogen.
2. Prolonged secretion of them can occasionally lead to exhaustion of beta cells.

4) ANS

1. Pancreas islets are richly innervated with sympathetic & parasympathetic nerves.
2. Sympathetic stimulation increase glucagon secretion and decrease insulin secretion during hypoglycemia (glycogenolysis, lipolysis).
3. Parasympathetic stimulation increase insulin secretion during hyperglycemia.
4. Glucose concentration could be detected by specialized neurons in hypothalamus, brain stem and liver.

Incretins

1. Incretins are intestinal hormones (GLP-1 & GIP).
2. They released in response to nutrient ingestion.
3. They potentiate glucose-induced insulin secretion.
4. Their effect is mediated through their binding with receptors.
5. Degraded by dipeptidyl-peptidase IV (DPP-IV).

- Two main incretins in human:

1. GIP: glucose-induced insulin releasing polypeptide
2. GLP: glucagon-like peptide

The incretin effect accounts for 50-70% of the total insulin secreted after glucose ingestion.

GLP-1 & GIP

1. GIP is secreted from K cells in upper GI (duodenum, proximal jejunum).
2. GLP-1 is secreted from L cells in lower GI (ileum, colon).
3. GLP-1 is also expressed in pancreatic alpha cells, neurons.
4. Including: hypothalamus, pituitary, tractus solitarius nucleus, reticular nucleus.

DPP-IV inhibitors

1. Sitagliptin, linagliptin, saxagliptin, alogliptin.
2. They are used with diet and exercise in T2DM.

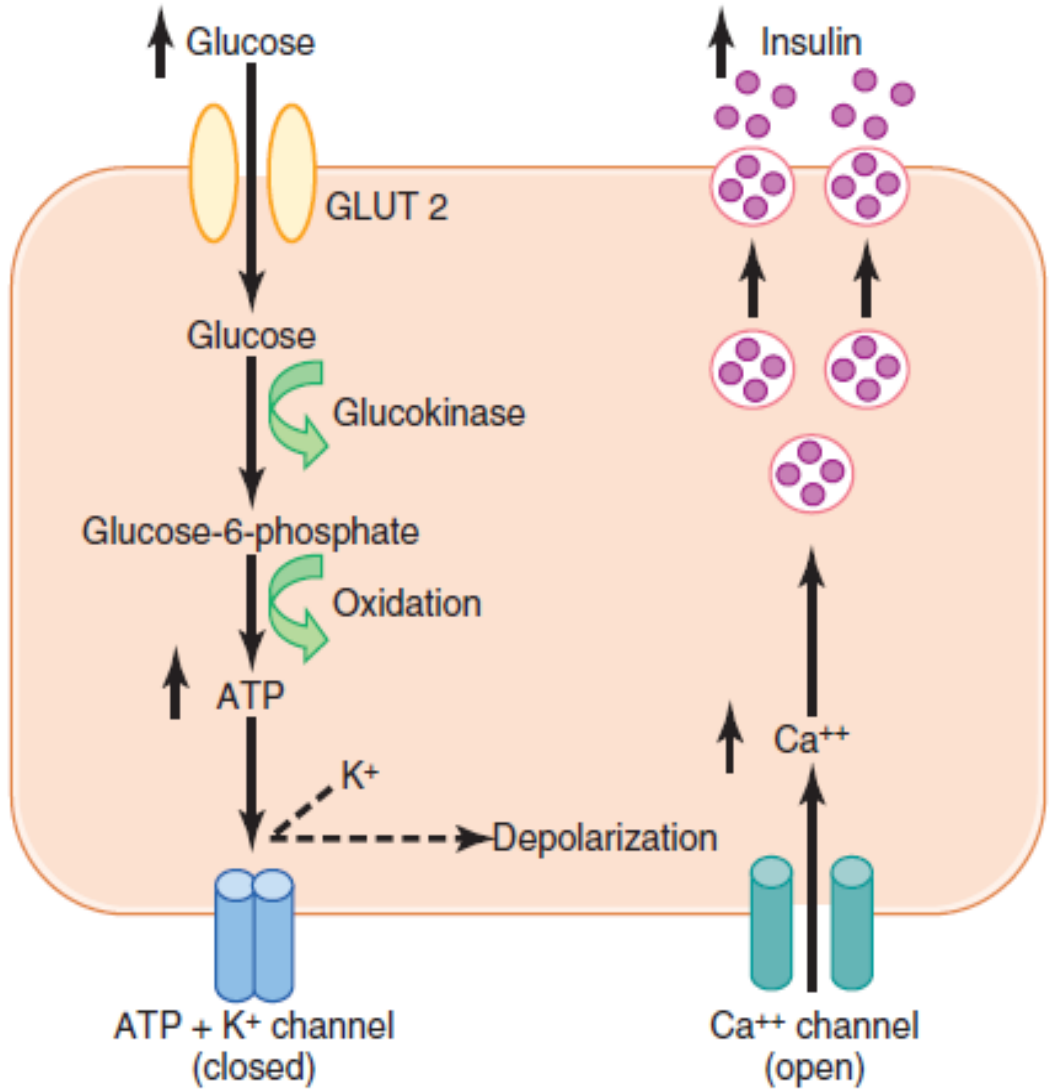
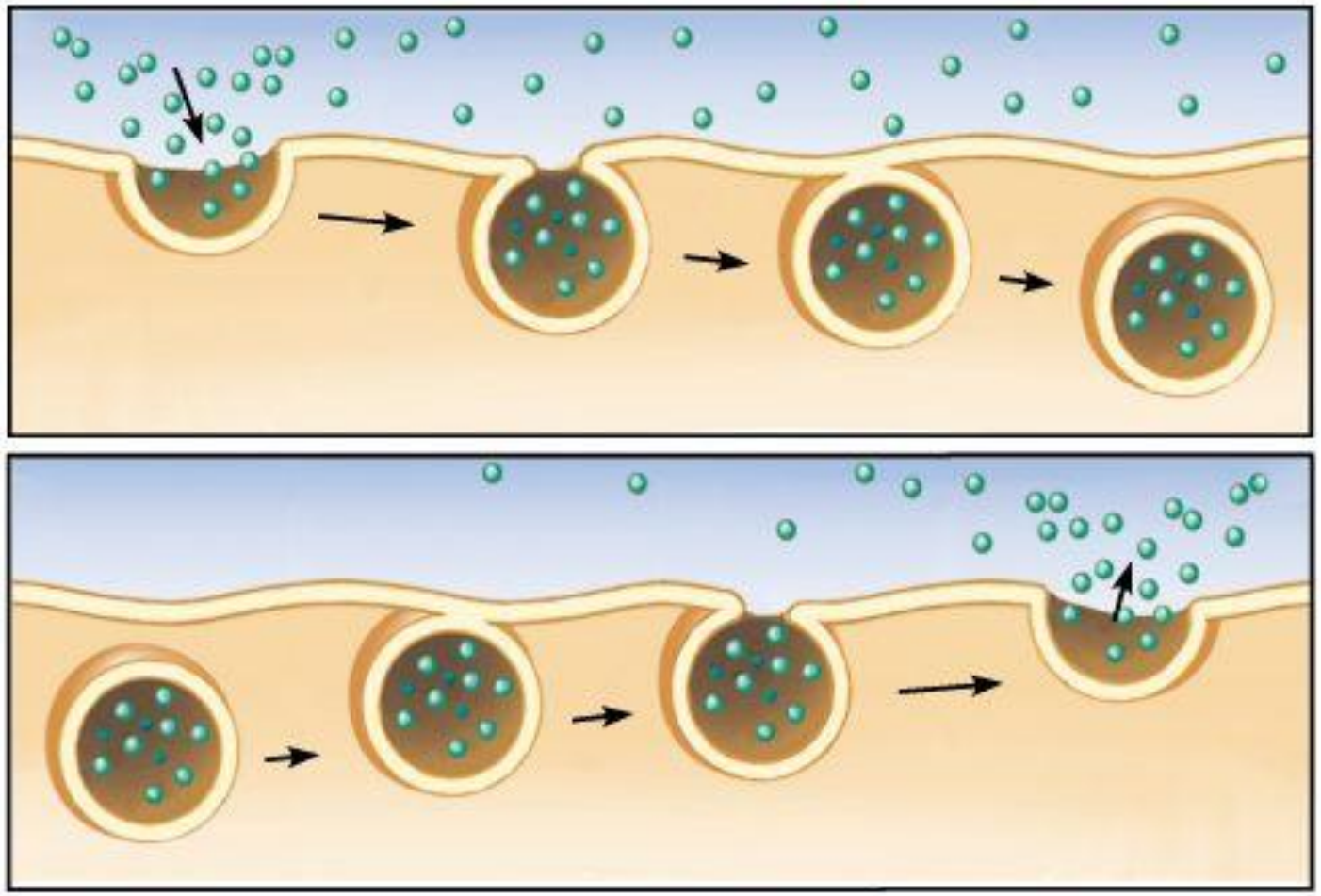


