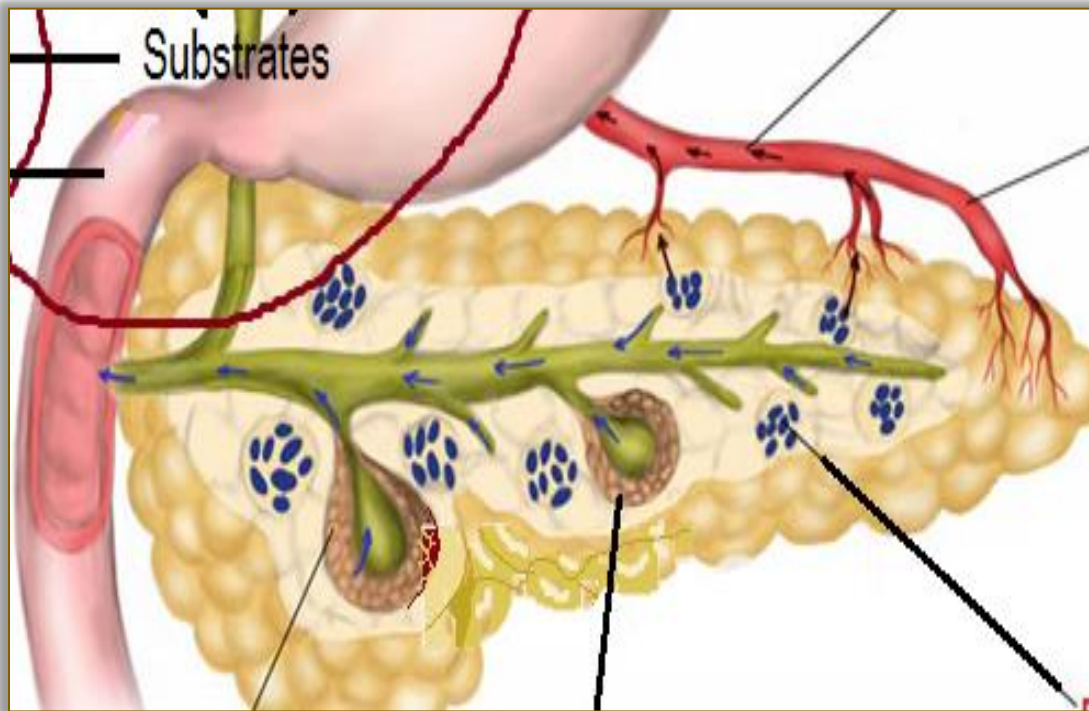


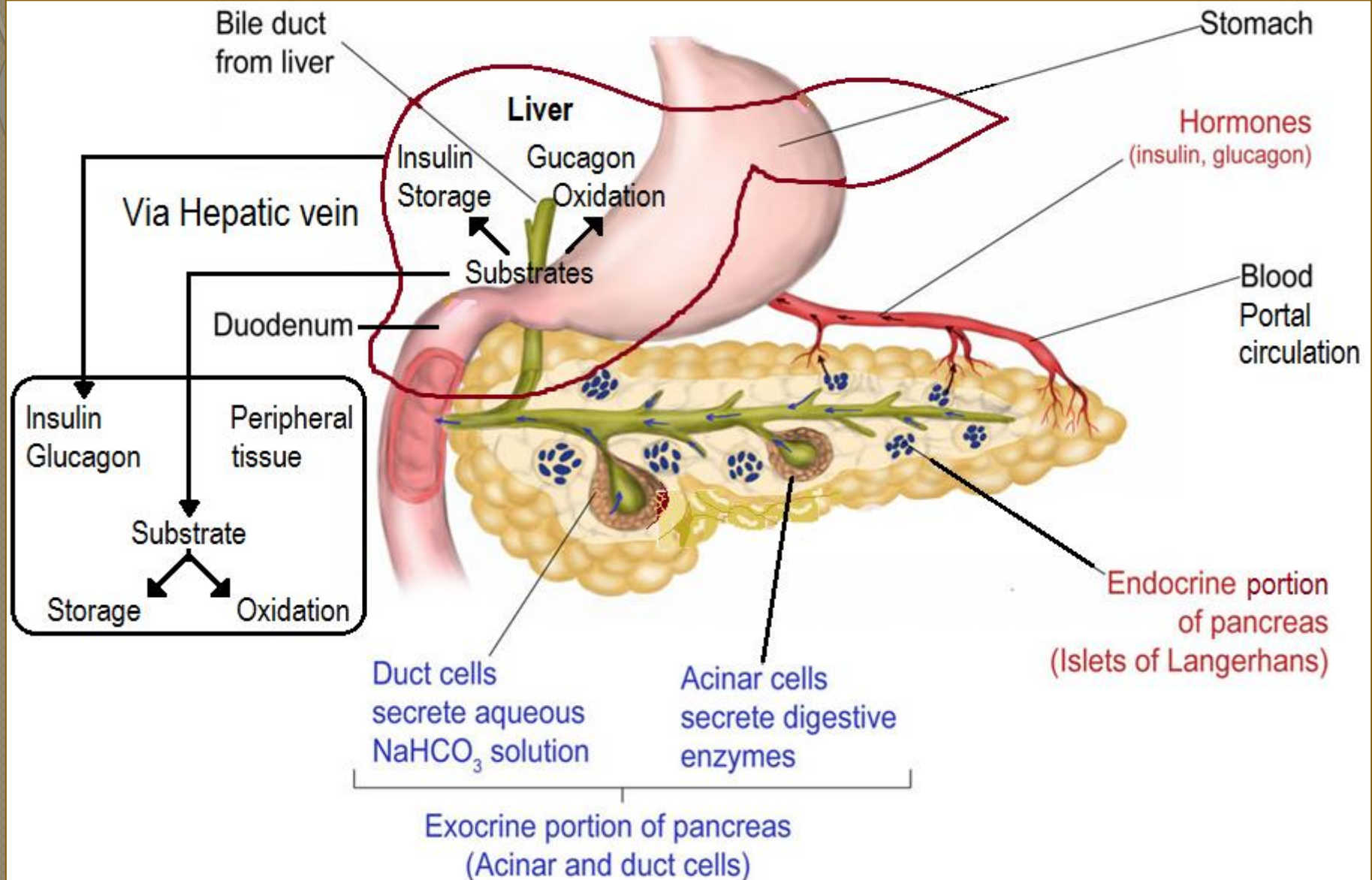
ENDOCRINE PANCREAS



Dr.Yashoda Kattimani
Physiology
MGMMCNM

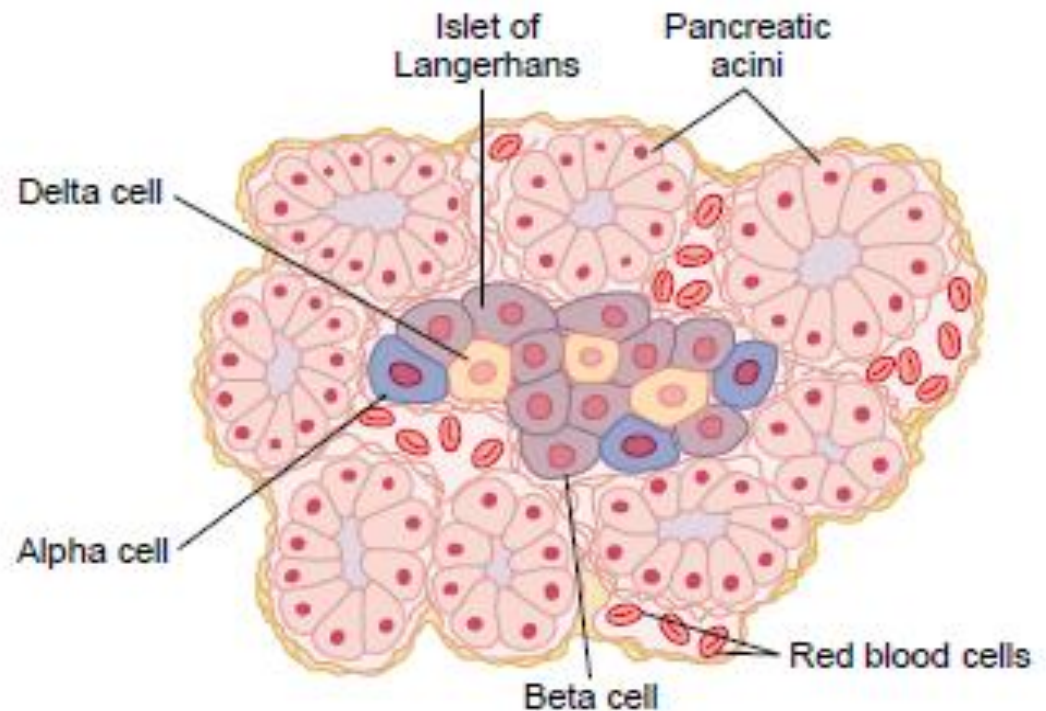
- 
- **Pancreas**-dual gland with exo- & endocrine functions
 - Origin: Endoderm of foregut
 - **Endocrine** – Islet cells: Spread all-over, mainly in tail (Paul Langerhans, 1869)
