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Physiology of endocrine Pancreas (insulin) (Lecture-1)

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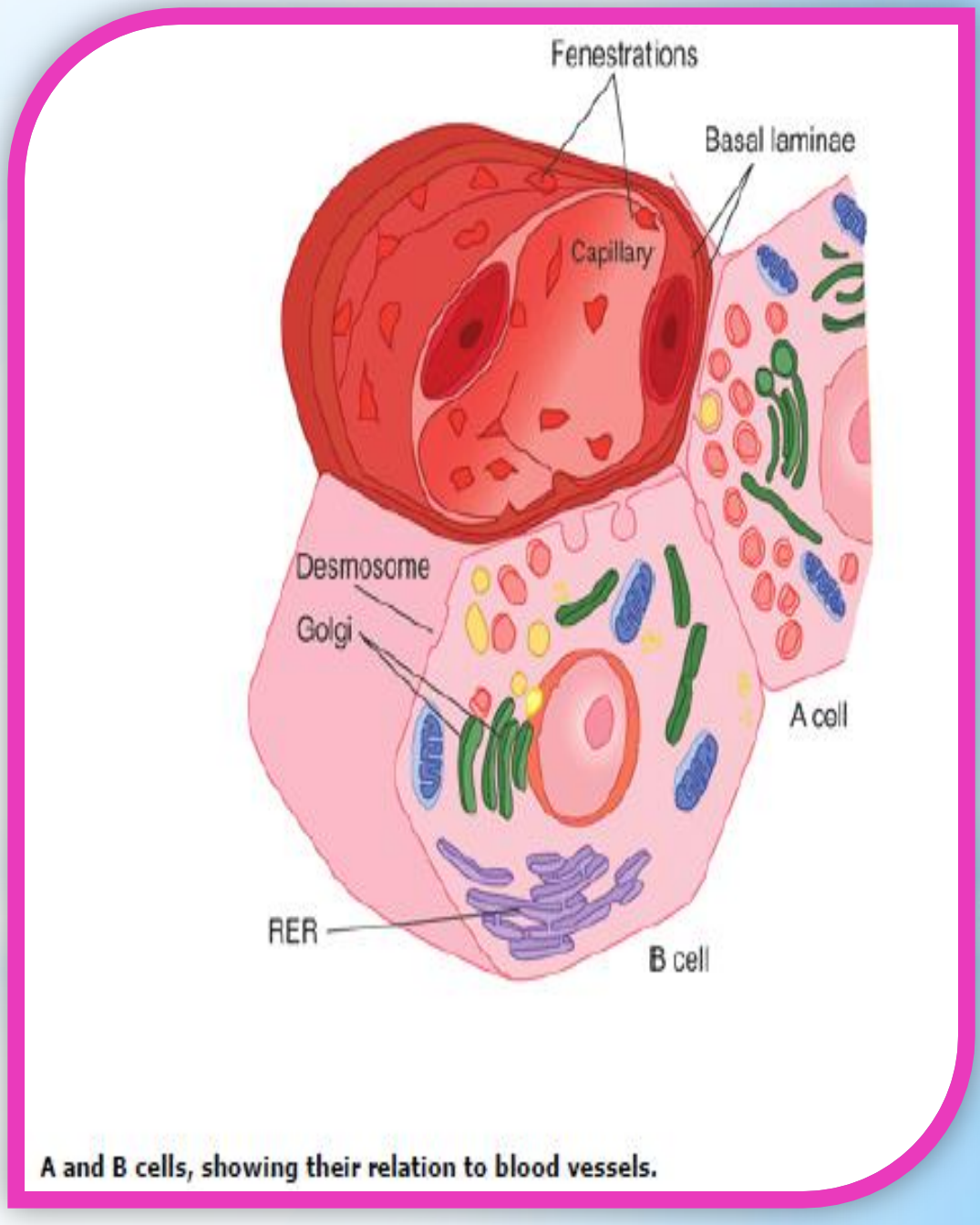
OBJECTIVES

At the end of this lecture you should be able to:

- **Identify:**
  - Structure, biosynthesis and mechanism of insulin secretion
  - Target cells of insulin
  - Mechanism of action of insulin
  - Insulin receptors
  - Glucose transporters (GLUTs)
- **Describe Metabolic effects of insulin on:**
  - Carbohydrate metabolism
  - Fat metabolism
  - Growth and protein metabolism
  - Na^+-K^+ pump
- **Identify regulation of insulin secretion**

- The human pancreas has 1 to 2 million islets of Langerhans
- The islets are organized around small capillaries into which its cells secrete their hormones.



A and B cells, showing their relation to blood vessels.

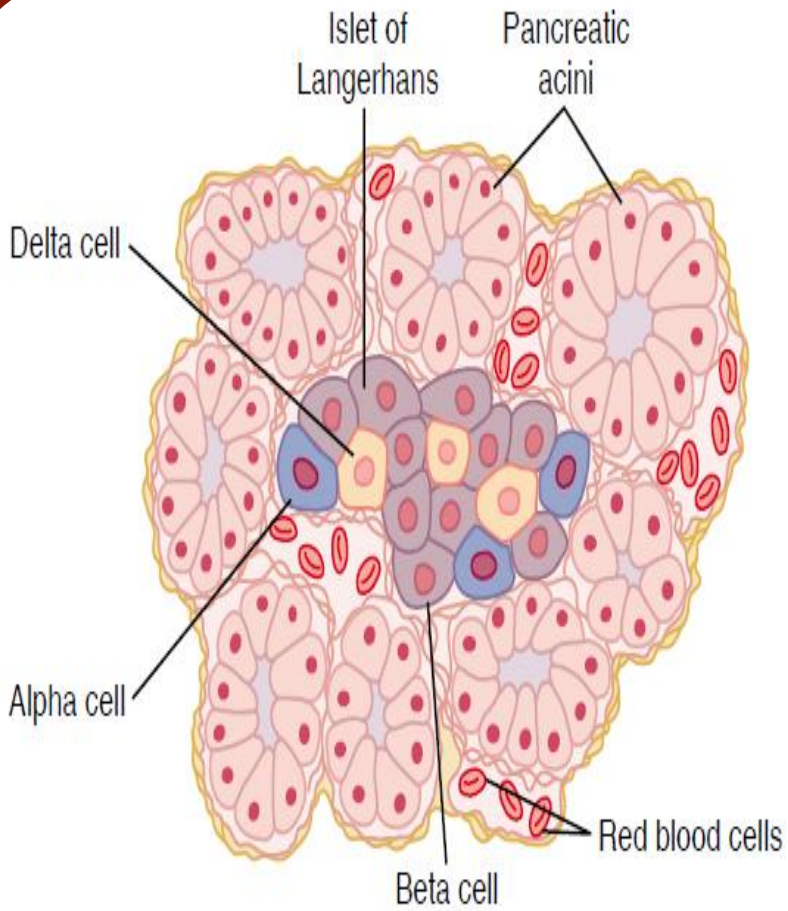
The islets contain three major types of cells:

*The β cells, (60 %), secrete insulin and amylin.

*The α cells, (25 %), secrete glucagon.

*The delta cells, (10%), secrete somatostatin.

*The PP cell, is present in small numbers and secretes pancreatic polypeptide hormone.