Figure 79-7. The basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

Endocytosis & exocytosis

Endocytosis →

Exocytosis →



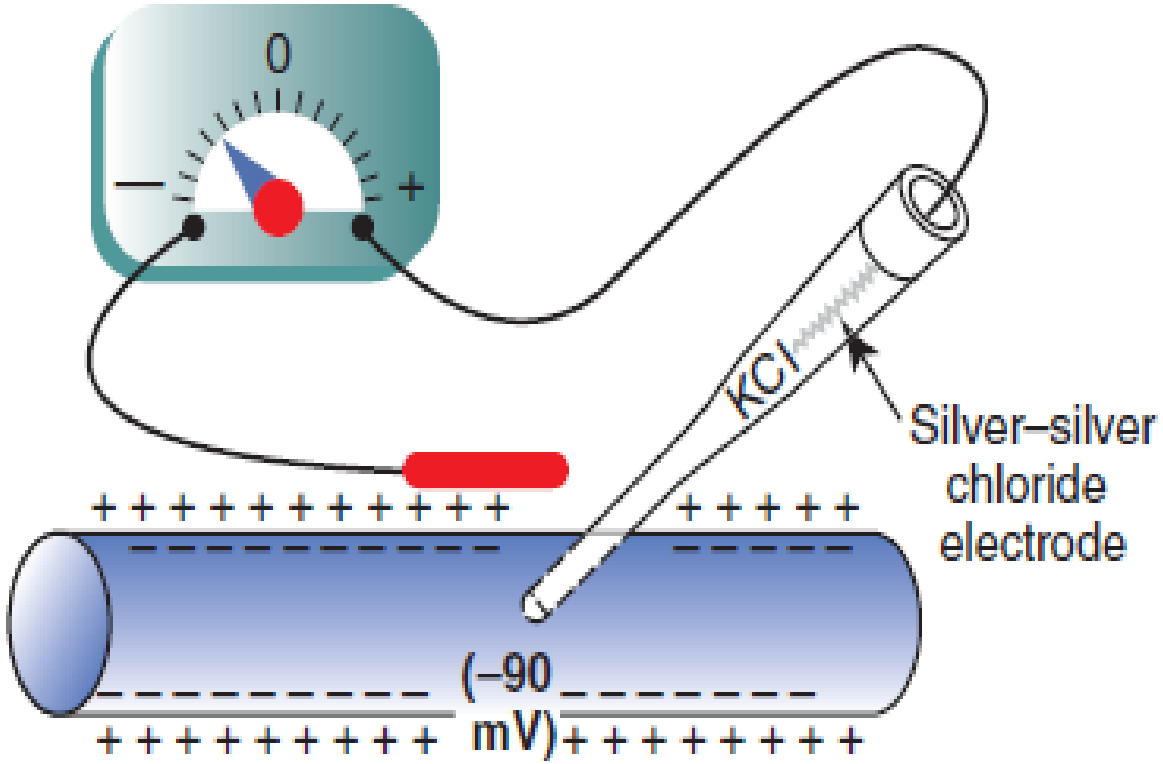
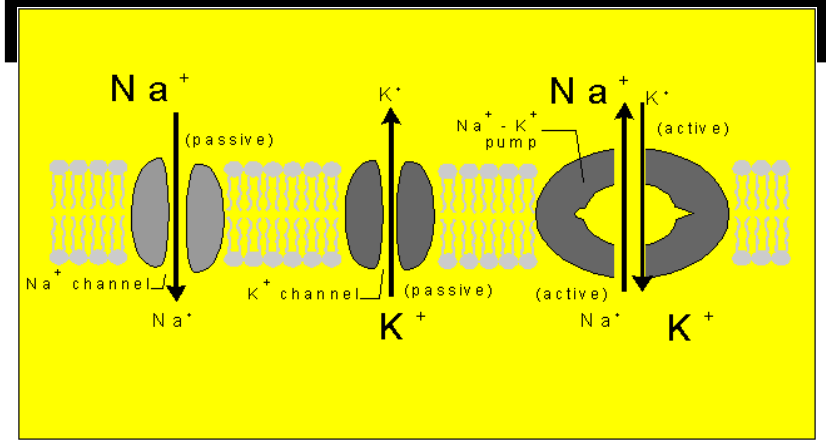
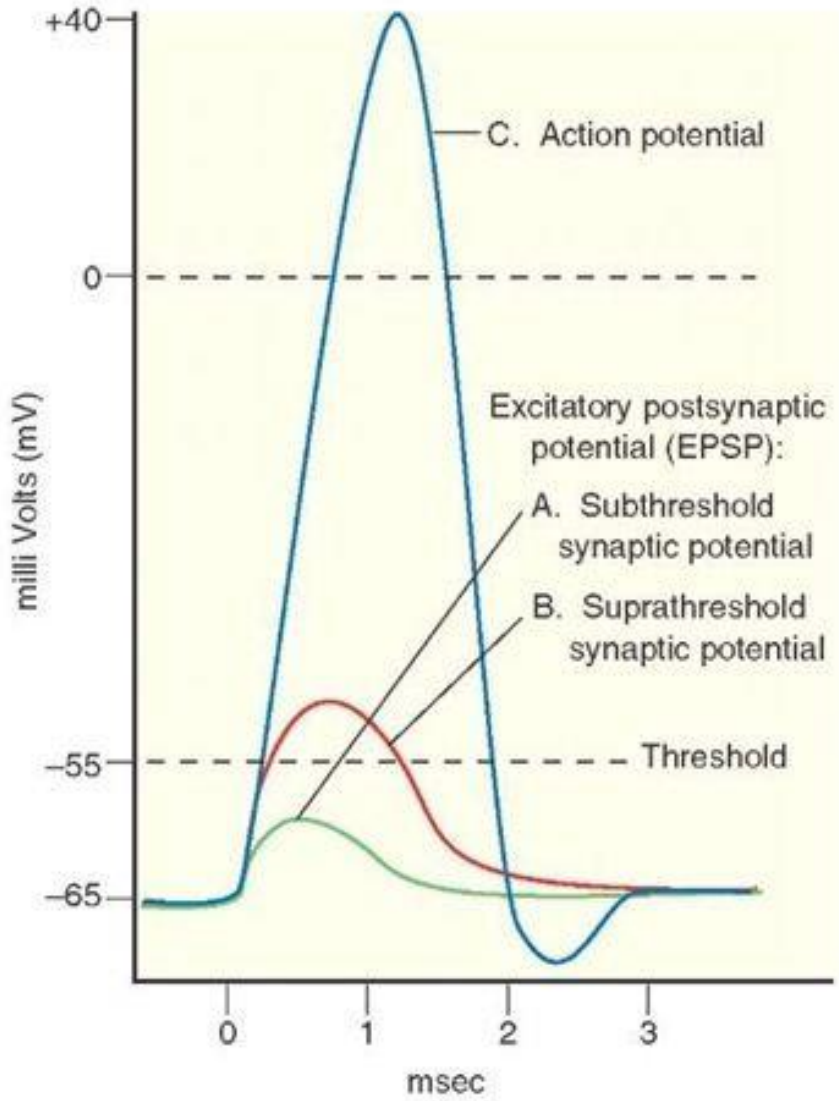