 - Produces 2 powerful hormones
 - insulin
 - glucagon
 - Also GI-neuropeptides, & protein hormone somatostatin

INTERLOCKED ENDO- & EXOCRINE FUNCTIONS



Islet cells of Langerhans

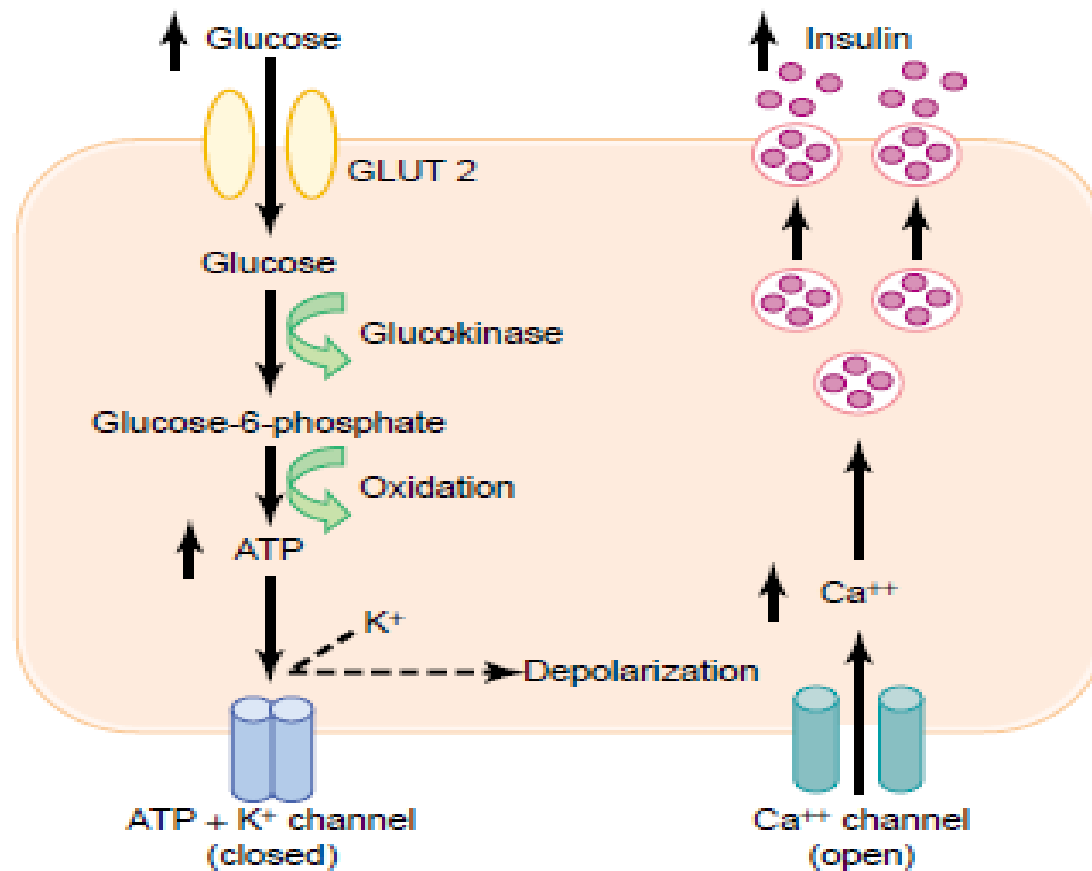
- **Islet Cell-Types:**
 - **α - cell** (15–25%): Glucagon
 - **β -cell** (70–80%): Insulin
 - **δ -cell:** Somatostatin
 - **F-cells:** GI-neuropeptides (e.g., gastrin)