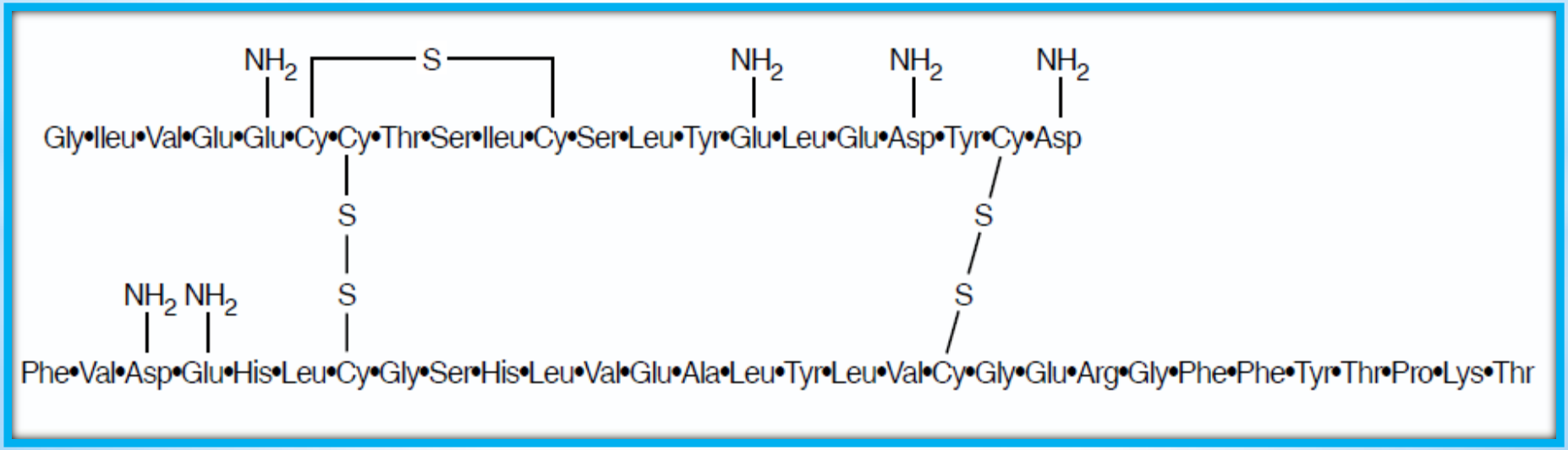


Physiologic anatomy of an islet of Langerhans in the pancreas.

* 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.
  * 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.



Insulin Biosynthesis

- Insulin RNA is translated to form an insulin preprohormone.
- The preprohormone is cleaved to form a proinsulin.
- Proinsulin is cleaved to form insulin and peptide fragments.
- About 1/6 of the final secreted product is in the form of proinsulin that has no insulin activity.

Insulin Metabolism

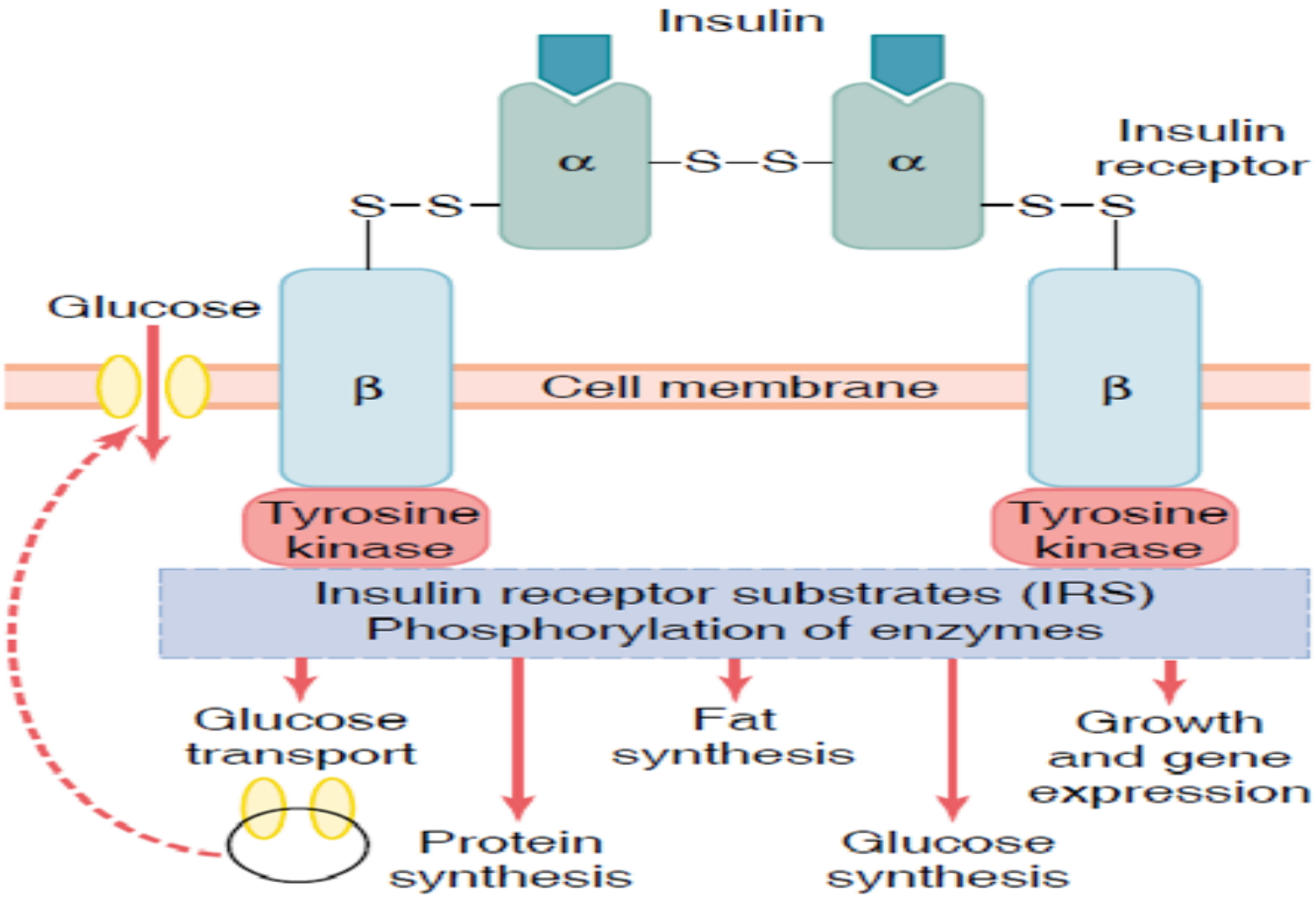
- Insulin circulates in the blood in an unbound form.
- It has a plasma half-life 6 min., so it is mainly cleared from the circulation within 10 to 15 min.
- Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme insulinase mainly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

Nonsuppressible insulin-like activity (NSILA)

* Plasma contains a number of substances with insulin-like activity in addition to insulin.
* Their activity is not suppressed by anti-insulin antibodies.
* 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)

Activation of target cell receptors by Insulin

- 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.
- To initiate its effects on target cells, insulin first binds with and activates a membrane receptor protein which causes the subsequent effects.



Activation of target cell receptors by Insulin

The Resulting Cellular Effects due to insulin stimulation are:

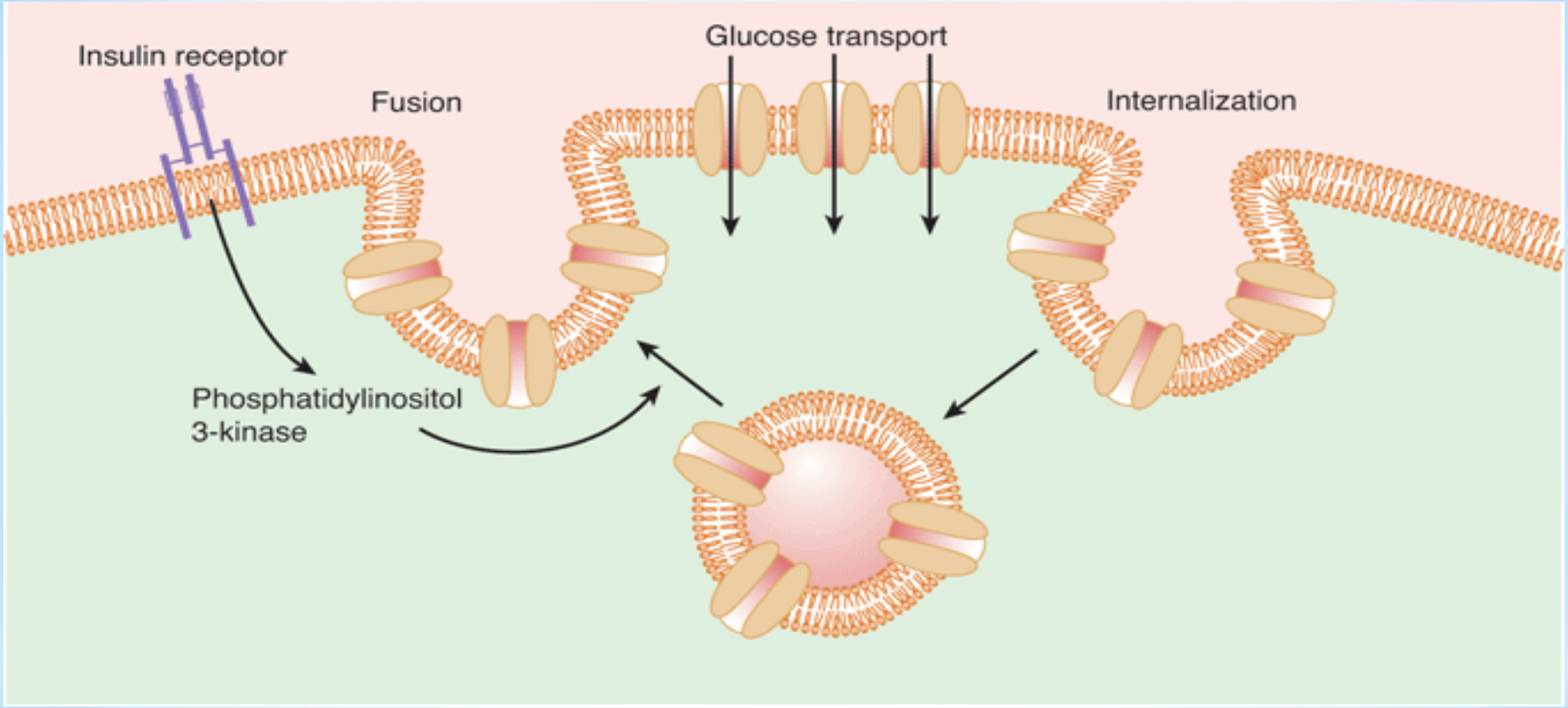
1. Increased glucose transport into the cells.
2. The cell membrane becomes more permeable to many of the AAs, K^+, and phosphate ions.
3. Slower effects occur to change the states of phosphorylation and activity levels of many more intracellular metabolic enzyme.
4. Much slower effects result from changed rates of translation of messenger RNAs at the ribosomes to form new proteins
5. Still slower effects result from changed rates of transcription of DNA in the cell nucleus. In this way, insulin remolds much of the cellular enzymatic machinery to achieve its metabolic goals.

GLUCOSE TRANSPORTERS(GLUTs)

* Insulin stimulates glucose entry into cells by increasing the number of GLUTs
* They are a family of closely related proteins that span the cell membrane and have their amino and carboxyl terminals inside the cell.
* They differ from the Na^+-dependent glucose transporters, SGLT 1 & SGLT 2, responsible for the secondary active transport of glucose in the intestine and renal tubules.
* Seven different GLUTs, named GLUT 1–7 in order of discovery, have been characterized.
* They contain 492 to 524 AA residues and their affinity for glucose varies.

GLUCOSE TRANSPORTERS (Cont.)

* GLUT 4 is the transporter in muscle and adipose tissue that is stimulated by insulin.
* GLUT 4 molecules is maintained within vesicles in the cytoplasm of insulin-sensitive cells. When the insulin receptors of these cells are activated, the vesicles move rapidly to the cell membrane by activating phosphatidylinositol 3-kinase.
* The vesicles fuse with cell membrane, inserting the transporters into the cell. When insulin action ceases, the transporter containing patches of membrane are endocytosed and moved back to the cell interior within 3 - 5 min. and the vesicles are ready for the next exposure to insulin.



- Cycling of GLUT 4 transporters through endosomes in insulin-sensitive tissues
  - Activation of the insulin receptor causes activation of phosphatidylinositol 3-kinase, which speeds translocation of the GLUT 4-containing endosomes into the cell membrane.
  - The GLUT 4 transporters then mediate glucose transport into the cell.

GLUCOSE TRANSPORTERS

	Function	Major Sites of Expression
GLUT 1	Basal glucose uptake	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	B cells of islets, liver, epithelial cells of small intestine, kidneys
GLUT 3	Basal glucose uptake	Brain, placenta, kidneys, many other organs
GLUT 4	Insulin-stimulated glucose uptake	Skeletal and cardiac muscle, adipose tissue, other tissues
GLUT 5	Fructose transport	Jejunum, sperm
GLUT 6	None	Pseudogene
GLUT 7	Glucose 6-phosphate transporter in endoplasmic reticulum	Liver, ? other tissues

WHAT ARE THE FUNCTIONS OF INSULIN?

FUNCTION OF INSULIN

- On Carbohydrate Metabolism
- On Fat Metabolism
- On Protein Metabolism
- On Growth
- On Na^+-K^+ Pump

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

Effect of Insulin on Carbohydrate Metabolism

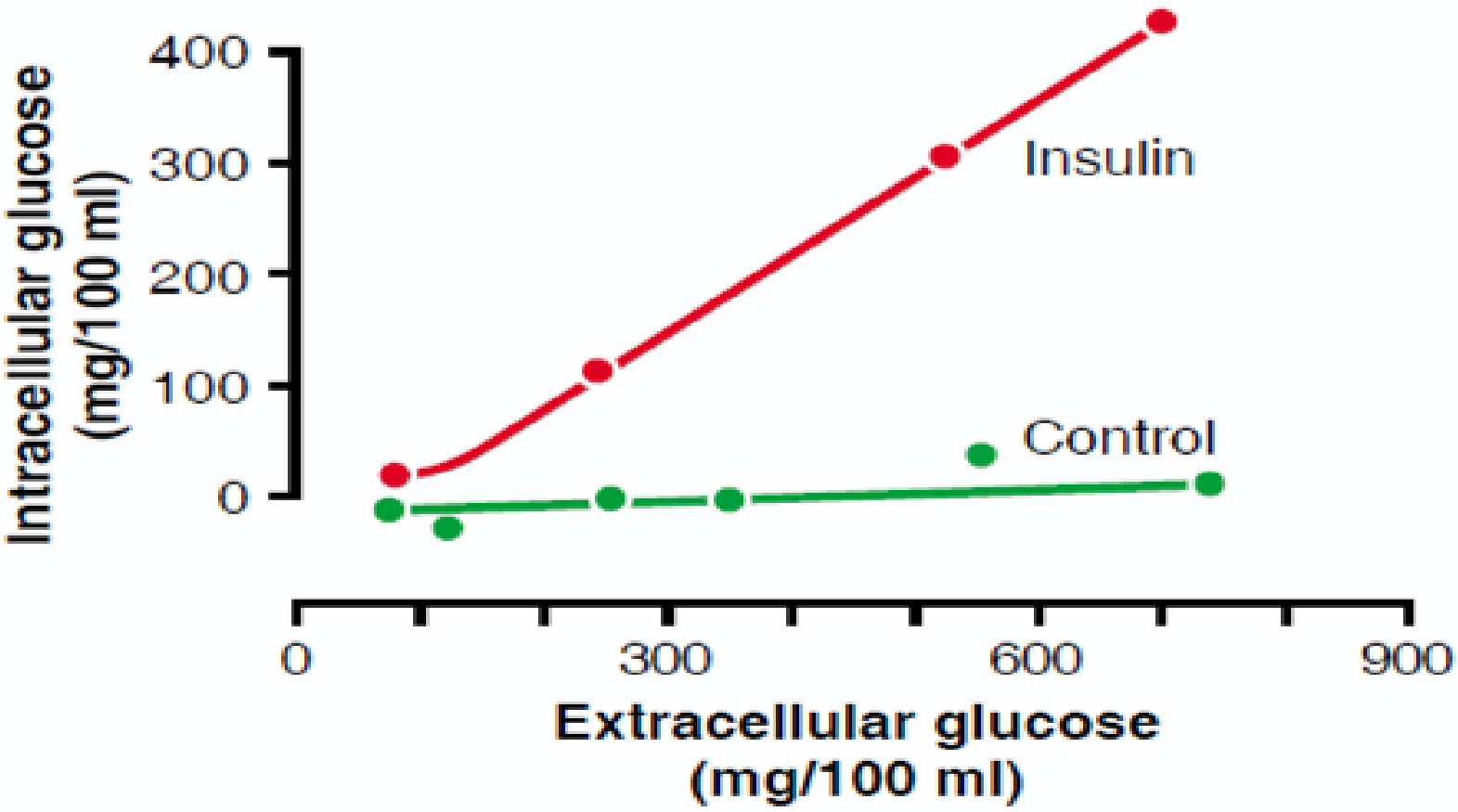
Insulin causes rapid uptake, storage, and use of glucose by almost all tissues of the body, (muscles, adipose tissue, and liver).

1- Insulin promotes muscle glucose uptake

Insulin increases the rate of transport of glucose into the resting muscle cell by at least 15-fold.

Under 2 conditions the muscles do use large amounts of glucose:

- During moderate or heavy exercise.
- During the few hours after a meal.



Effect of insulin in enhancing the concentration of glucose inside muscle cells. Note that in the absence of insulin (control), the intracellular glucose remains near zero

2- insulin stimulates storage of glycogen in muscle up to a limit of 2 to 3 % concentration

3- Insulin promotes liver uptake, storage, and use of glucose

This occurs by several steps:

1. It inactivates liver phosphorylase.

2. It causes enhanced uptake of glucose from the blood by the liver cells by increasing the activity of the enzyme glucokinase.

3. It increases the activities of the enzyme glycogen synthase.

The net effect of all these actions is to increase the amount of glycogen in the liver to a total of 5 - 6 % of the liver mass.

Glucose release from the Liver between meals.

In between meals, the liver releases glucose back into the circulating blood:

1. The decreasing blood glucose causes the pancreas to decrease its insulin secretion.

2. The lack of insulin stops further synthesis of glycogen in the liver.

3. The lack of insulin (along with increase of glucagon) activates the enzyme phosphorylase.

4. The enzyme glucose phosphatase becomes activated by the insulin lack and causes the phosphate radical to split away from the glucose.

Thus, the liver removes glucose from the blood when it is present in excess after a meal and returns it to the blood when the blood glucose concentration falls between meals

4- Insulin promotes conversion of excess glucose into FA which are packaged as TG in VLDL and transported to the adipose tissue and deposited as fat.

5- Insulin inhibits gluconeogenesis in the liver by:

- Decreasing the quantities and activities of the liver enzymes required for gluconeogenesis.
- Decreasing the release of AA from muscle and other extrahepatic tissues.

6- Insulin increases glucose transport by most other cells of the body (except brain). In adipose cells, insulin promotes deposition of fat.

Lack of effect of insulin on glucose uptake & usage by the brain

* The brain cells are permeable to glucose and can use glucose without the intermediation of insulin.
* The brain cells normally use only glucose for energy and can use other energy substrates, such as fats, only with difficulty.
* When the blood glucose falls too low, into the range of 20 to 50 mg/100 ml, symptoms of hypoglycemic shock develop, characterized by progressive nervous irritability that leads to fainting, seizures, and even coma.

Effect of Insulin on Fat Metabolism

1- Insulin promotes fat synthesis by different factors:

A. Insulin increases the transport of glucose into the liver cells. Additional glucose becomes available to form fat.

B. An excess of citrate and isocitrate ions formed when excess amounts of glucose are used for energy have a direct effect in activating acetyl-CoA carboxylase needed for FA synthesis.

C. Insulin activates lipoprotein lipase in the capillary walls of the adipose tissue, which splits TG again into FA, which are absorbed into the adipose cells and converted to TG and stored.

2- Insulin promotes storage of fat in adipose cells.

A. Insulin inhibits the action of hormone-sensitive lipase that causes hydrolysis of TG already stored in the fat cells. Therefore, FA release from the adipose tissue is inhibited.

B. Insulin promotes glucose transport into the fat cells where it is used to synthesize minute amounts of FA, and large quantities of α-glycerol phosphate. This substance supplies the glycerol that combines with FA to form the TG in adipose cells.

Effects of insulin deficiency on fat metabolism

- The enzyme hormone-sensitive lipase in the fat cells becomes activated and causes hydrolysis of the stored TG
- The plasma concentration of free FA rise and become the main energy substrate used by all tissues of the body.
- Plasma concentrations of cholesterol and phospholipid increase.
- Excessive amounts of acetoacetic acid is formed in the liver cells. Some of the acid is also converted into ß-hydroxybutyric acid and acetone (ketone bodies) i.e ketosis.

Effect of Insulin on Protein Metabolism

1. Insulin shares with GH the capability of increasing the uptake of AA

2. Insulin increases the translation of messenger RNA.

3. Insulin increases the rate of transcription of selected DNA genetic sequences in the cell nuclei.

4. Insulin inhibits the catabolism of proteins by cellular lysosomes.

5. In the liver, insulin depresses the rate of gluconeogenesis.

In summary, insulin promotes protein formation and prevents the degradation of proteins.

Effects of insulin lack on protein metabolism

- Catabolism of proteins increases.
- Protein synthesis stops.
- Large quantities of AA are dumped into the plasma.
- The plasma AA concentration rises.
- Most of the excess AA are used either directly for energy or as substrates for gluconeogenesis.
- This degradation of the AA leads to enhanced urea excretion in the urine.
- The resulting protein wasting can lead to extreme weakness and deranged functions of the organs.

Effect of Insulin on Growth

- Because insulin is required for the synthesis of proteins, it is as essential for growth.
- Insulin and GH interact synergistically to promote growth, each performing a specific function that is separate from that of the other.
- Each promotes cellular uptake of a different selection of AA, all of which are required if growth is to be achieved.

*Role of insulin (and other hormones) in "switching" between CHO and lipid metabolism

- When the glucose concentration is low, insulin secretion is suppressed and fat is used for energy everywhere except in the brain.
- When the glucose concentration is high, insulin secretion is stimulated and CHO is used instead of fat, and the excess blood glucose is stored in the form of liver glycogen, liver fat, and muscle glycogen.
- GH and cortisol are secreted in response to hypoglycemia, and inhibit cellular utilization of glucose, promoting fat utilization.
- Epinephrine increases plasma glucose concentration (glycogenolysis) and enhancing the utilization of fat.

Insulin Effects on Carbohydrate, Fat, and Protein Metabolism

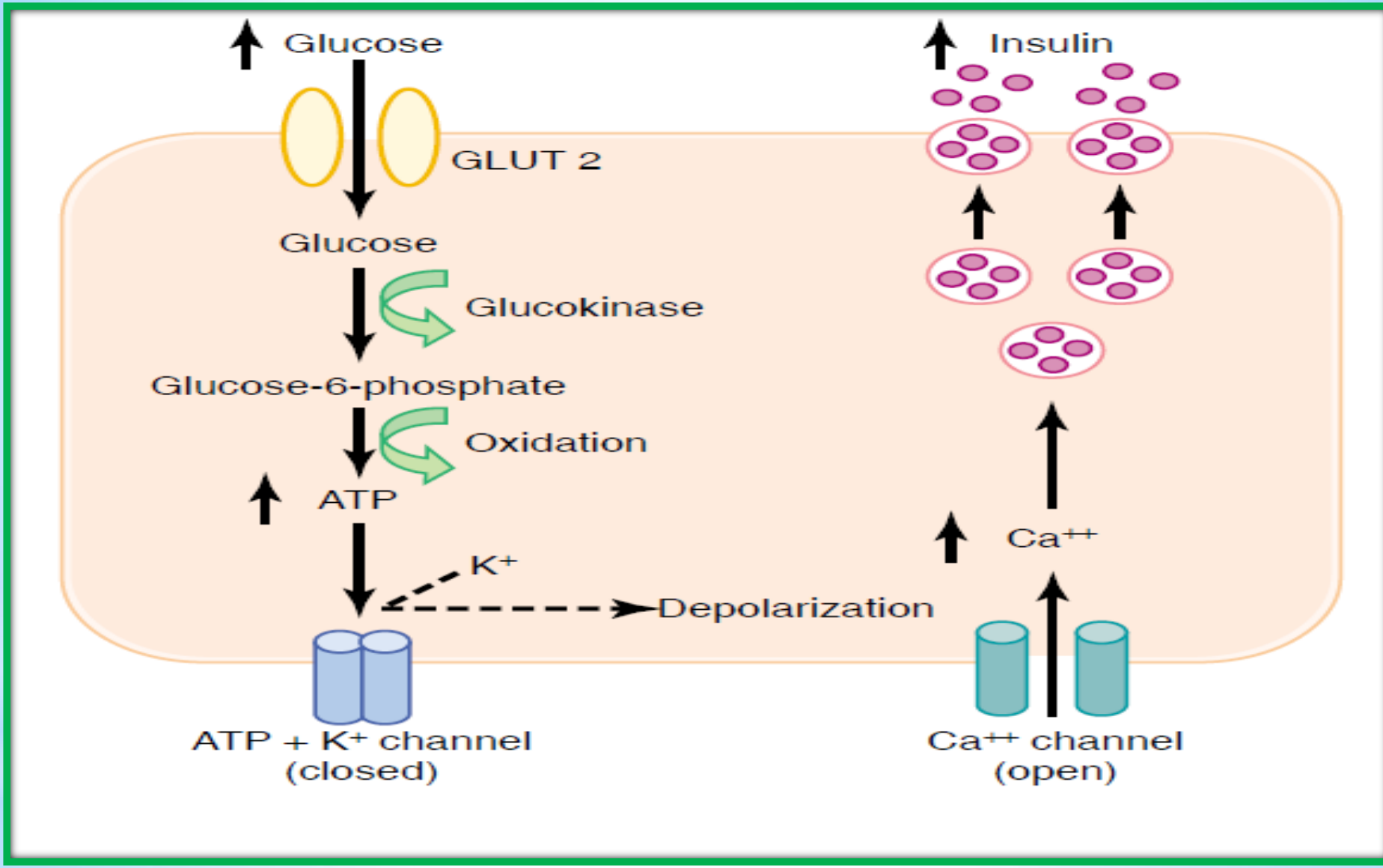
Metabolic effects	Insulin stimulates	Insulin inhibits
Carbohydrate metabolism	Glucose transport in adipose tissue and muscle Rate of glycolysis in muscle and adipose tissue Glycogen synthesis in adipose tissue, muscle, and liver	Glycogen breakdown in muscle and liver Rate of glycogenolysis gluconeogenesis in the liver
Lipid metabolism	Fatty acid and triacylglycerol synthesis in tissues Uptake of triglycerides from the blood into adipose tissue and muscle Rate of cholesterol synthesis in the liver	Lipolysis in adipose tissue, lowering the plasma fatty acid level Fatty acid oxidation in muscle and liver Ketogenesis
Protein metabolism	Amino acid transport into tissues Protein synthesis in muscle, adipose tissue, liver, and other tissues	Protein degradation in muscle Urea formation

Effect of Insulin on Na^+-K^+ pump

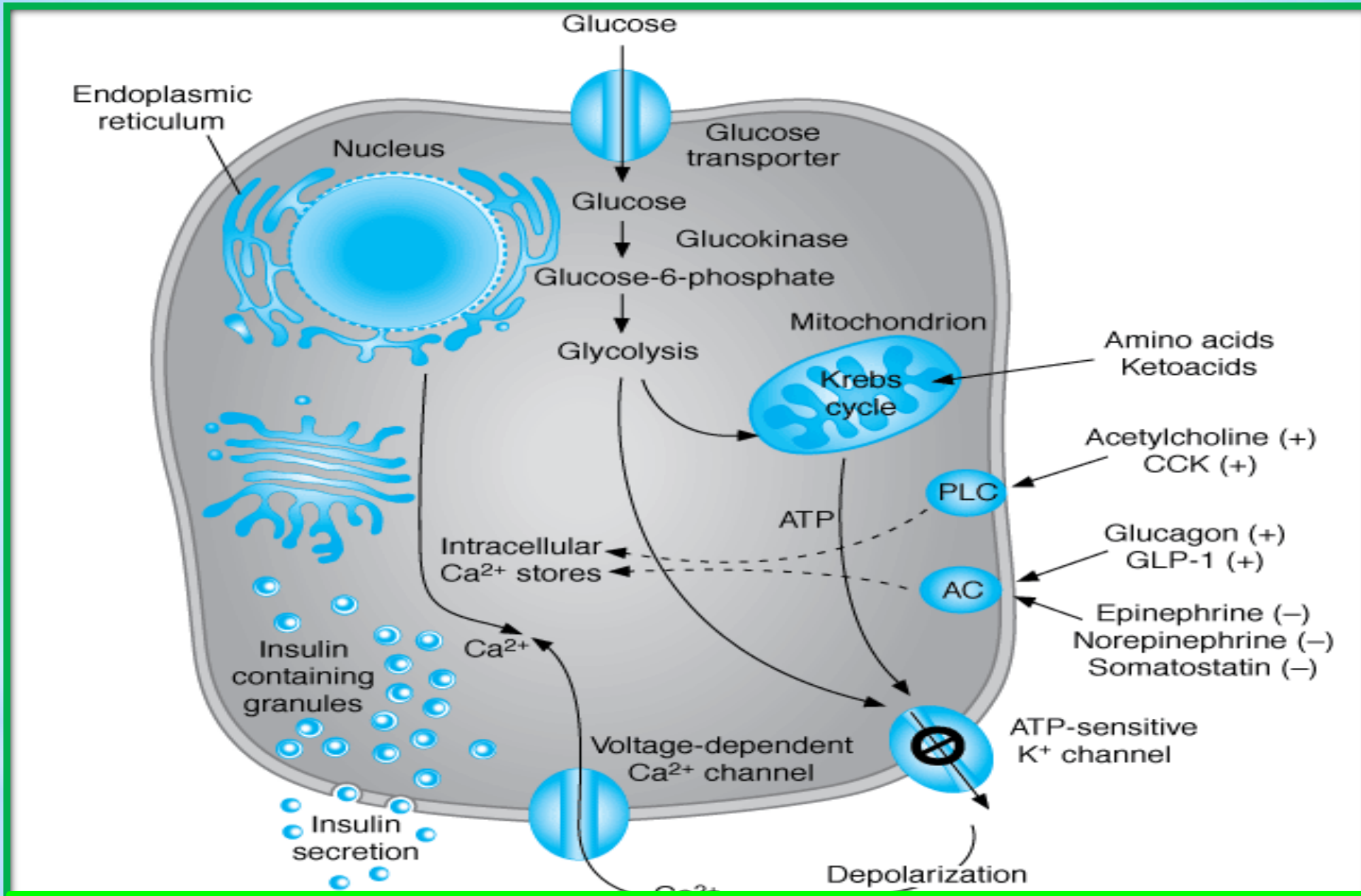
- Insulin causes K^+ to enter cells, with a resultant lowering of the extracellular K^+ concentration.
- The reason for the intracellular migration of K^+ is still uncertain. However, insulin increases the activity of Na^+–K^+ ATPase in cell membranes, so that more K^+ is pumped into cells.
- Infusions of insulin and glucose are very effective for the temporary relief of hyperkalemia in patients with renal failure.
- **Hypokalemia** often develops when patients with diabetic acidosis are treated with insulin.

Mechanisms of Insulin Secretion

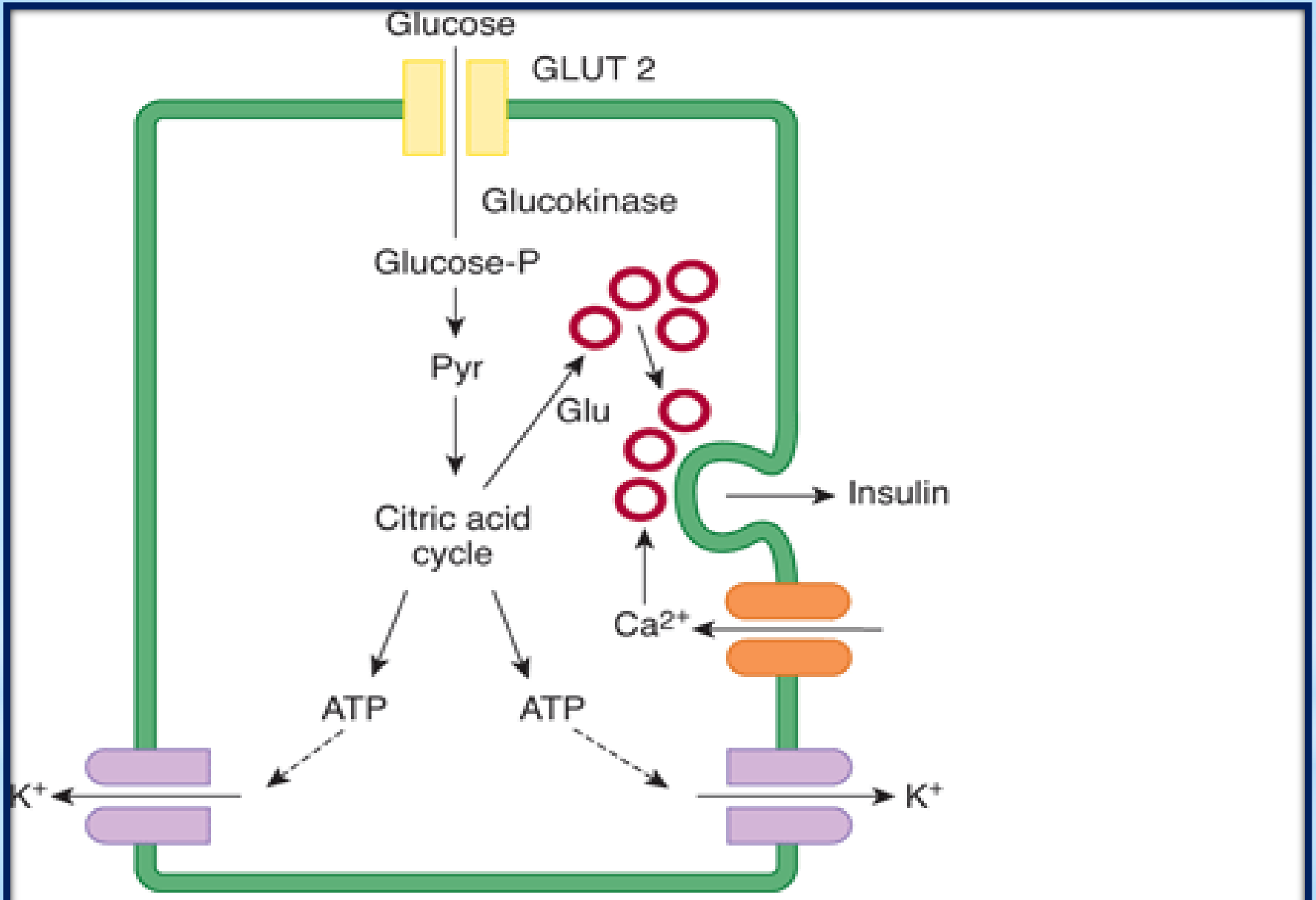
* Glucose enters ß cells by GLUT 2 transporters.
* Glucose influx that is proportional to the blood concentration in the physiologic range.
* Once inside the cells, glucose is phosphorylated to G-6-P by glucokinase.
* The G-6-P is oxidized to form ATP, which inhibits the ATP-sensitive K^+ channels of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



Basic mechanism of glucose stimulation of insulin secretion by β cells of pancreas



Regulation of insulin release


Glucose
GLUT 2
Glucokinase
Glucose-P
Pyr
Glu
Citric acid cycle
Insulin
Ca^{2+}
ATP
ATP
K^+
K^+

Factors Affecting Insulin Secretion

* Certain AA can be metabolized by ß cells to increase intracellular ATP levels and stimulate insulin secretion.
* Glucagon and GIP, as well as Ach increase intracellular Ca^{++} levels through other signaling pathways and enhance the effect of glucose, although they do not have major effects on insulin secretion in the absence of glucose.
* Somatostatin and norepinephrine (by activating α-adrenergic receptors), inhibit exocytosis of insulin.
* Sulfonylurea drugs stimulate insulin secretion by binding to the ATP-sensitive K^+ channels and blocking their activity. This results in a depolarizing effect that triggers insulin secretion.

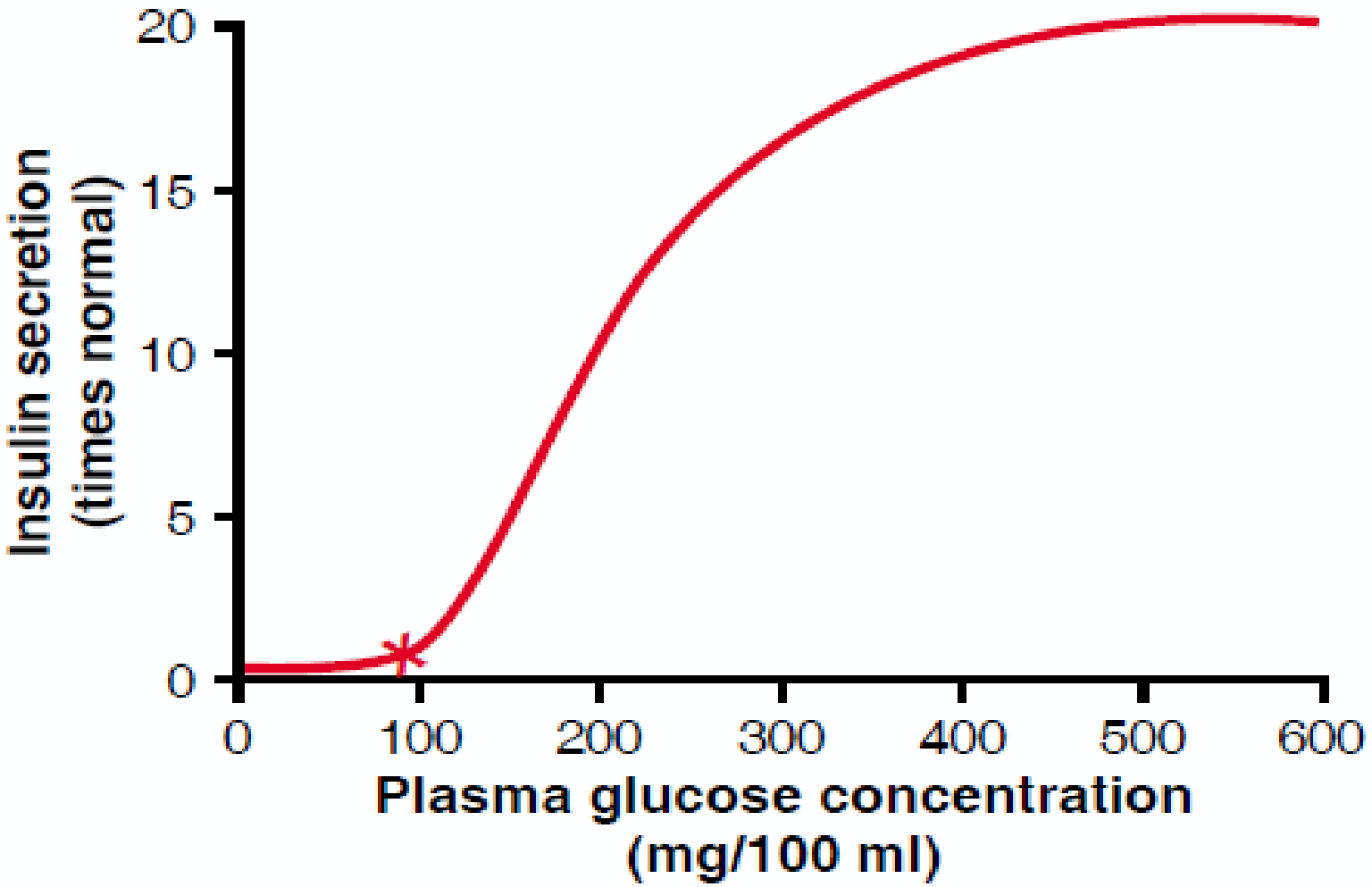
Factors and conditions that increase or decrease insulin secretion

Increase insulin secretion

* Increase blood glucose
* Increase blood FFA
* Increase blood AA
* GIT hormones, gastrin, secretin, cholecystokinin, and GIP
* Hormones , glucagon, GH, cortisol
* Parasympathetic stimulation
* B-Adrenergic stimulation
* Insulin resistance
* Sulfonylurea drugs.

Decrease insulin secretion

* Decreased blood glucose
* Fasting
* Somatostatin
* α-Adrenergic stimulation
* Leptin



Approximate insulin secretion at different plasma glucose levels

Physiology of endocrine Pancreas (Glucagon & somatostatin) (Lecture-2)

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OBJECTIVES

At the end of this lecture you should be able to:

- Identify metabolic effects of glucagon on:
  - Glucose metabolism
  - Fat metabolism
  - Heart
- Describe regulation of glucagon secretion
- Identify actions of somatostatin
- Describe interactions between pancreatic islets hormones

- Glucagon is secreted by the *alpha cells* of the islets of Langerhans when the blood glucose concentration falls.
- Glucagon is a large polypeptide and is composed of a chain of 29 AA.
- It has several functions that are opposed to those of insulin.
- Most important of these functions is to increase the blood glucose concentration, ***(it is hyperglycemic hormone)***.

WHAT ARE FUNCTIONS OF GLUCAGONE?

Effects on Glucose Metabolism

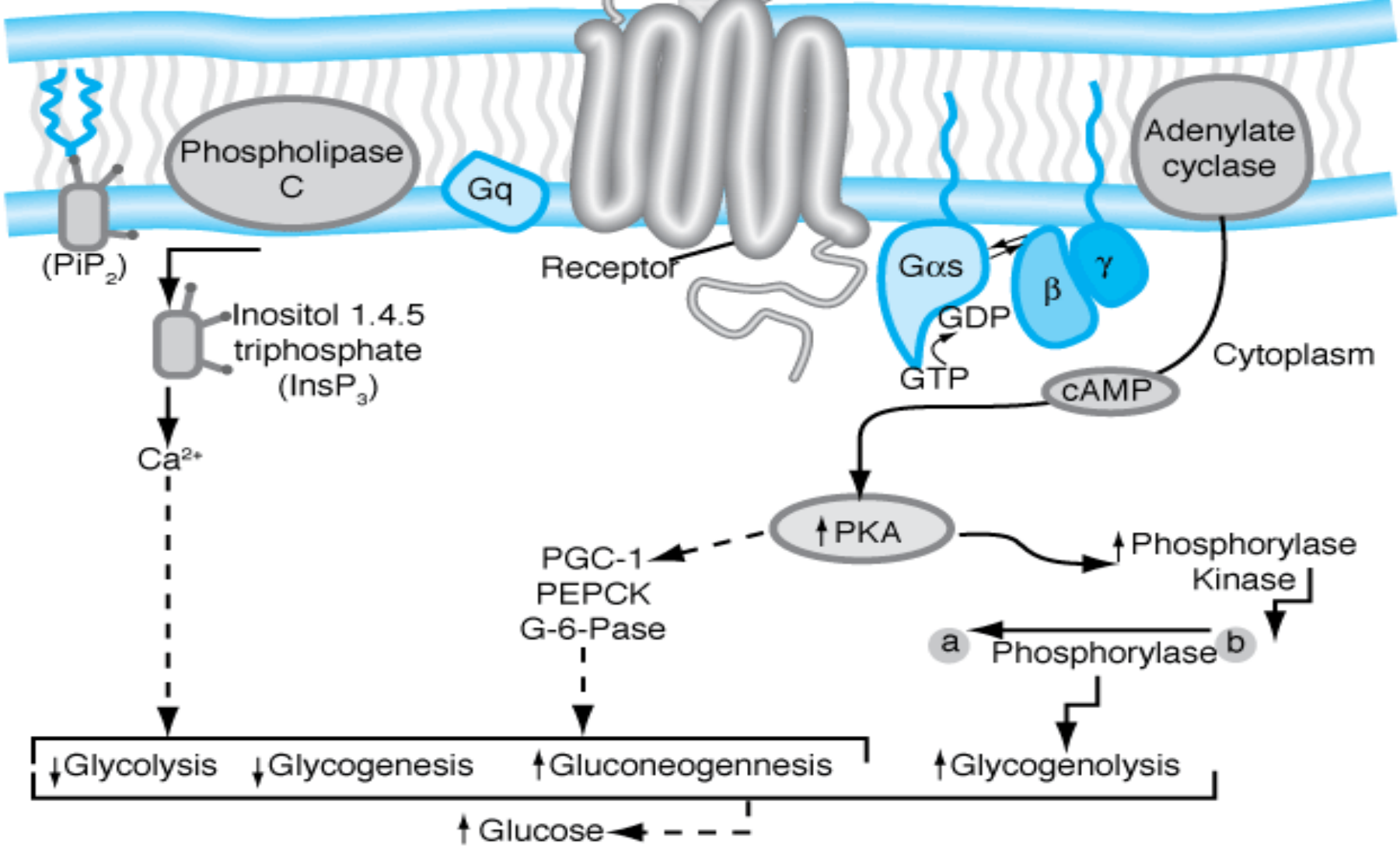
The major effects of glucagon on glucose metabolism are:

- Breakdown of liver glycogen (*glycogenolysis*)
- Increased *gluconeogenesis* in the liver.

Both of these effects greatly enhance the availability of glucose to the other organs of the body.

Glucagon receptor-mediated cellular effects

- Glucagon binds to G protein-coupled receptor (GPCR) on target cells → activates *adenylyl cyclase* → formation of *cAMP* → activates *protein kinase regulator protein* → activates *protein kinase* → activates *phosphorylase b kinase* → converts *phosphorylase b* into *phosphorylase a* → activation of enzymes responsible for control of glucose metabolism.
- The ultimate result is an increase in hepatic glucose production through increased gluconeogenesis and glycogenolysis.



Glucagon receptor-mediated cellular effects

G-6-Pase, glucose-6-phosphatase; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1, peroxisome proliferator-activated receptor-coactivator-1; PIP2, phosphatidylinositol 4,5-biphosphate.

How Glucagon Increases Gluconeogenesis?

- Glucagon increases the rate of AA uptake by the liver cells and their conversion to glucose by gluconeogenesis.
- This is achieved by activating multiple enzymes that are required for AA transport and gluconeogenesis, especially activation of the enzyme system for converting pyruvate to phosphoenolpyruvate, a rate-limiting step in gluconeogenesis.

Other Effects of Glucagon

- Glucagon *activates adipose cell lipase*, making increased quantities of FA available to the energy systems of the body.
- Glucagon also inhibits the storage of TG in the liver.
- Glucagon in very high concentrations also:
  - Enhances the strength of the heart.
  - Increases blood flow in some tissues, especially the kidneys.
  - Enhances bile secretion.
  - Inhibits gastric acid secretion.

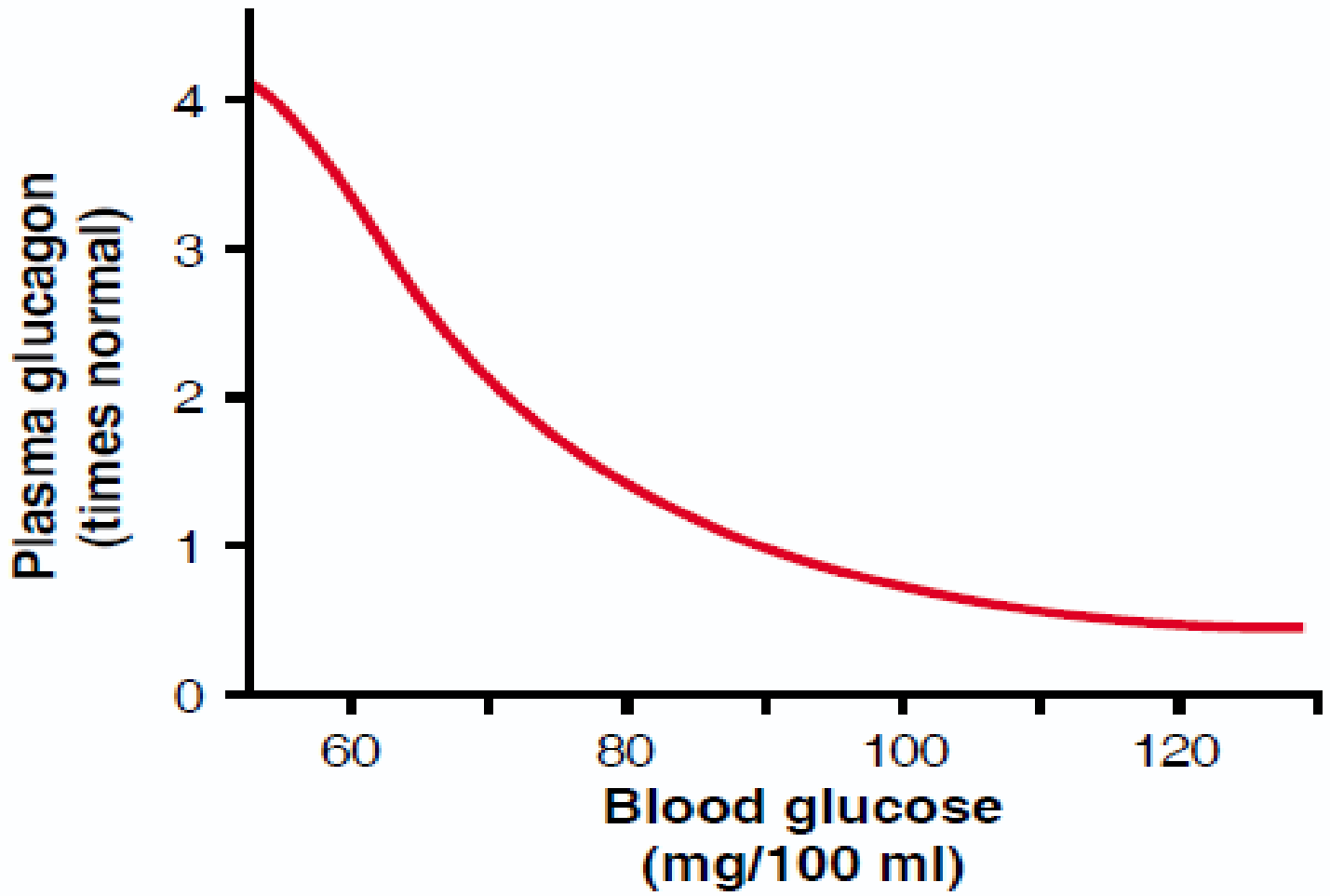
All these effects are probably of minimal importance in the normal function of the body.

Effects of Glucagon on Hepatic Glucose Metabolism

Effect on target enzyme	Metabolic response
Increased expression of glucose-6-phosphatase	Frees glucose to enter the circulation
Suppression of glucokinase	Decreases glucose entry into the glycolytic cascade
Phosphorylation (activation) of glycogen phosphorylase	Stimulates glycogenolysis
Inhibition of glycogen synthase	Inhibits glycogen synthesis
Stimulation of phosphoenolpyruvate carboxykinase expression	Stimulates gluconeogenesis
Inactivation of phosphofructokinase-2 (PFK-2) and activation of fructose-6-phosphatase. PFK-2 is the kinase activity and fructose-2,6-bisphosphatase (F-2,6-BPase) is the phosphatase activity of the bifunctional regulatory enzyme, phosphofructokinase-2/fructose-2,6-bisphosphatase (PFK-2/F-2,6-BPase).	Inhibits glycolysis Stimulates gluconeogenesis
Suppression of activity of the pyruvate kinase	Decreases glycolysis

Regulation of Glucagon Secretion

- A d*ecrease* in the blood glucose concentration to hypoglycemic levels can increase the plasma concentration of glucagon several fold. Conversely, increasing the blood glucose to hyperglycemic levels decreases plasma glucagon.
- High concentrations of AA as occur in the blood after a protein meal *stimulate* the secretion of glucagon.
- In exhaustive exercise, the blood concentration of glucagon often increases 4-5 folds due to increased circulating AA and ß-adrenergic stimulation of the islets of Langerhans.



Approximate glucagon secretion at different plasma glucose levels

Somatostatin

- It is secreted from the *δ cells* of the islets of Langerhans.
- It is a polypeptide containing only 14 amino acids.
- It has an extremely short half-life of only 3 minutes in the circulating blood.
- It has the same chemical substance as *growth hormone inhibitory hormone*, which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

Stimuli for Somatostatin Secretion

Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include:

- Increased blood glucose
- Increased amino acids
- Increased fatty acids
- Increased concentrations of several of the GI hormones released from the upper GIT in response to food intake.

Functions of Somatostatin

Somatostatin has multiple inhibitory effects as follows:

1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon.

2. Somatostatin decreases the motility of the stomach, duodenum, and gallbladder.

3. Somatostatin decreases both secretion and absorption in the GIT.

The principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood. At the same time somatostatin decreases the utilization of the absorbed nutrients by the tissues, thus making food available over a longer period of time.

Amylin (islet amyloid polypeptide)

- It is a 37–amino acid peptide hormone that belongs to the calcitonin family.
- It is synthesized as a small precursor, undergoes post-translational modification (amidation), is stored in -granules, and is released along with insulin and C-peptide.
- Plasma amylin concentrations increase after a meal or glucose infusion.

Functions of Amylin

- It appears to work with insulin to regulate plasma glucose concentrations in the bloodstream,
- It suppresses the postprandial secretion of glucagon
- It slows gastric emptying.
- In muscle, amylin opposes glycogen synthesis and activates glycogenolysis and glycolysis, thereby increasing lactate production.
- Circulating amylin is increased in obesity, hypertension, and gestational diabetes;

It is low or absent in type 1 diabetes mellitus.

In type 2 diabetes, the secretion of amylin is impaired before that of insulin.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