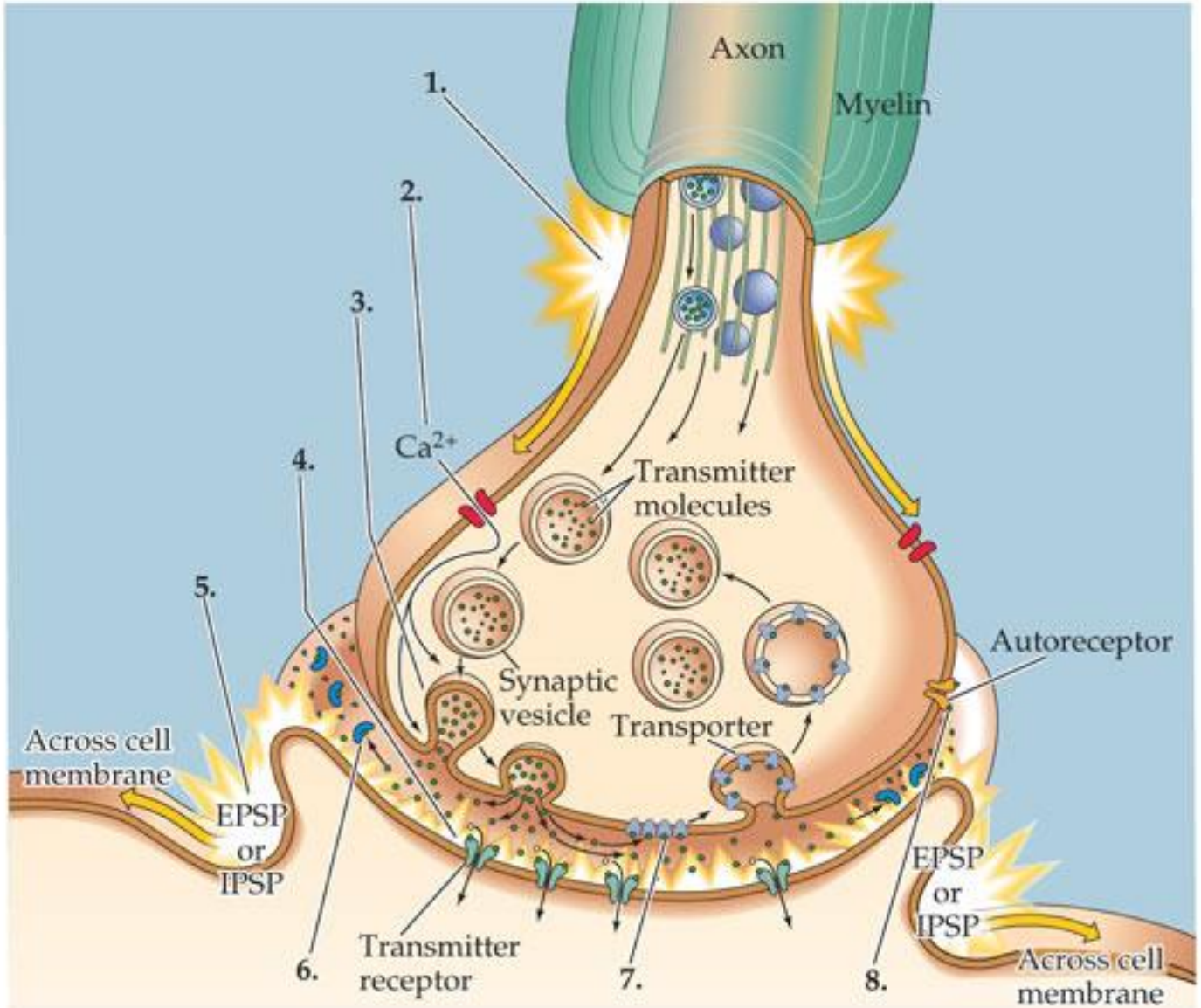
Figure 5-2. Measurement of the membrane potential of the nerve fiber using a microelectrode.

Resting Potential



In a resting neuron (one that is not conducting an impulse), there is a difference in electrical charges on the outside and inside of the plasma membrane. The outside has a positive charge and the inside has a negative charge.


+40
0
–55
–65
milli Volts (mV)
C. Action potential
Excitatory postsynaptic potential (EPSP):
A. Subthreshold synaptic potential
B. Suprathreshold synaptic potential
Threshold
0
1
2
3
msec