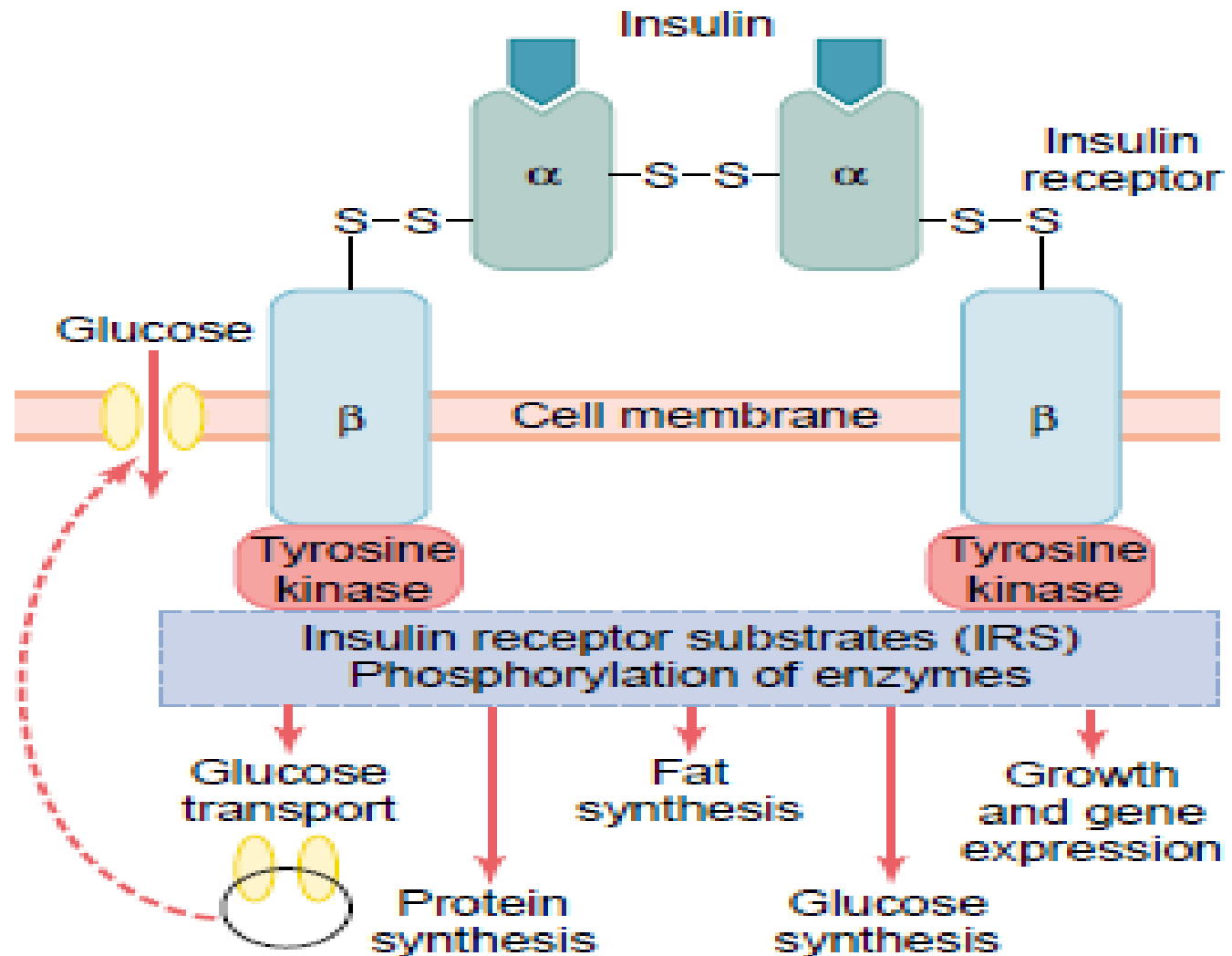
Chemistry & synthesis- Insulin

- Historical Milestones:
 - 1921: Banting & Best (Toronto)
 - 1922: Clinical use of pure extract of insulin
 - Detailed 'AA' structure of insulin by Sanger (1952) & 3D-structure by Dorothy (1969)
- Synthesis :
 - *Insulin preprohormone*
 - *Proinsulin*
 - *Insulin*
- *Circulates in unbound form*
- *Degraded by insulinase in liver, lesser extent in kidney & muscle*
- **Note:**
 - Human insulin have virtually replaced animal insulin for the treatment of DM
 - Production by *recombinant DNA technique*

Mechanisms of Insulin Secretion



Activation of target cell - Insulin receptor



FUNCTIONS & ACTION OF INSULIN

- Main target organs:
 - Liver,
 - Muscle,
 - Adipocyte
- Actions mainly on:
 - **Cell membrane & metabolism**
- Strongly **anabolic**:
 - Thrust to
 - ❖ **Facilitate fuel storage**
 - ❖ **Inhibit release of substrates**

Effect of Insulin on Carbohydrate Metabolism

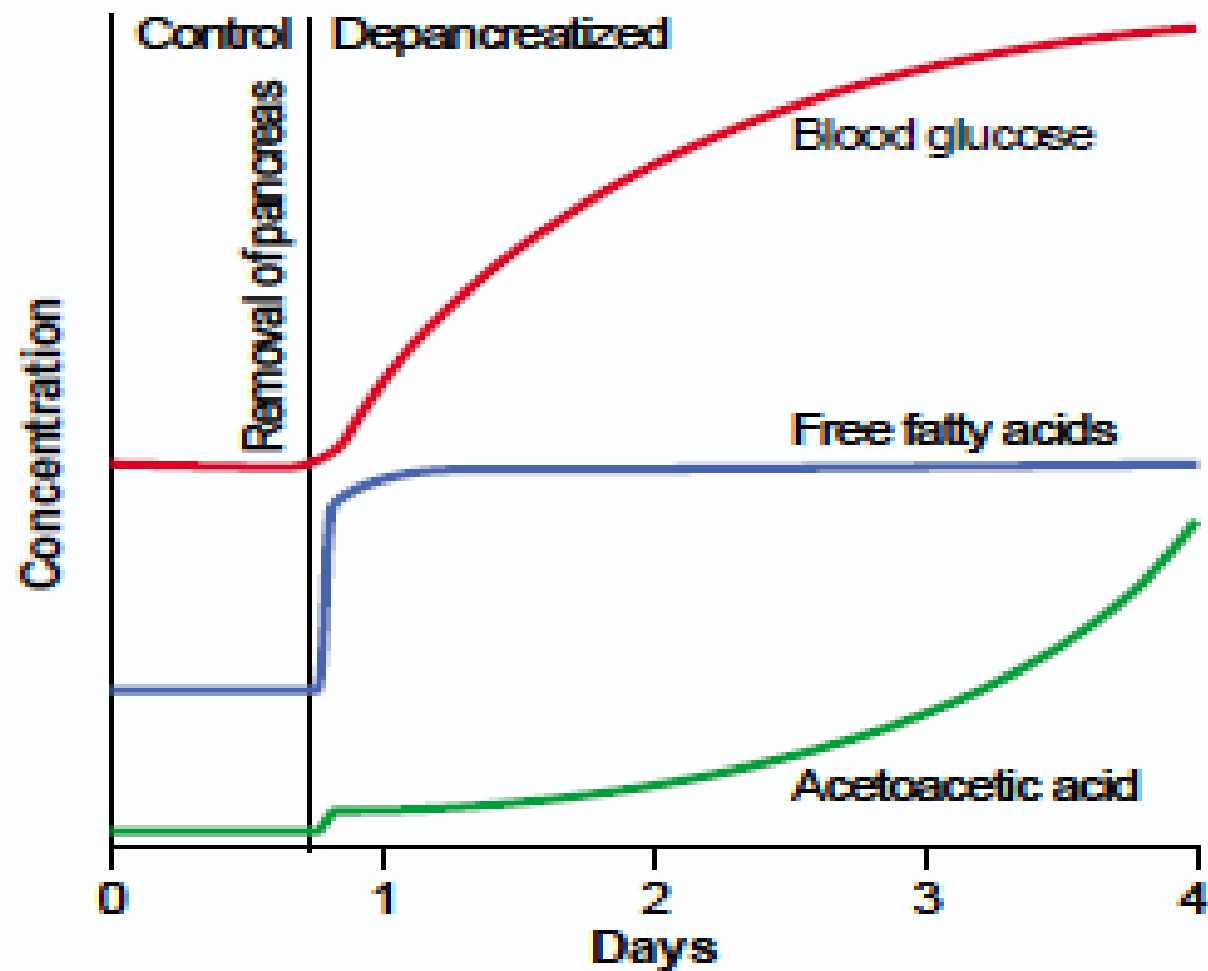
- Insulin Promotes **Muscle** Glucose Uptake and Metabolism
- Storage of Glycogen in Muscle.
- Insulin Promotes **Liver** Uptake, Storage, and Use of Glucose
- *inactivates liver phosphorylase,*
- *increasing the activity of the enzyme glucokinase,*
- increases the activities of the enzymes that promote glycogen synthesis
- Insulin Promotes Conversion of Excess Glucose into Fatty Acids and Inhibits Gluconeogenesis in the **Liver**

Effect of Insulin on Fat Metabolism

- **Insulin Promotes Fat Synthesis and Storage**
- *Insulin increases the transport of glucose into the **liver** cells.*
- *Most of the fatty acids are then synthesized within the liver itself and used to form triglycerides*
- *Transported to adipose tissue*

- 
- **Role of Insulin in Storage of Fat in the Adipose Cells.**
 - *Insulin inhibits the action of hormone-sensitive lipase.*
 - *Insulin promotes glucose transport through the cell membrane into the fat cells*
 - *Conversion of glucose onto glycerol*

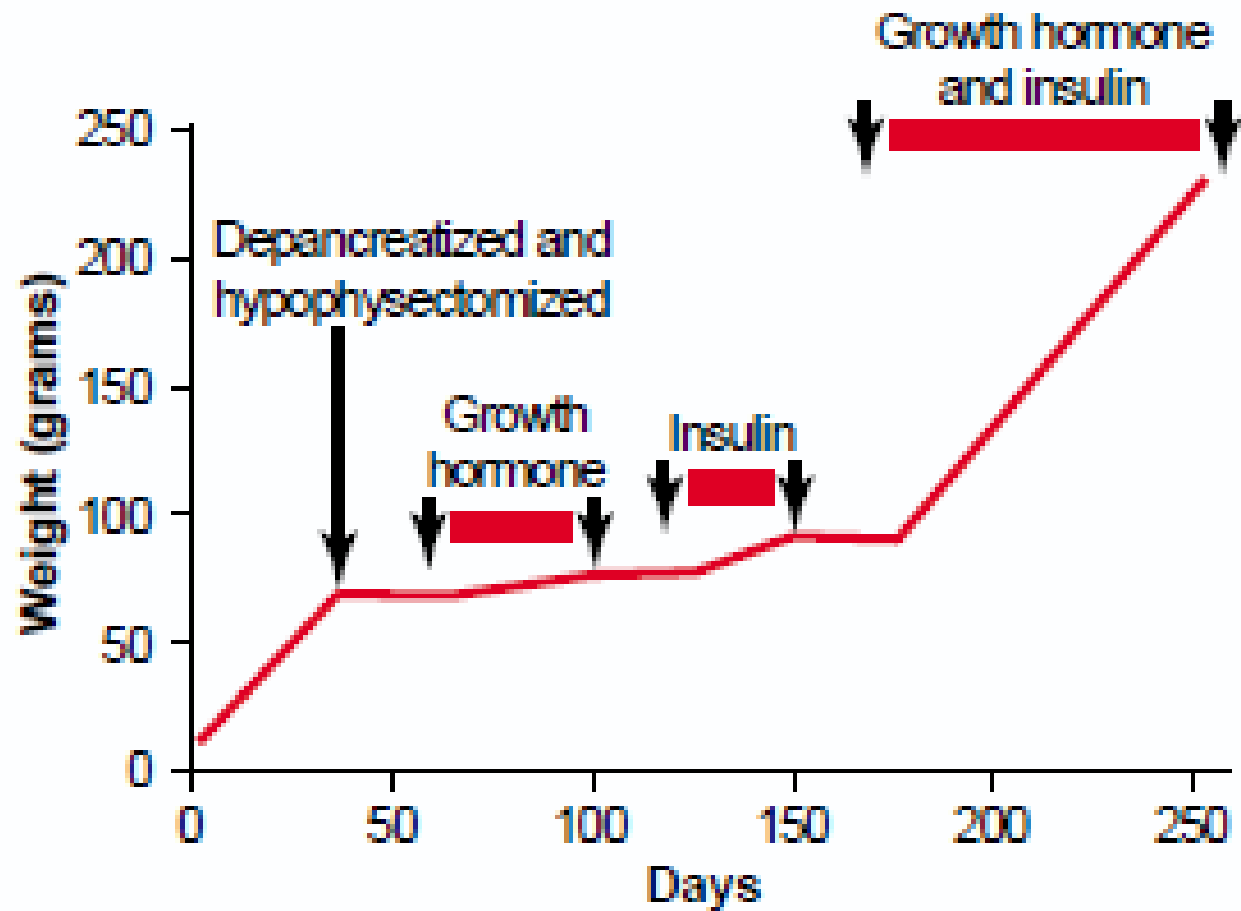
- 
- Insulin Deficiency Increases Use of Fat for Energy
 - Insulin Deficiency Causes Lipolysis of Storage Fat and Release of Free Fatty Acids.
 - Insulin Deficiency Increases Plasma Cholesterol and Phospholipid Concentrations.
 - Excess Usage of Fats During Insulin Lack Causes Ketosis and Acidosis.
 - Insulin Lack Causes Protein Depletion and Increased Plasma Amino Acids.