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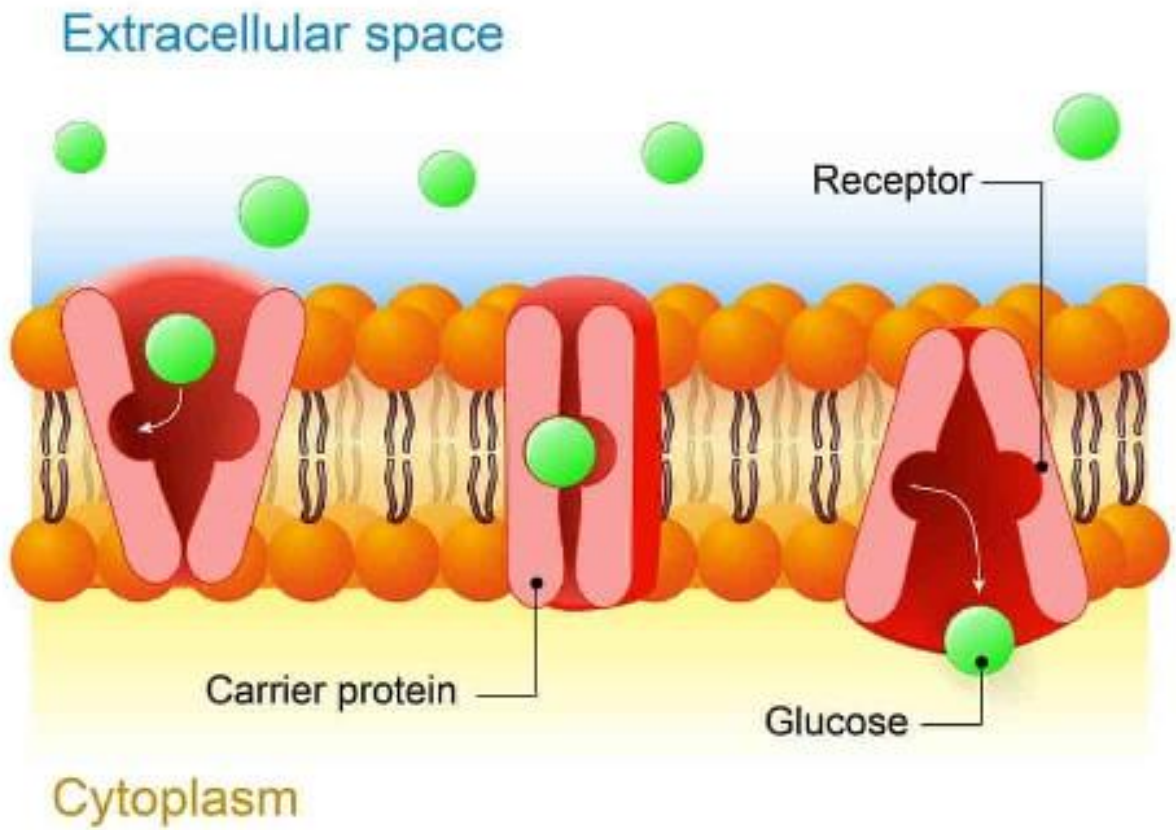
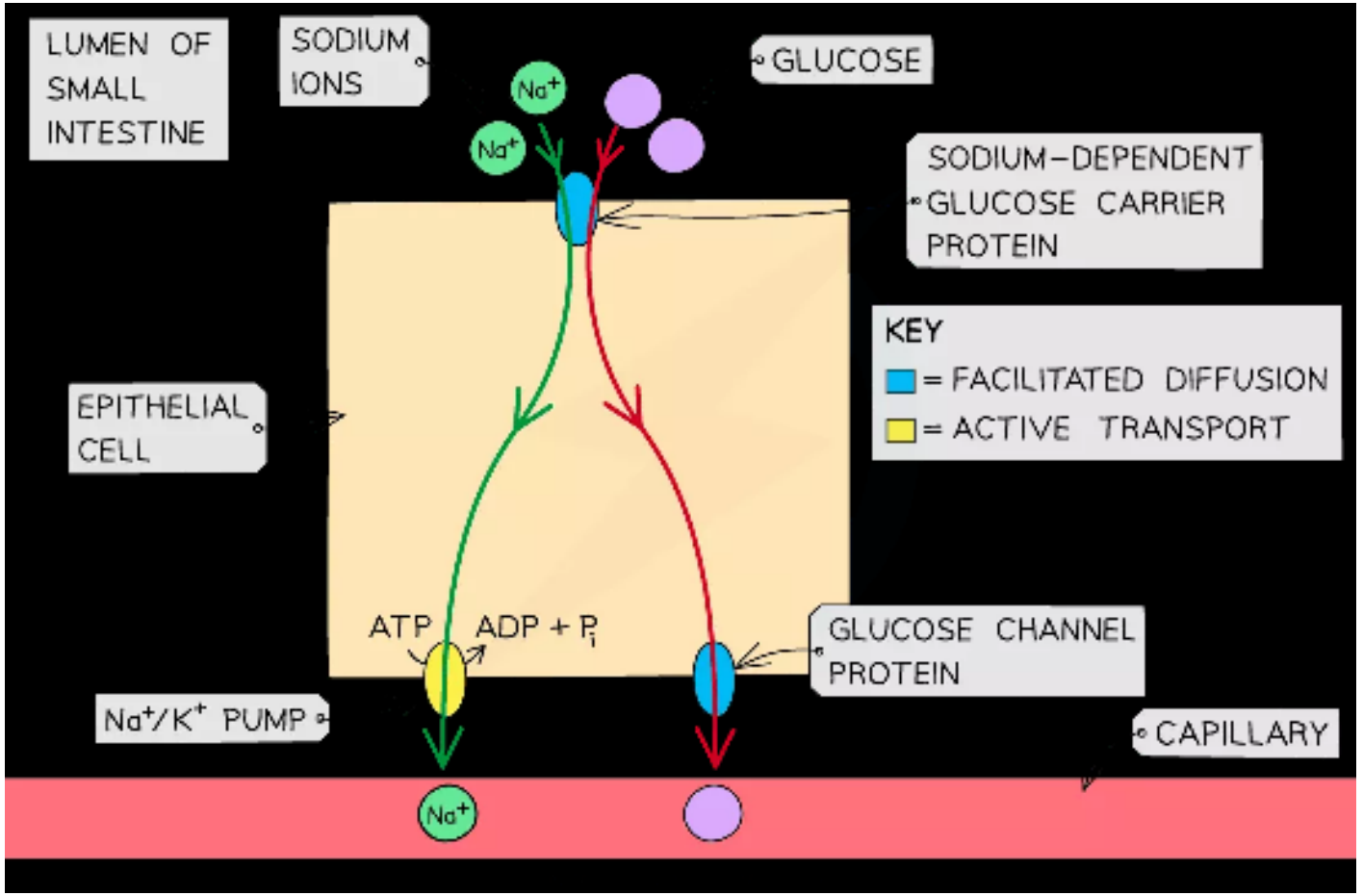
	Function	K_m (mM)[a]	Major Sites of Expression
Secondary active transport (Na^1-glucose cotransport)			
SGLT 1	Absorption of glucose	0.1–1.0	Small intestine, renal tubules
SGLT 2	Absorption of glucose	1.6	Renal tubules
Facilitated diffusion			
GLUT 1	Basal glucose uptake	1–2	Placenta, blood-brain barrier, brain, red cells, kidneys, colon, many other organs
GLUT 2	B-cell glucose sensor; transport out of intestinal and renal epithelial cells	12–20	B cells of islets, liver, epithelial cells of small intestine, kidneys
GLUT 3	Basal glucose uptake	<1	Brain, placenta, kidneys, many other organs
GLUT 4	Insulin-stimulated glucose uptake	5	Skeletal and cardiac muscle, adipose tissue, other tissues
GLUT 5	Fructose transport	1–2	Jejunum, sperm
GLUT 6	None	—	Pseudogene
GLUT 7	Glucose 6-phosphate ransporter in endoplasmic reticulum	—	Liver, ? other tissues

FACILITATED DIFFUSION



Co-tansport or symport



SGLT-2 inhibitor

1. Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin
2. It lowers BS by excretion of glucose in urine.