Effect of Insulin on Protein Metabolism and on Growth

- Insulin Promotes Protein Synthesis and Storage.
- Insulin increases AA uptake by tissues.
- Insulin and Growth Hormone Interact Synergistically to Promote Growth.



OVERALL EFFECTS OF INSULIN

- **Hypoglycemic:**

Promotes:

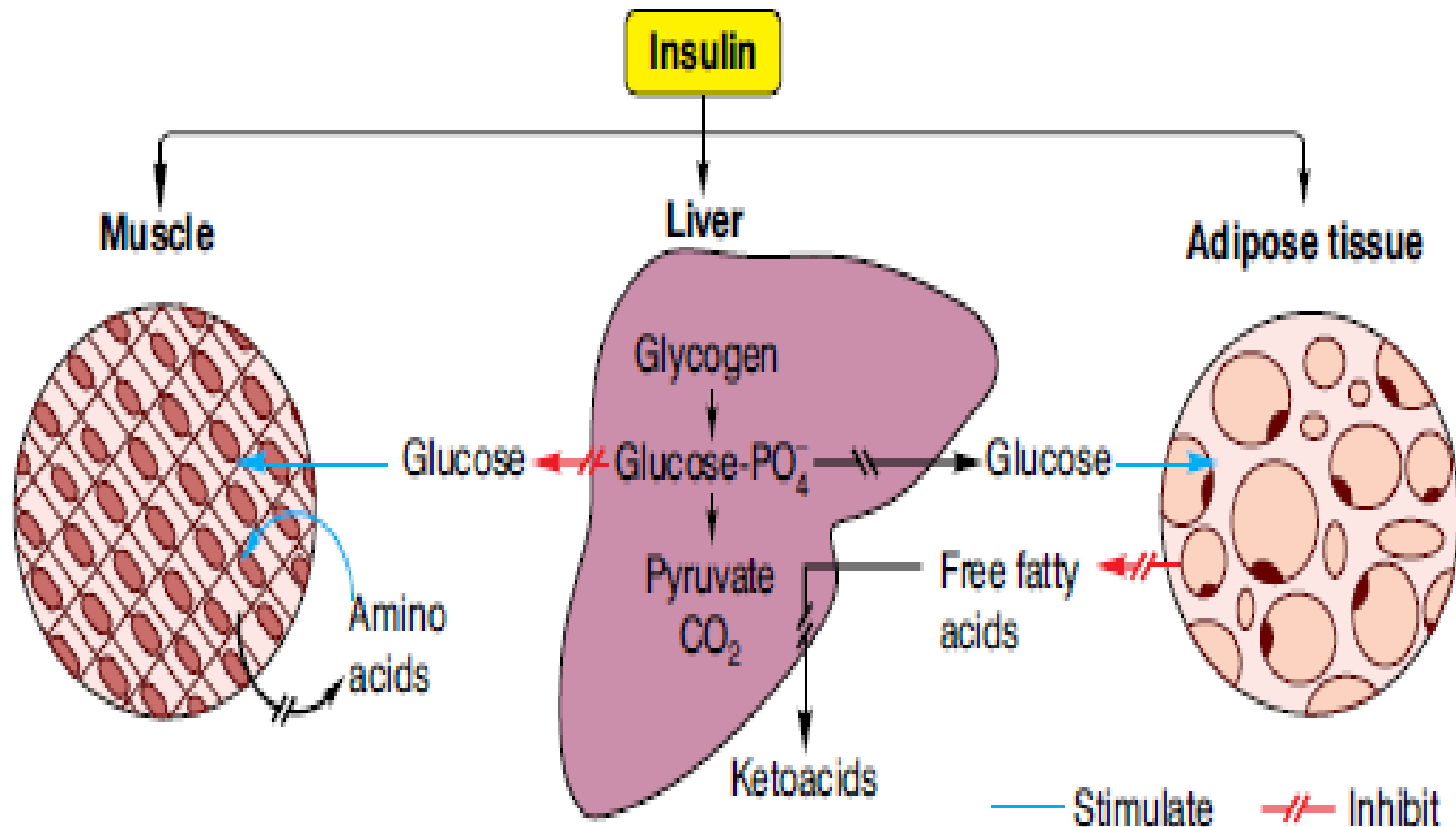
- Glucose uptake & catabolism,
- Glycogen synthesis → liver & muscle (**glycogenesis**),
- Inhibit **glycogenolysis & gluconeogenesis**

- **Anabolic:**

Promotes:

- Glycogenesis,
- 'AA' uptake, ↓ breakdown & ↑ synthesis of proteins
- FFA & TGL synthesis

Principle Target Of Insulin For Its Metabolic Effects



Factors and Conditions That Increase or Decrease Insulin Secretion

Increase Insulin Secretion

- Increased blood glucose
- Increased blood free fatty acids
- Increased blood amino acids
- Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)
- Glucagon, growth hormone, cortisol
- Parasympathetic stimulation; acetylcholine
- β -Adrenergic stimulation
- Insulin resistance; obesity
- Sulfonylurea drugs (glyburide, tolbutamide)

Decrease Insulin Secretion

- Decreased blood glucose
- Fasting
- Somatostatin
- α -Adrenergic activity
- Leptin