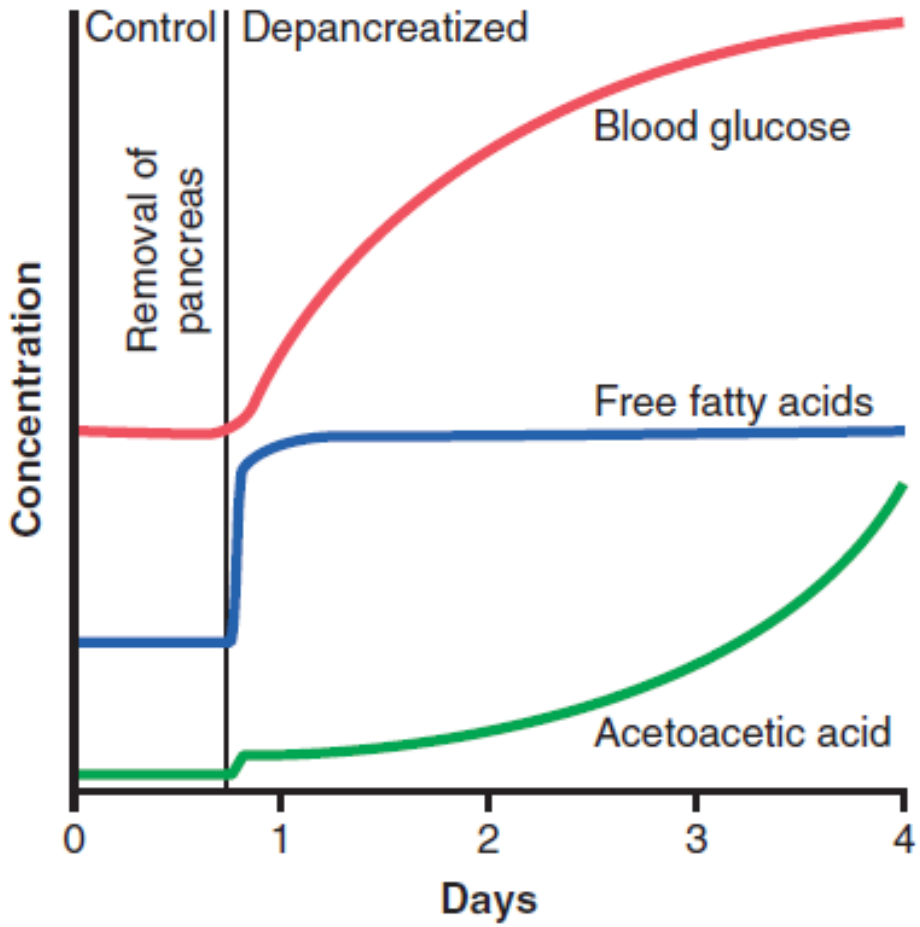
Effect of insulin on fat storage

1. Insulin increase fat storage and FFAs synthesis.
2. Glycogen will not be synthetized if proceed 5-6%.
3. “Lypoprotein lipase” on the wall of capillaries.
4. “hormone-dependent lipase” inside the fat cells.
5. Insulin suppresses hormone-dependent lipase.

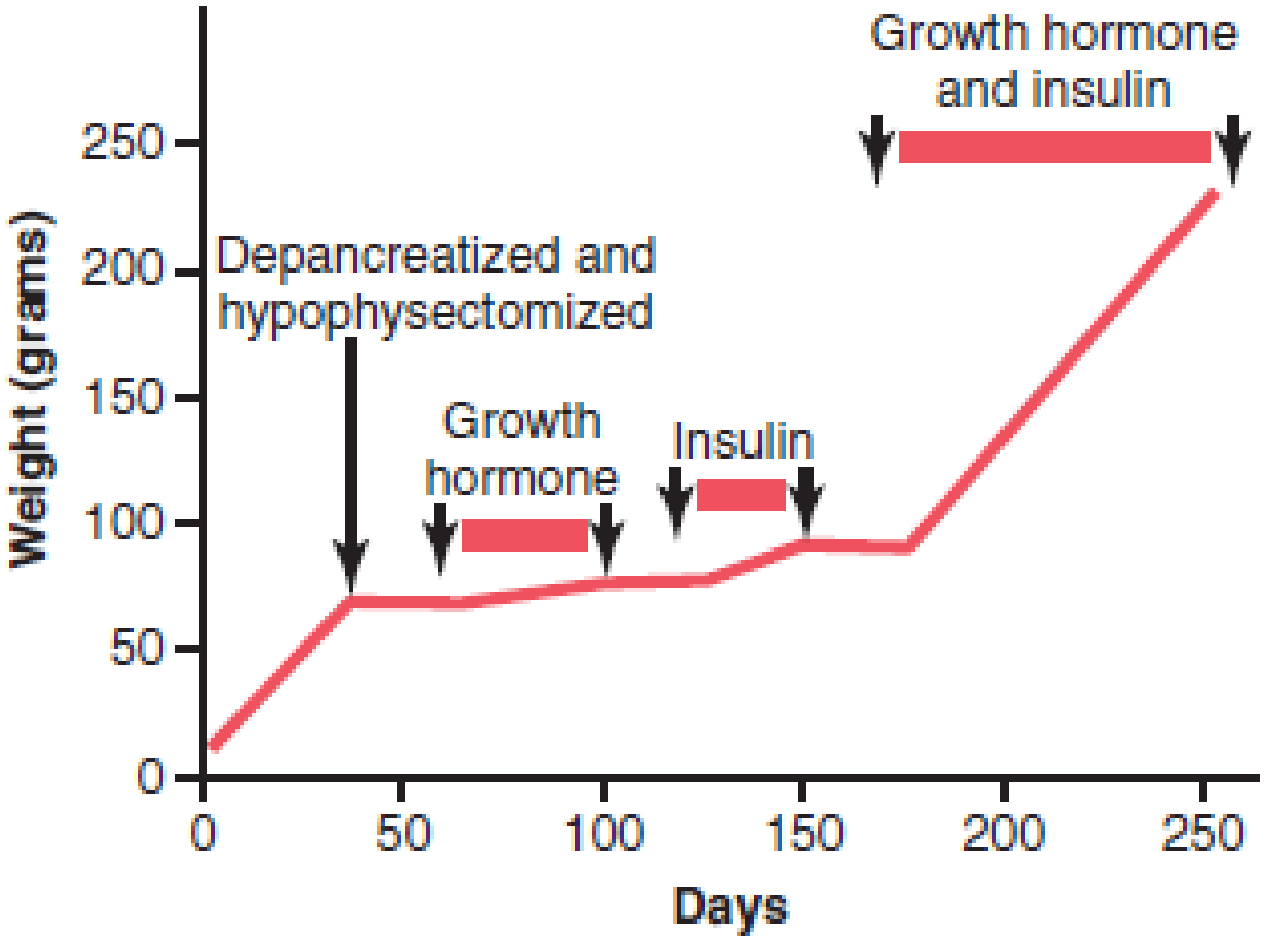
- Lack of insulin → activation of carnitine pathway
- Acetyl-coA production
- Aceto-acetic production
- Beta-hydroxyl butyric acid
- aceton