Glucagon

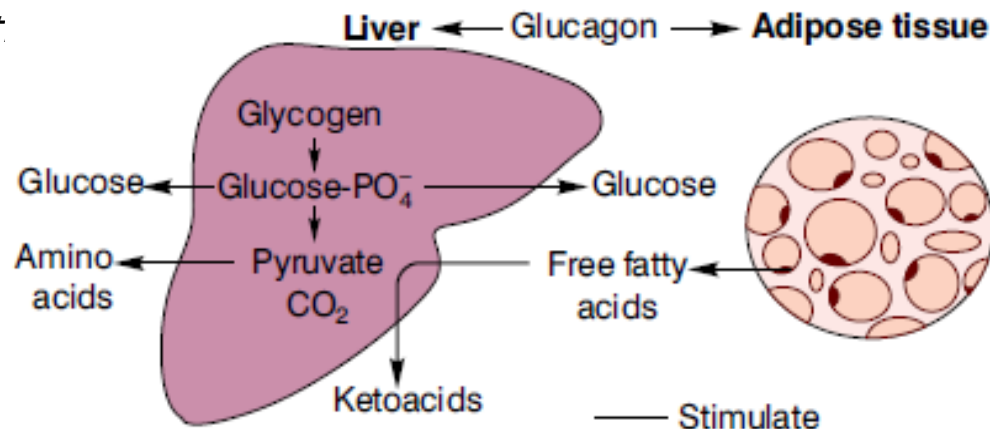
- secreted by the *alpha cells of the* islets of Langerhans when the blood glucose concentration falls,
- *Hyperglycemic hormone.*

ACTIONS & FUNCTIONS OF GLUCAGON

- Anti-insulinic & hyperglycemic
 - Other anti-insulinic hormones: Cortisol, GH, thyroid, E/NE, FFA, insulin-Ab
- Mechanism of action:
 - $R + G\text{-prot} \rightarrow \uparrow cAMP \text{ \& } Ca^{2+}$
- Secretion & action of glucagon & insulin are reciprocal (i.e., when one is needed, the other is not)

Final Goal $\rightarrow$ Glucose Homeostasis

- Calorigenic actions
 - *Hepatic glycogenolysis.*
 - *Neoglucogenesis in muscles*
 - *Adipocytes' lipolysis*
 - *Stimulate secret.*



Effects on Glucose Metabolism

Glucagon Causes *Glycogenolysis* and Increased Blood Glucose Concentration.

1. Glucagon activates *adenylyl cyclase* in the hepatic cell membrane,
2. Which causes the formation of *cyclic adenosine monophosphate*,
3. Which activates *protein kinase regulator protein*,
4. Which activates *protein kinase*,
5. Which activates *phosphorylase b kinase*,
6. Which converts *phosphorylase b* into *phosphorylase a*,
7. Which promotes the degradation of glycogen into glucose-1-phosphate,
8. Which then is dephosphorylated; and the glucose is released from the liver cells.

- 
- Glucagon Increases Gluconeogenesis.
 - Other Effects of Glucagon
 - -*activates adipose cell lipase,*
 - -enhances the strength of the heart;
 - - increases blood flow in some tissues, especially the kidneys;
 - - enhances bile secretion; and
 - -inhibits gastric acid secretion.

Regulation of Glucagon Secretion

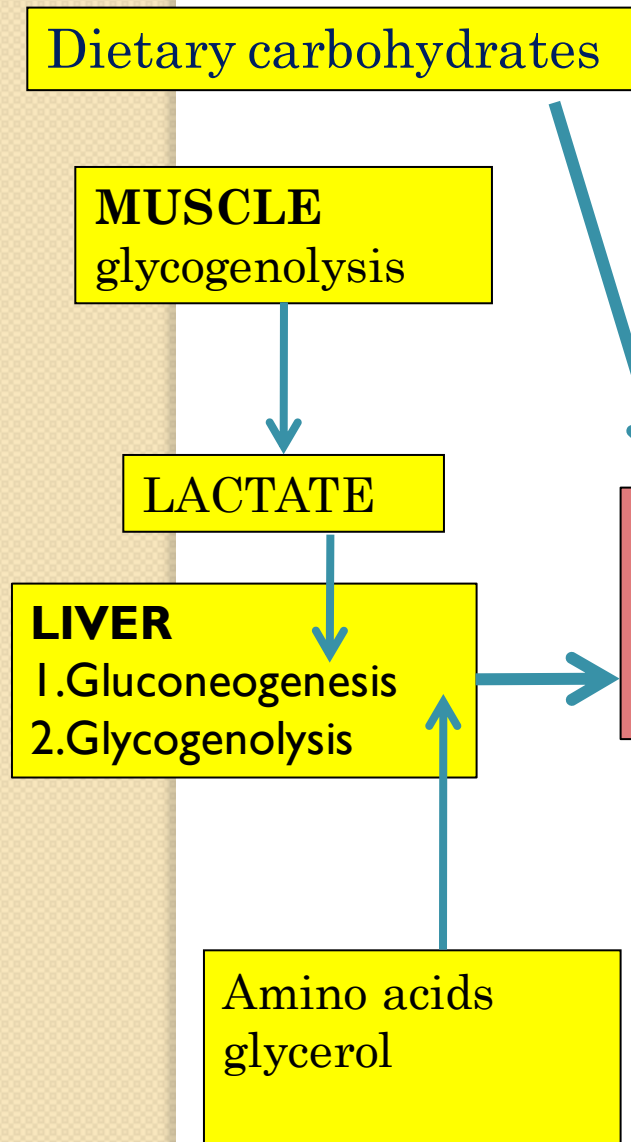
- Increased Blood Glucose Inhibits Glucagon Secretion
- Increased Blood Amino Acids Stimulate Glucagon Secretion.
- Exercise Stimulates Glucagon Secretion.

REGULATION OF GLUCAGON SECRETION

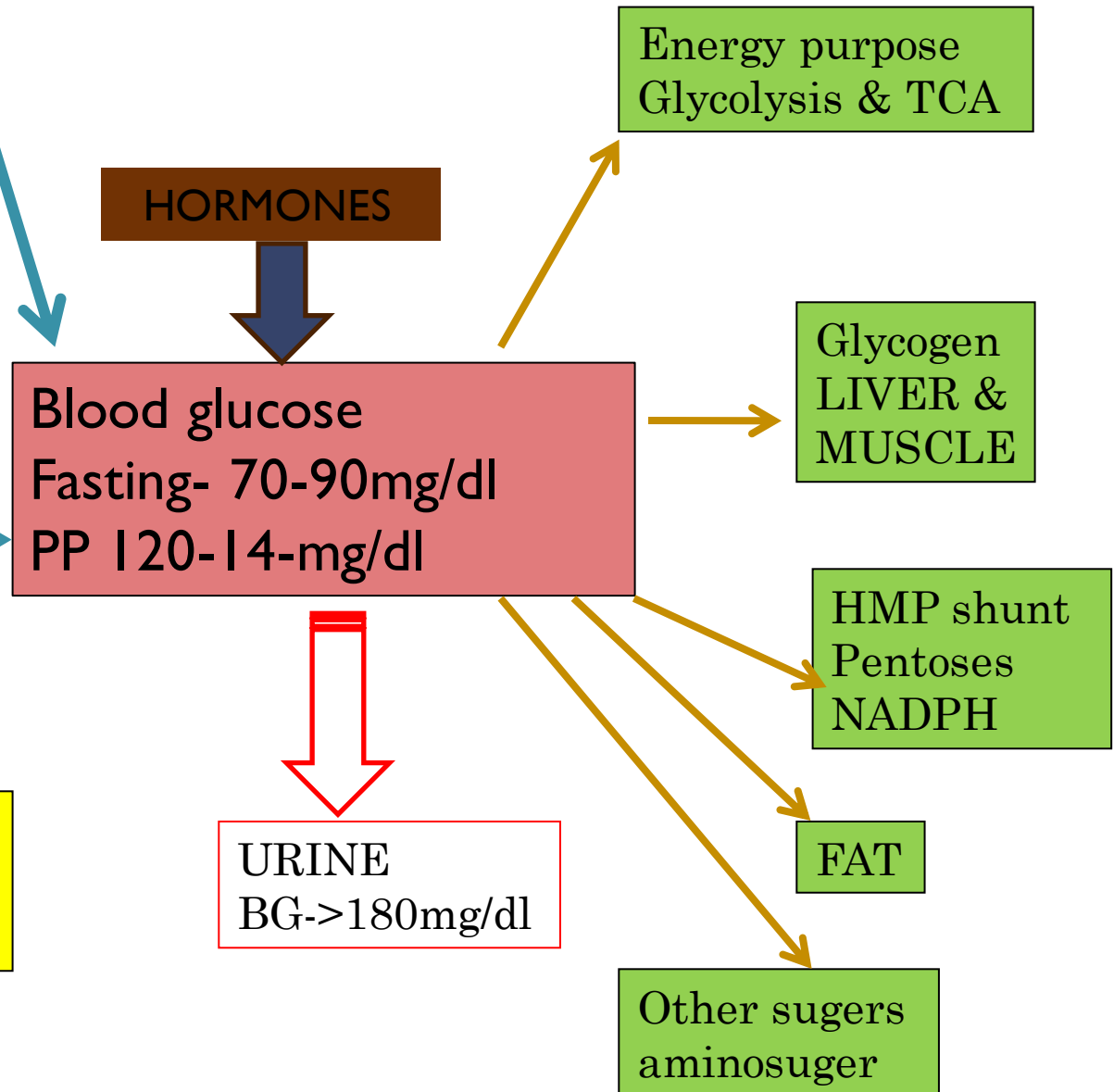
- Substrate Regulation:
 - Stimulatory: Fall in plasma 'G' (< 100 mg/dl) or rise in 'AA'
 - Inhibitory: FFA
- Gut-Hormones are stimulatory
- Paracrine influence of insulin & somatostatin → inhibitory
- SNS: stimulatory
- Other Pancreatic Hormones:
 - Somatostatin → hypothalamic peptide mainly to inhibit GH, insulin & glucagon.
 - Pancreatic polypeptides
- **Somatostatin Inhibits Glucagon and Insulin Secretion**

BLOOD GLUCOSE HOMEOSTASIS

SOURCES



UTILIZATION



Liver—as glucostat and buffer system

- The various glucoregulatory hormones of the body are designed to maintain circulating glucose concentrations in a relatively narrow range.
- In the fasting state, glucose leaves the circulation at a constant rate.
- To keep pace with glucose disappearance, endogenous glucose production is necessary.
- For all practical purposes, the sole source of endogenous glucose production is the liver

In the liver ,

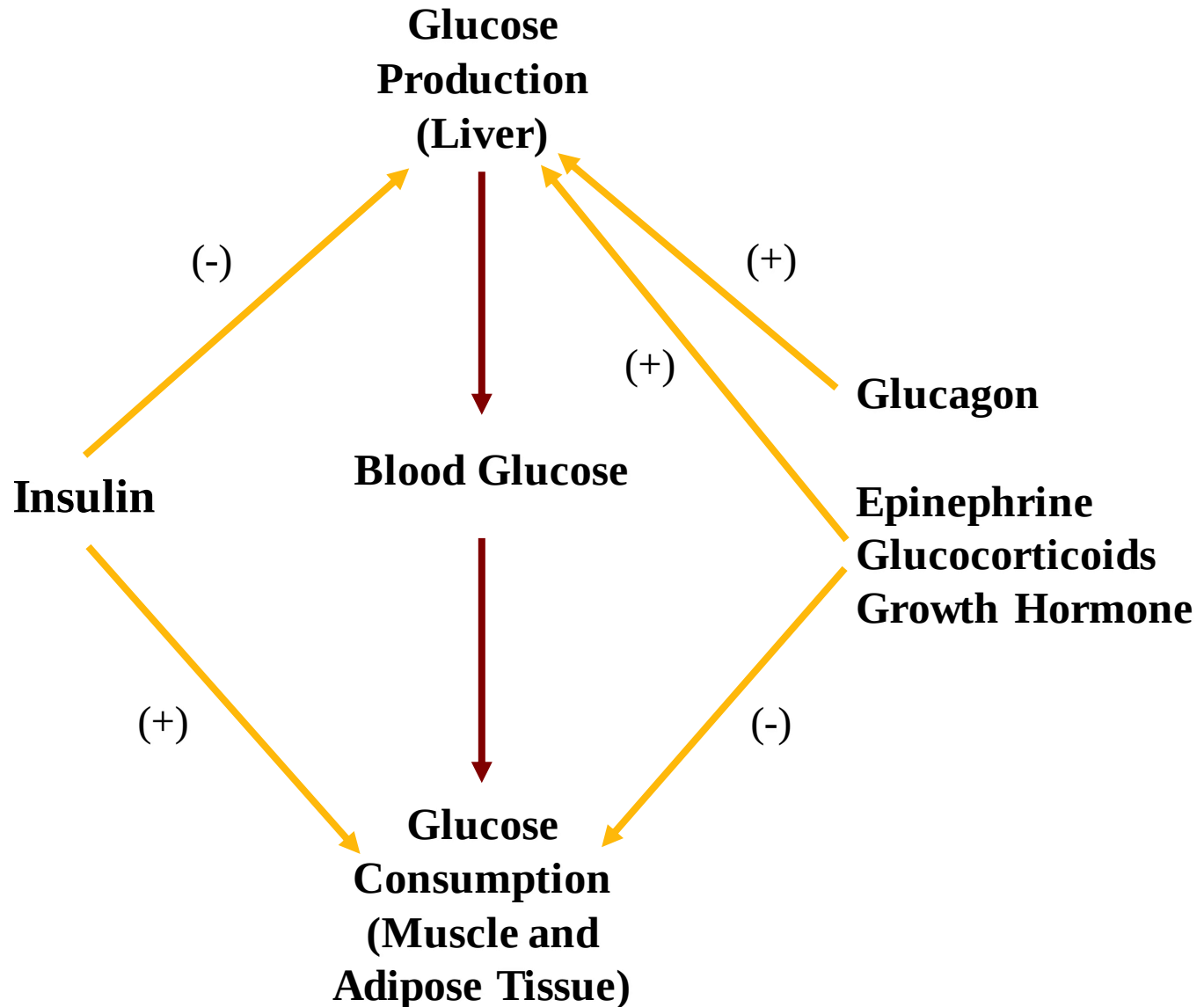
there is net uptake of glucose when plasma glucose is high