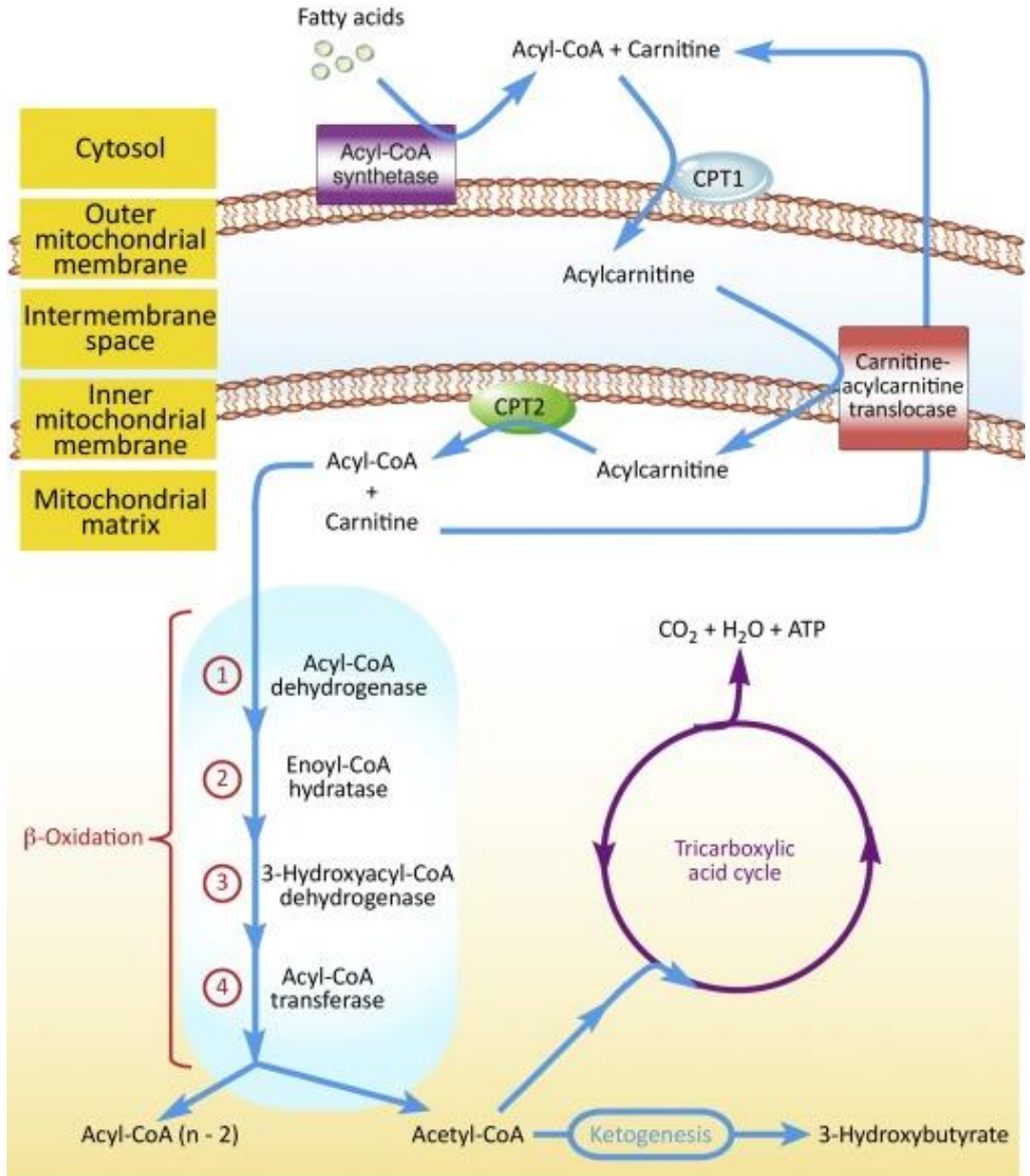
} Keton bodies → Acidosis

Effects of the lack of “insulin”



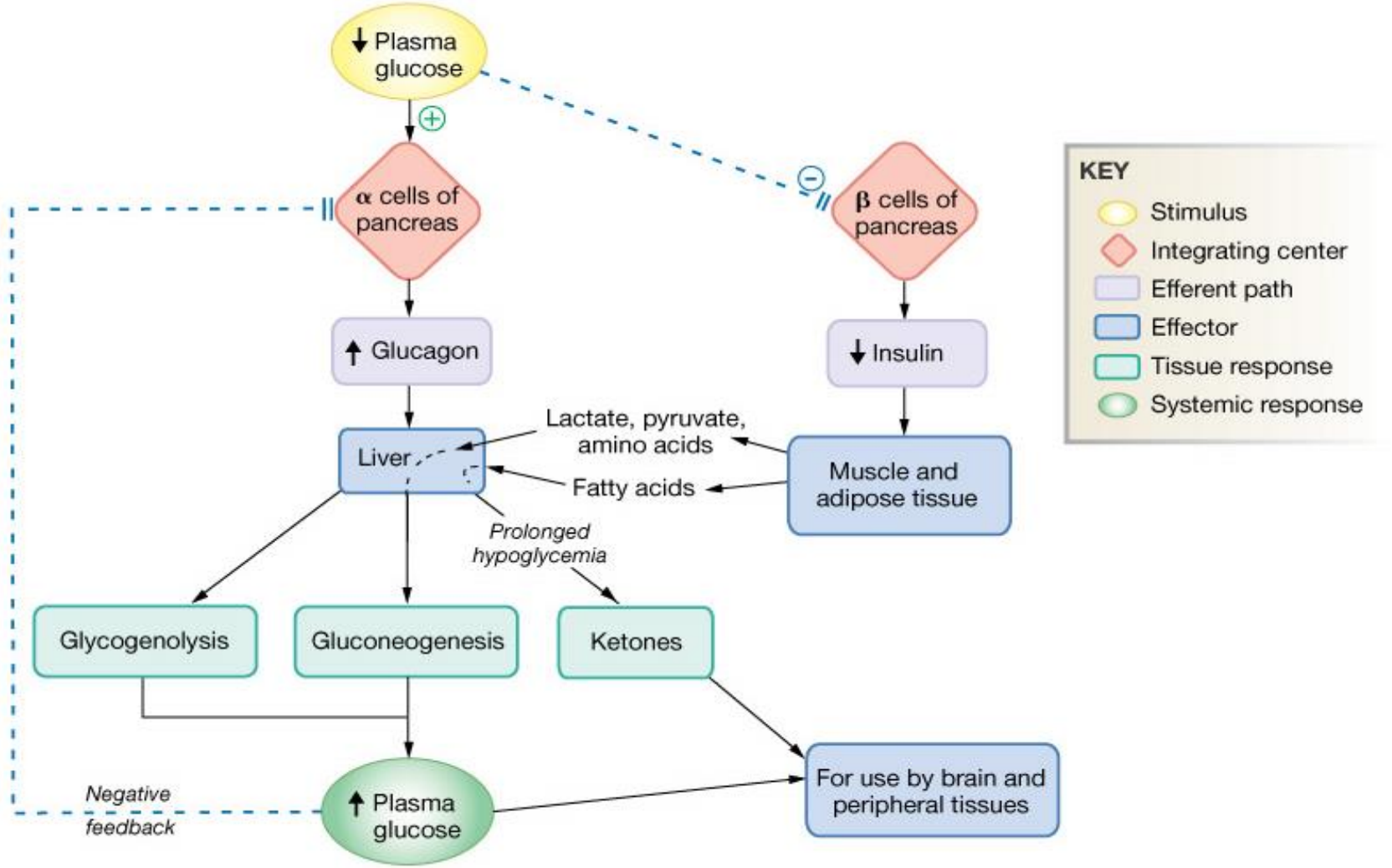
Effect of insulin and GH on growth





Trends in Biochemical Sciences

Glucagon Action on Cells: Dominates in Fasting State Metabolism



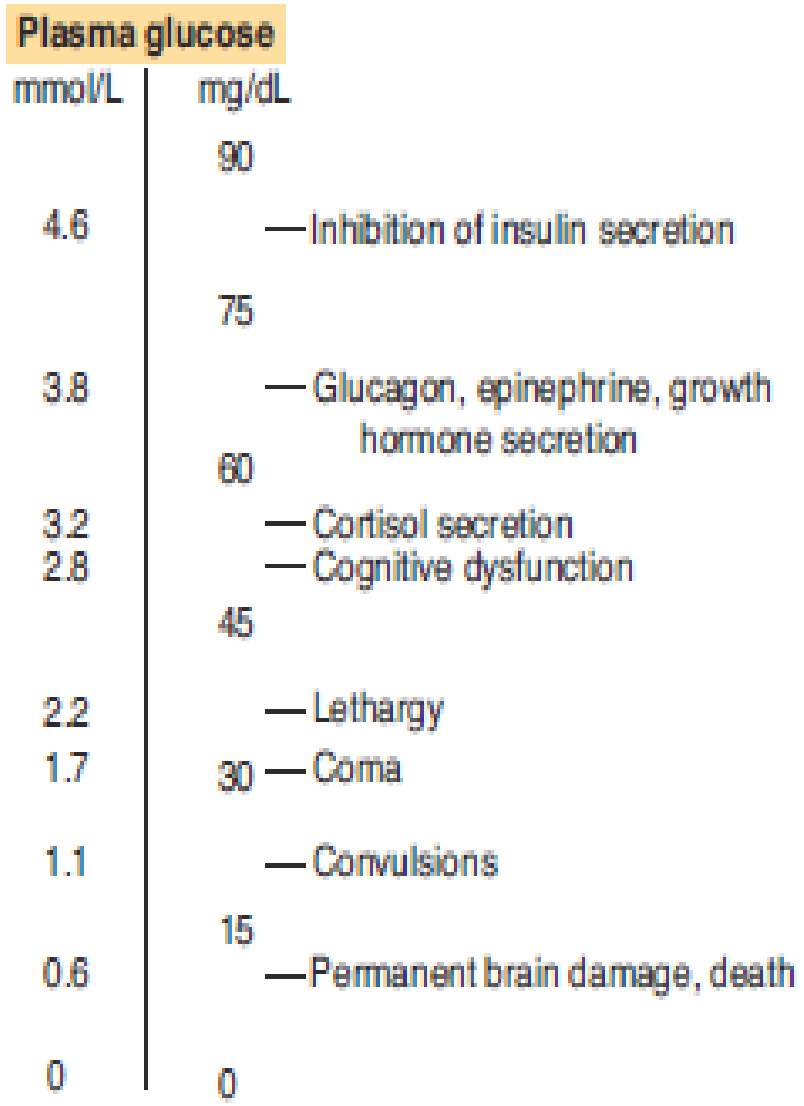


FIGURE 21–10 Plasma glucose levels at which various effects of hypoglycemia appear.

D cells

- Somatostatin
- SS14 & SS28
- Both form inhibit the secretion of insulin, glucagon and PP.
- Somatostatin-secreting pancreatic tumors or somatostatinoma → hyperglycemia and diabete.
- Slow gastric empying & dyspepsia &↓acid secretion.

F cells

- 36 Aas & linear.
- Closely related to Polypeptide YY & neuropeptide Y.
- Slow the absorbtion of food in humans.
- However its exact physiologic function is still uncertain.