there is net discharge when plasma glucose is low

Thus functioning a sort of “glucostat”
maintaining constant glucose level.

But this function is not automatic, is
affected by various hormones.

Hormonal Interactions in the Maintenance of Blood Glucose Concentration



APPLIED PHYSIOLOGY: *DIABETES MELLITUS*

Diabetes = 'siphon/running through' *Mellitus* = 'sweet'

Conceptually, *madhumeha* 'melting of body-tissue & excretion in urine'

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin

- **Characteristics**

- Hyperglycemia
- Glycosuria

- **Types**

- Primary-DM:
 - ❖ Type 1 (IDDM)
 - ❖ Type 2 (NIDDM)

- **Symptoms**

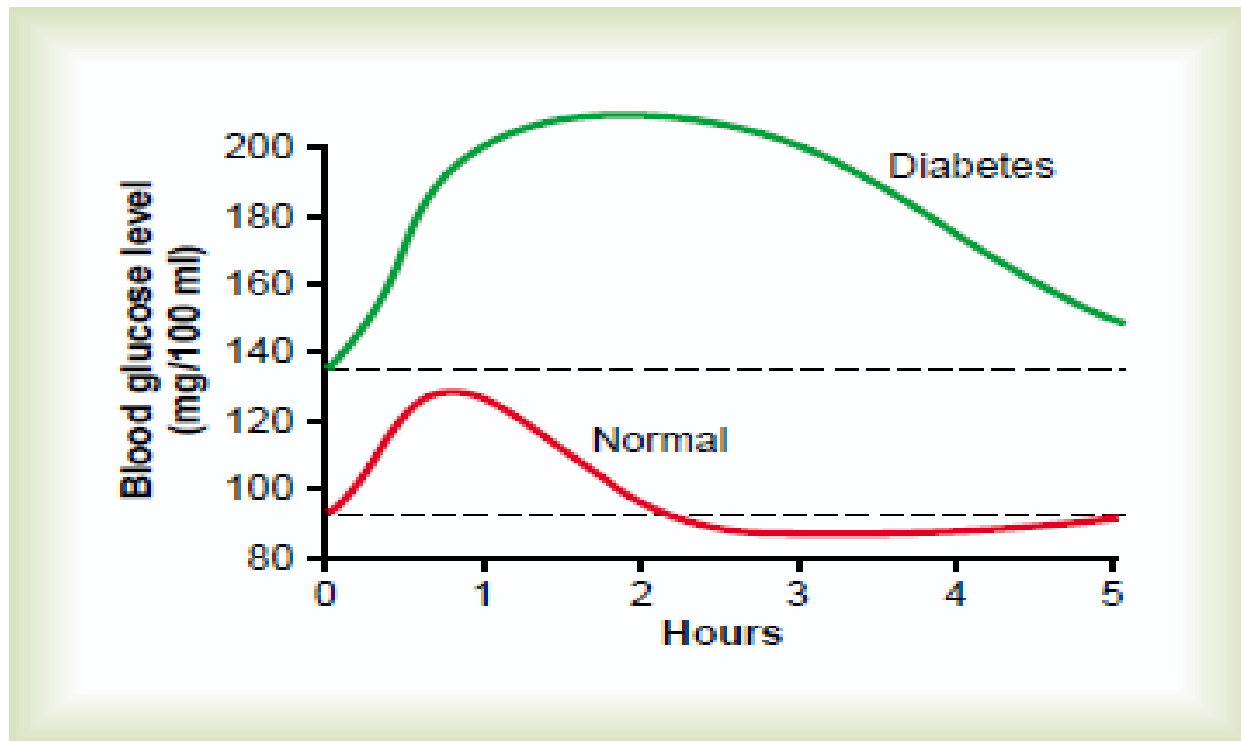
- Primarily 3-Ps:
 - ❖ *Polyuria*,
 - ❖ *Polydipsia*
 - ❖ *Polyphagia*
 - ❖ *Glycosuria, body-wasting*

- **Diagnostic Tests**

- FBG & PPBG ,GTT: For detection of hyperglycemia & glycosuria
- Serum insulin levels
- Others, e.g., HbA₁C, lipid profile etc.

- **Treatment Strategy**

- Insulin,Diet, change in lifestyle, exercise & drugs



Some Causes of Insulin Resistance

- **Obesity/overweight** (especially excess visceral adiposity)
- Excess glucocorticoids (Cushing's syndrome or steroid therapy)
- Excess growth hormone (acromegaly)
- Pregnancy, **gestational diabetes**
- **Polycystic ovary disease**
- Lipodystrophy (acquired or genetic; associated with lipid accumulation in liver)
- **Autoantibodies to the insulin receptor**
- Mutations of insulin receptor
- Mutations of the peroxisome proliferators' activator receptor γ (PPAR γ)
- Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
- Hemochromatosis (a hereditary disease that causes tissue iron accumulation)

Table 78–3

Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

Feature	Type I	Type II
Age at onset	Usually <20 years	Usually >30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin