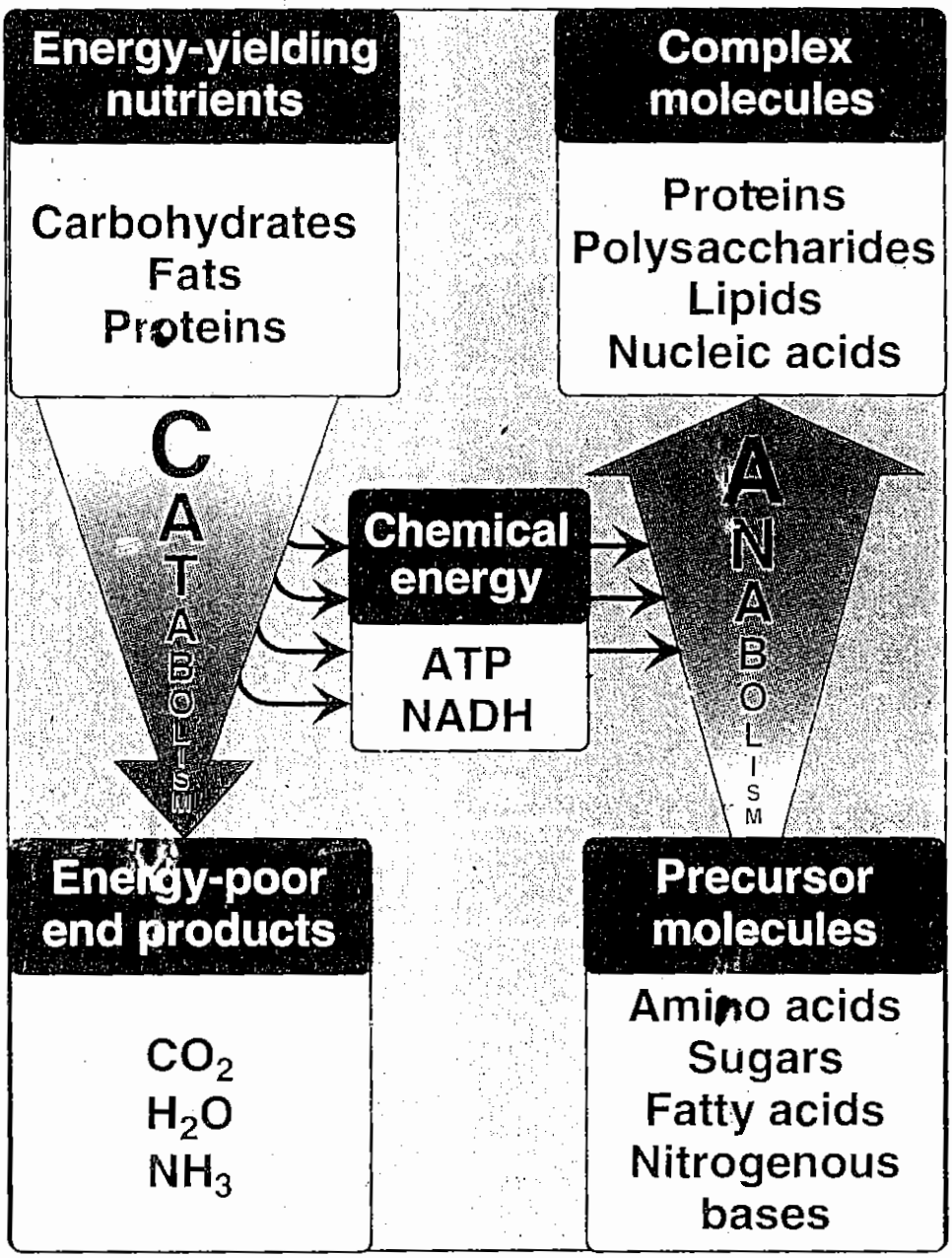
GLYCOLYSIS

- INTRODUCTION



Regulation of Metabolism:-

- Signals from within the cell
- Communication between cells (Intercellular)
- SECOND MESSENGER SYSTEMS
  - Ca^{2+}/phosphatidylinositol system
  - Adenylcyclase system

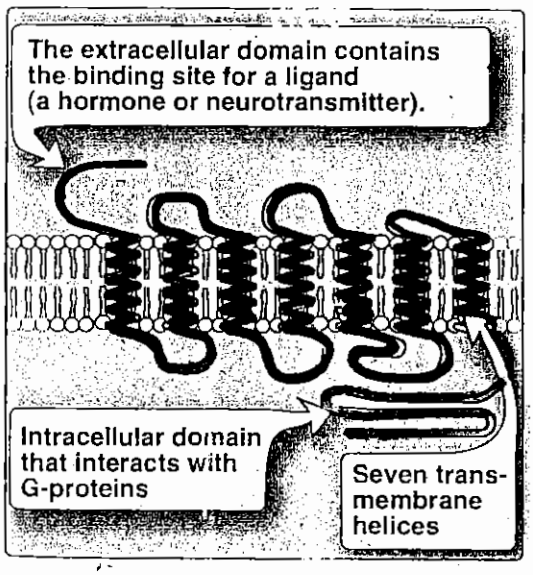


Figure 8.6
Structure of a typical membrane receptor.

- Adenyl Cyclase

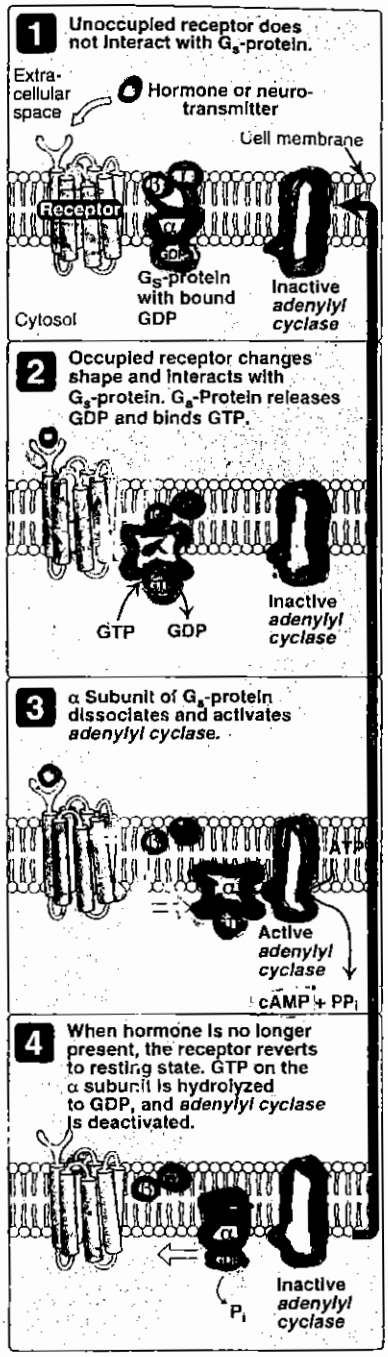
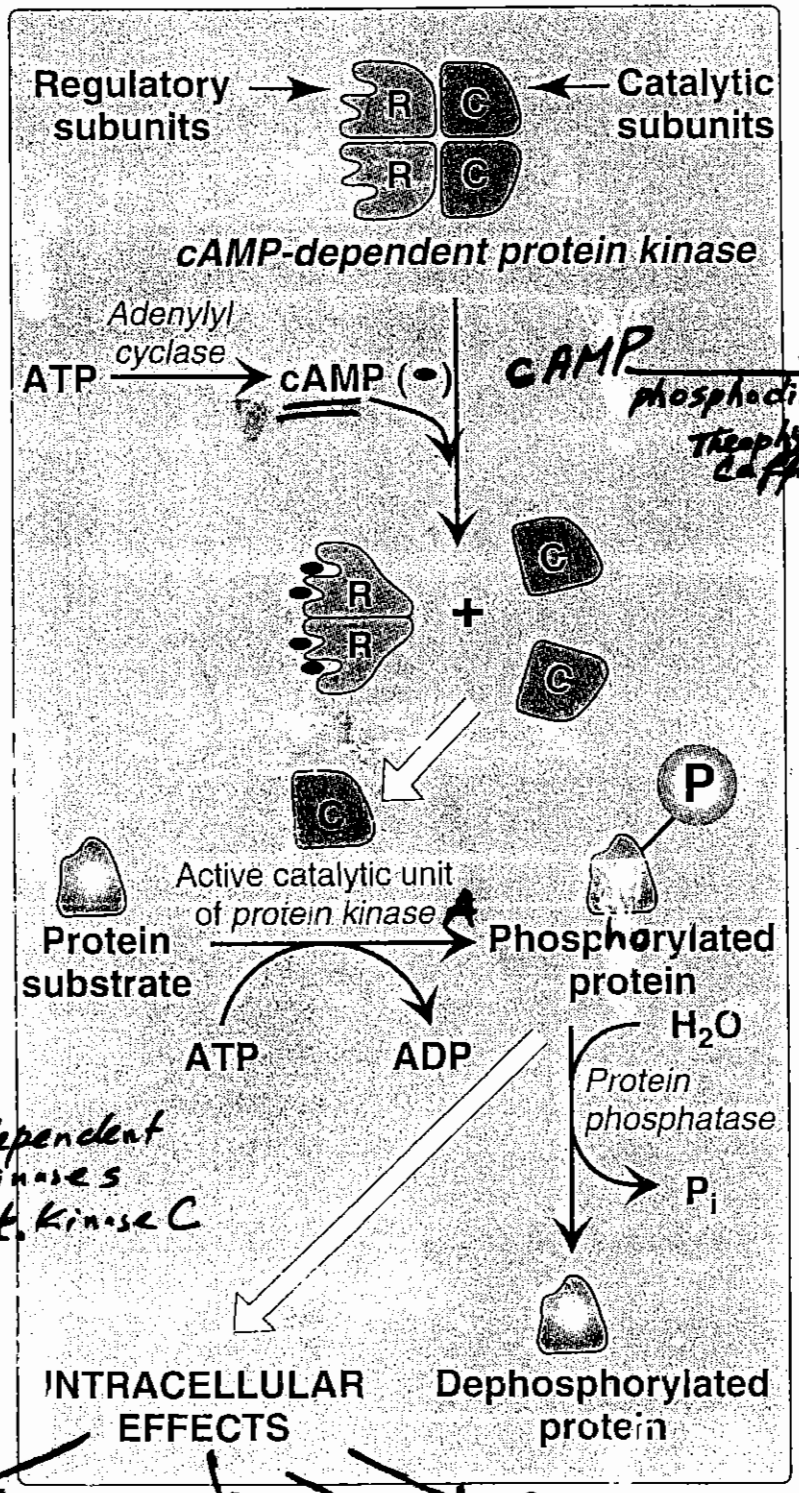


Figure 8.7
The recognition of chemical signals by certain membrane receptors triggers an increase (or, less often, a decrease) in the activity of *adenylyl cyclase*.

Actions of cAMP



- cAMP-independent protein kinases e.g. Prot. Kinase C

bind to promotor regions of DNA

Cells ion channels

Inhibited enzymes

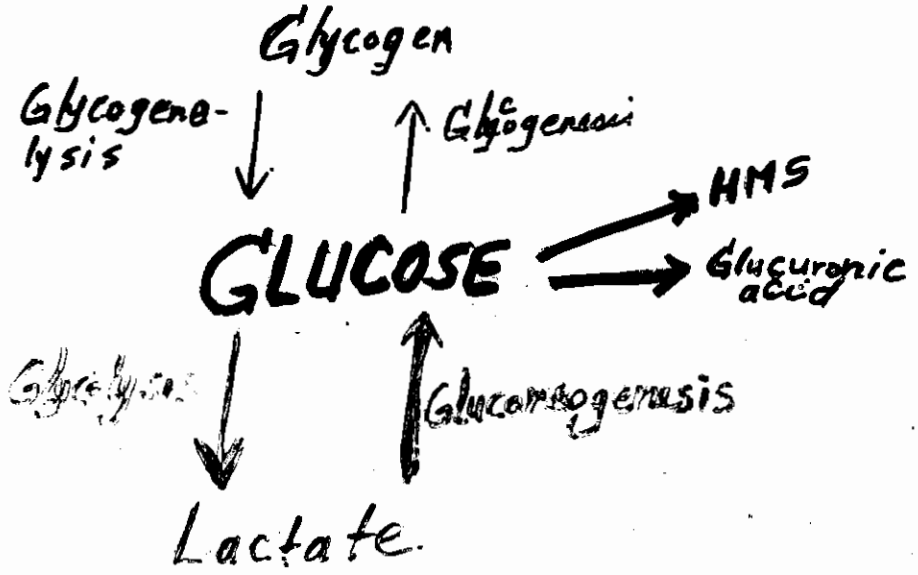
Activated enzymes

CARBOHYDRATE METABOLISM

- OBJECTIVE :-

- Utilization of Glu → Energy
- Non-Carbohydrate → Glu
- Storage of Glu → Glycogen
- Release of Glu from Glycogen
- HMS (PPP) → NADPH → GSH
- Glucuronic acid → Drug metabolism
- Interconversion of Sugar

- Over-all Picture :-

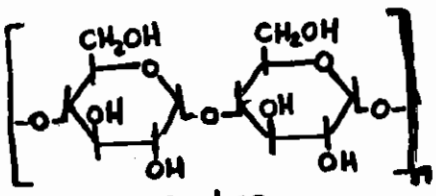


Dietary Carbohydrates :-

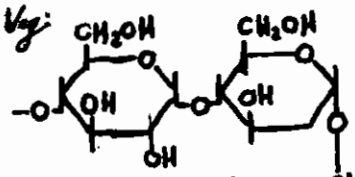
- → 40 – 50% of Caloric intake
- 60% of Carbohydrate → STARCH
- Sucrose, small ammount of Fru, Glu in → fruit, honey, Veg; Lactose (animal)

No sp. sugar required

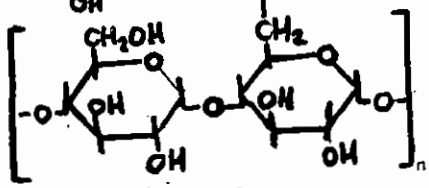
Glu ⟷ all other sugars



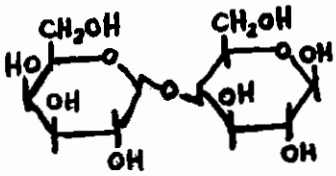
Amylose



STARCH

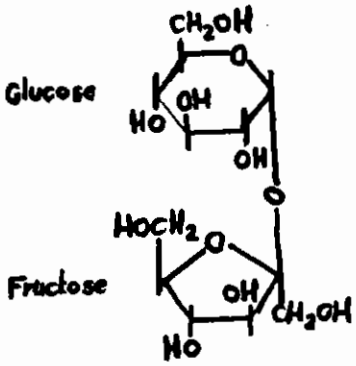


Amylopectin

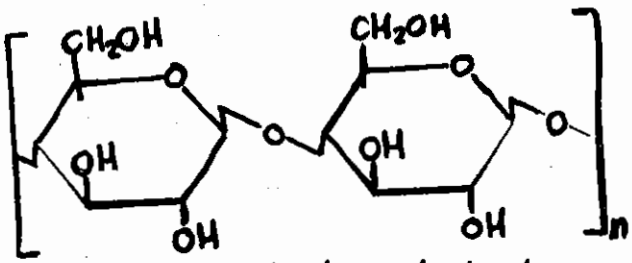


Galactose Glucose

Lactose



Sucrose

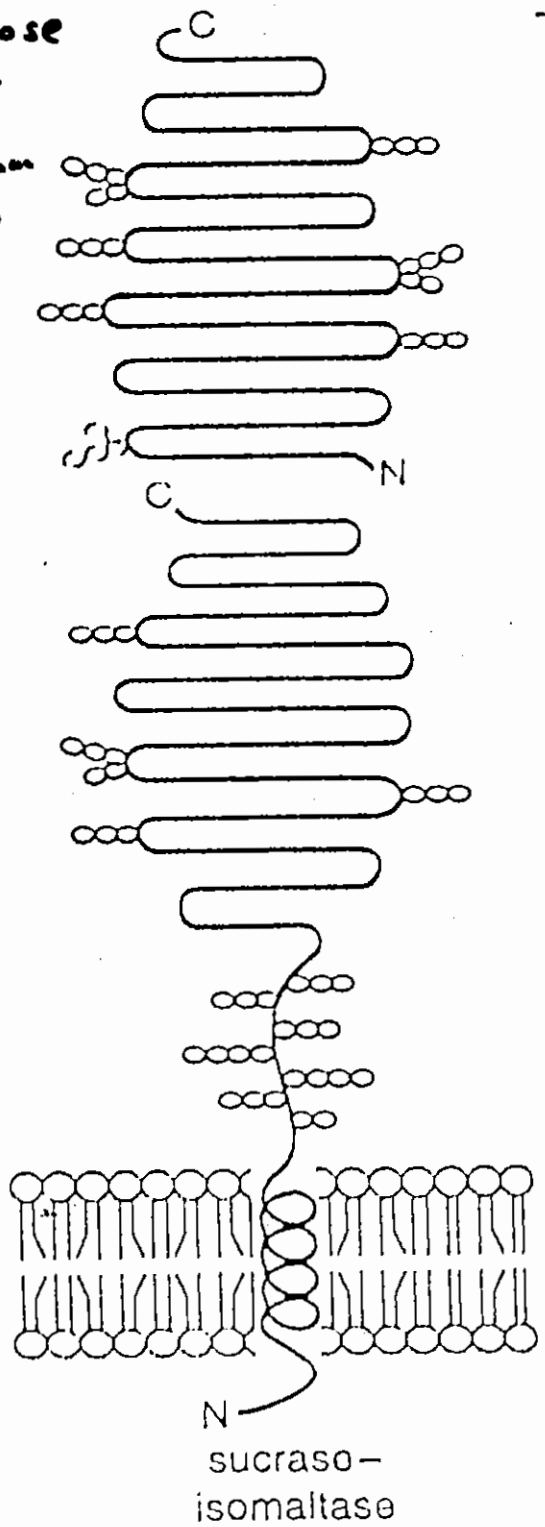


β-1,4-glycosidic bond in cellulose

Sucrase-Isomaltase Complex

Specificity:-
maltose, sucrose and Isomaltose

Location:-
rich in jejunum and lower below



sucrase (only sucrase activity) + high maltose and maltotriose activity

} → they account for more than 80% of maltase activity

isomaltase (performs most of the hydrolysis) + high maltose and maltotriose activity

→ lumen of the intestine

Connecting segment (stalk)

Transmembrane segment of absorptive cell

Cytoplasmic domain

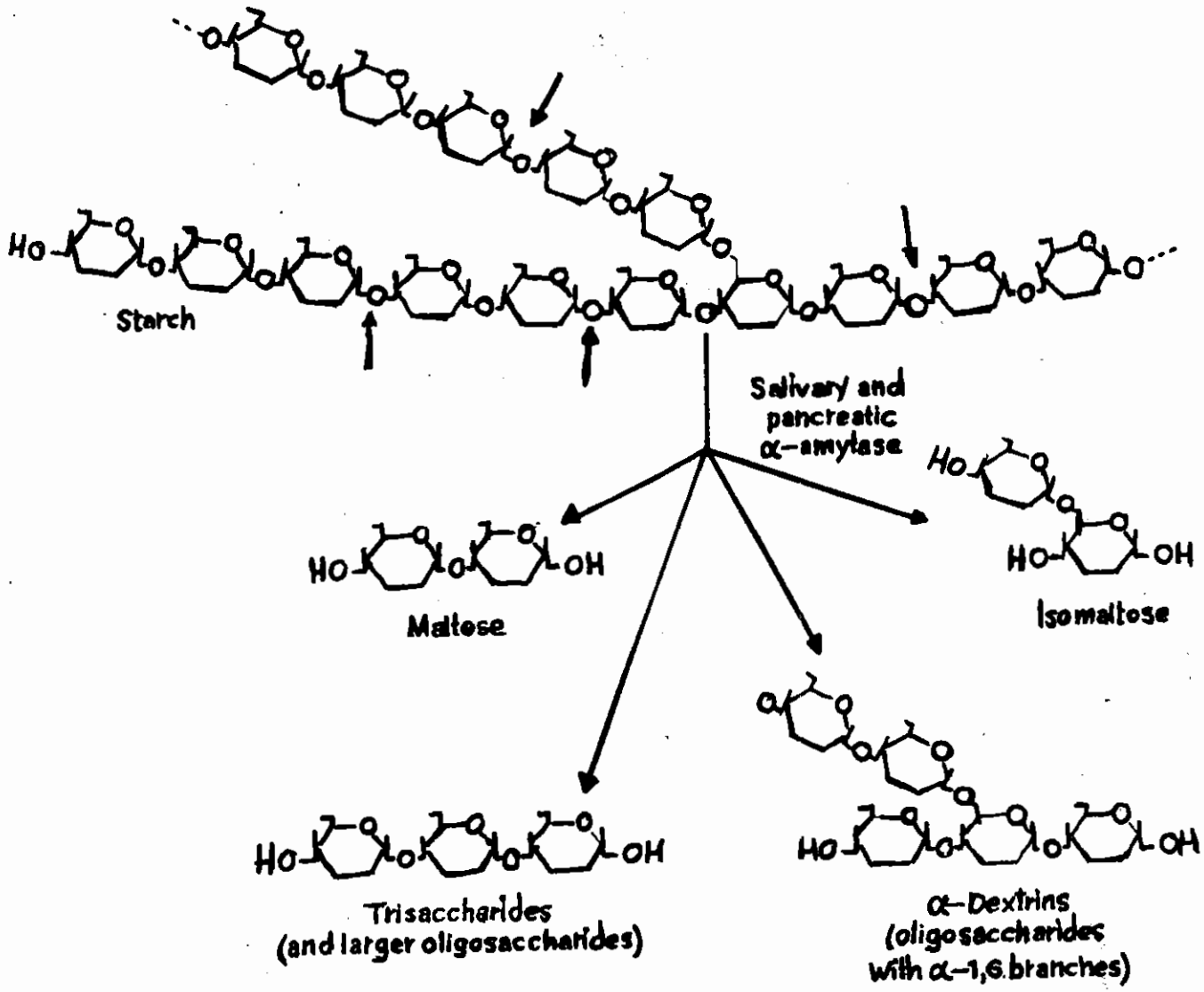
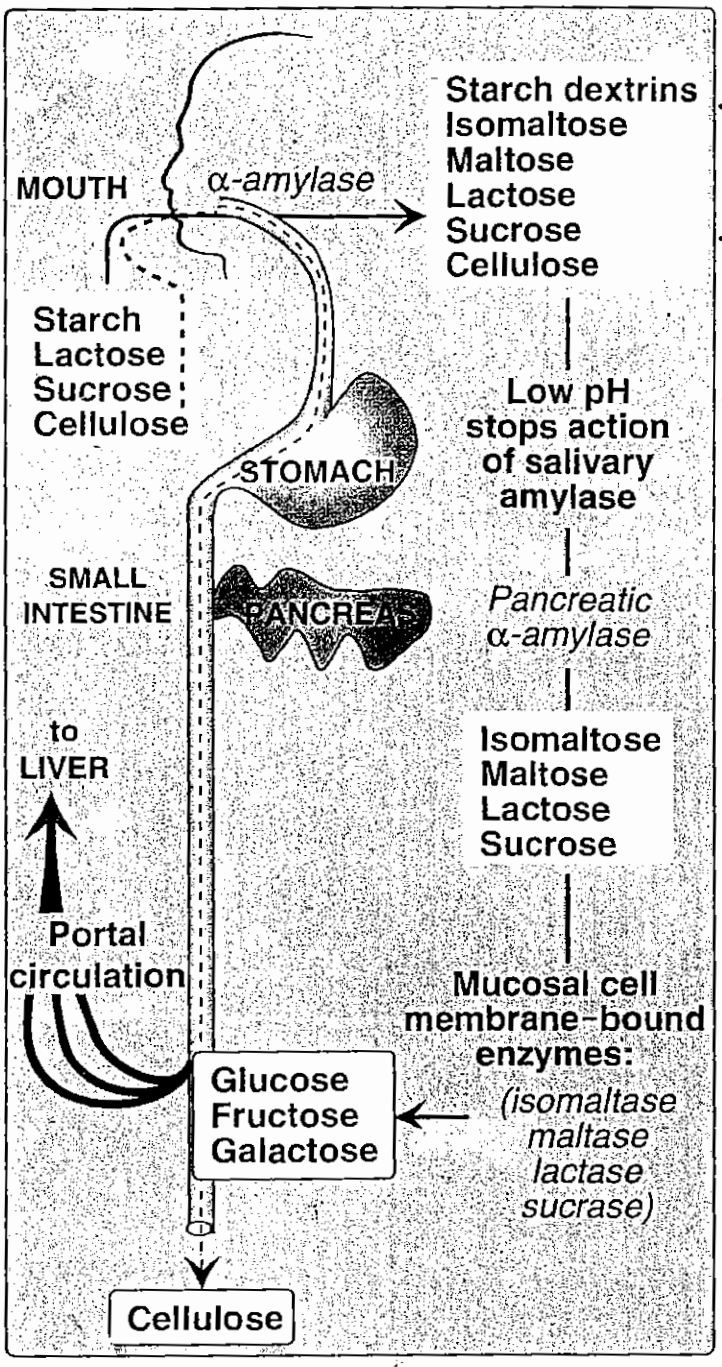


Fig. 25.12. Action of salivary and pancreatic α-amylase, on STARCH

Digestion of Carbohydrate



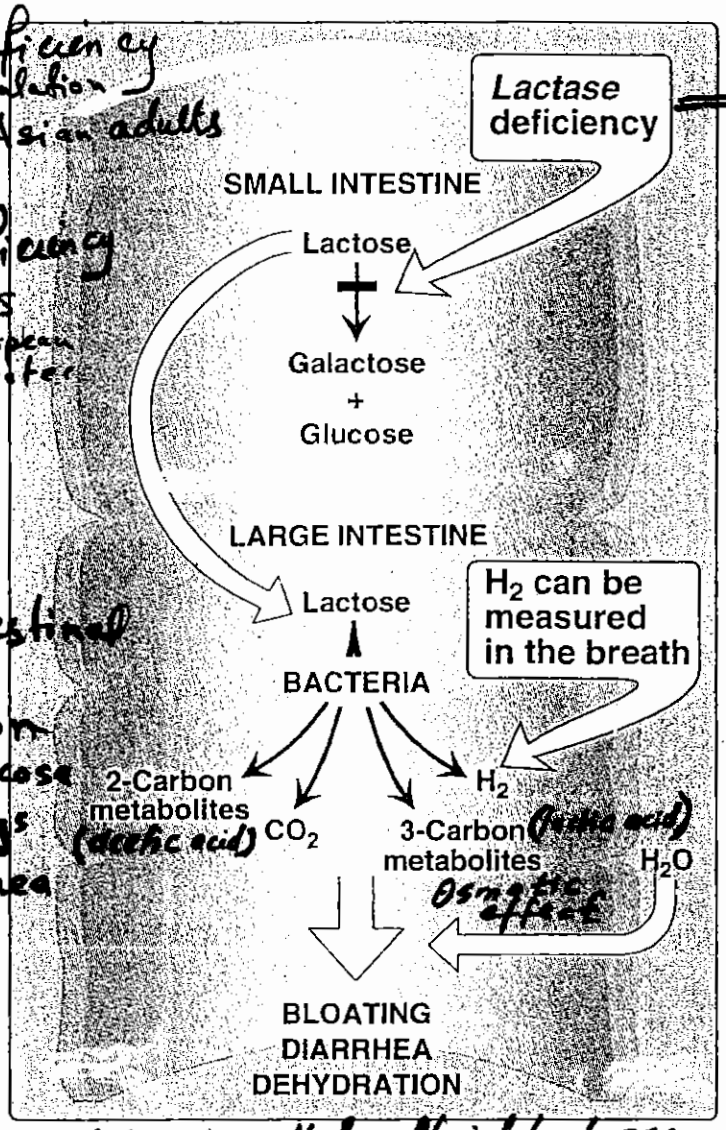
- Isomaltase:- α-1→6 in Isomaltose
- Maltase α-1→4 in maltose and maltotriose
- Sucrase α-1→2 in sucrose
- Lactase β-1→4 in Lactose
- Trehalase α-1→1 in trehalose in mushrooms and other fungi

- Sucrase + isomaltase
  single protein $\xrightarrow{\text{split}}$ two associated subunits complexed
- maltase + exoglucosidase (glucoamylase) $\xrightarrow{\text{no split}}$
  similar complex; α-1,4 in limit dextrins
- Trehalase

Abnormal Degradation of Disaccharides

- Lactase deficiency
  - > ½ World's population
  - 90% African + Asian adults
- Sucrase (isomaltase) deficiency
  - 10% Askimos
  - 2% North European are heterozygotes

ADULT HYPOLACTASIA



1 L of extracellular fluid lost per 9 gr of lactose in 1 glass of milk.

Causes:-
- Genetics
- Variety of Intestinal diseases
- Malnutrition
- Injury of mucosa e.g. by drugs
- Severe diarrhea

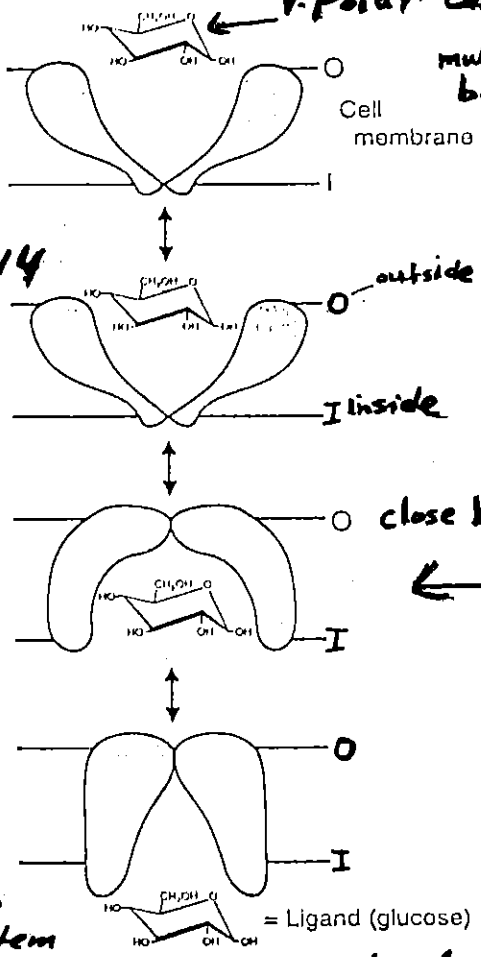
Maximal activity → 1 month of age
declines → adult level at 5 to 7 yr. age (10% of Infant level)

Absorption of Sugars

V. polar can not diffuse

A- Na^+ - independant facilitated diffusion transport

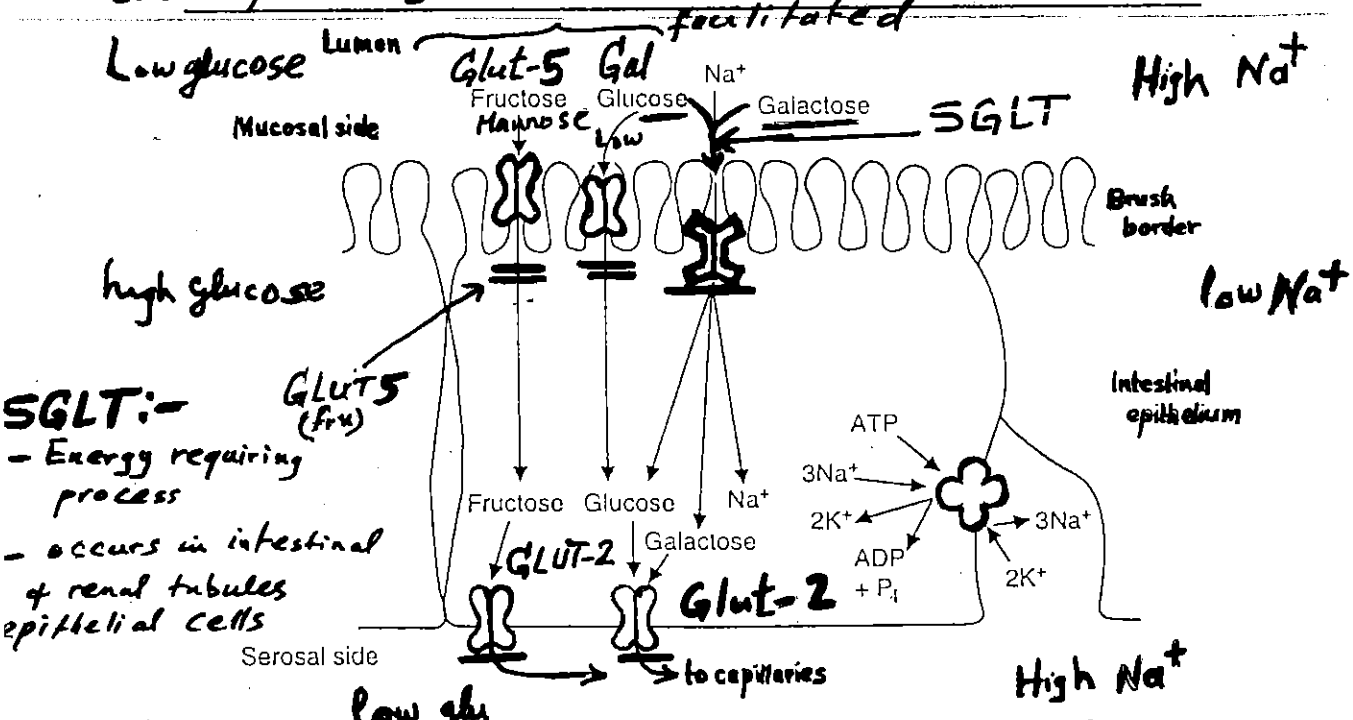
multiple gr. on protein bind - OH of glu and close behind it



- Glut-1 → Glut-14
- Glu movements follow conc. gradient
- two conformational states

two conformational states

B- Na^+ (SGLT) - monosaccharide cotransporter system



SGLT:-
- Energy requiring process
- occurs in intestinal & renal tubules epithelial cells

= Na^+- glucose cotransporters SGLT

= Facilitated glucose transporters GLUT

= Na^+,K^+- ATPase

Transporter | Occurance | Function

I Sodium dependent-Transporter:- SGLT

(7)

Small intestine and kidney — Active uptake from lumen of intestine, reabsorption of glu in proximal tubule of kidney against conc. gradient

II. Facilitative Bidirection Transporters

GLUT-1 — Erythrocyte + Blood-brain barrier, also retinal, placental, testis-barriers — uptake of Glu $K_m = 1mM$

GLUT-2 — Liver, Pancreatic β-cell, small intestine, kidney (serosal surface) Bidirectional — Rapid uptake and release of Glu
- $K_m = \sim 15mM$
- High V_{max}
- Glucose sensor

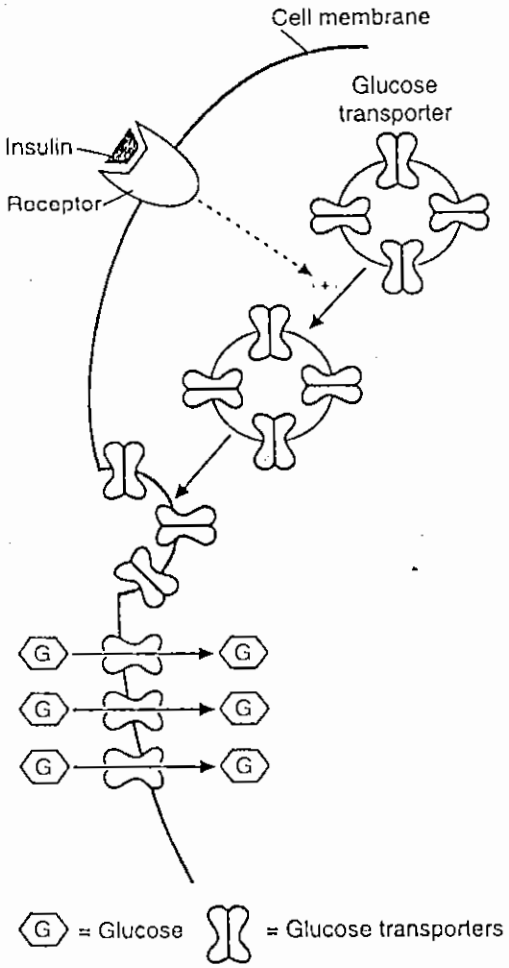
GLUT-3 — brain, kidney, placenta (Major transporter in CNS) — uptake of Glu $K_m = \sim 1mM$ (High affinity)

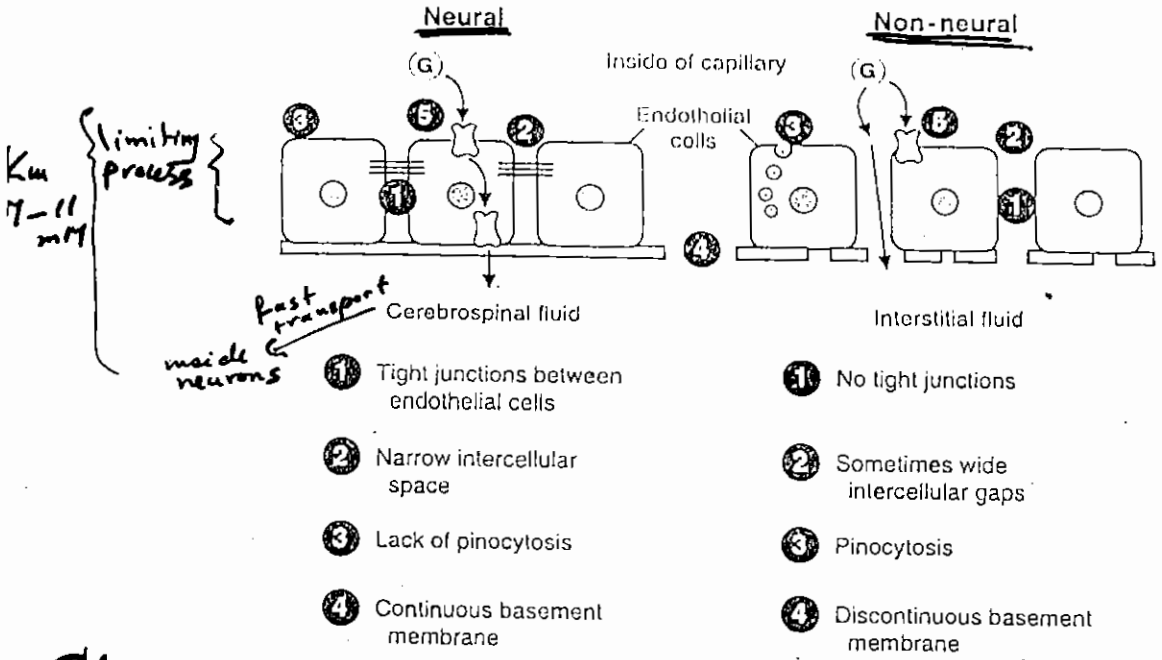
GLUT-4 — Heart and skeletal muscle, adipose tissue — Insulin stimulated uptake of glu $K_m = \sim 5mM$

GLUT-5 — Small intestine + spermatozoa — absorption of fructose

GLUT-7 — at endoplasmic reticulum membrane of glucogenic tissue (liver and kidney)

stimulation by Insulin of Glucose transport into muscle and adipose Tissues

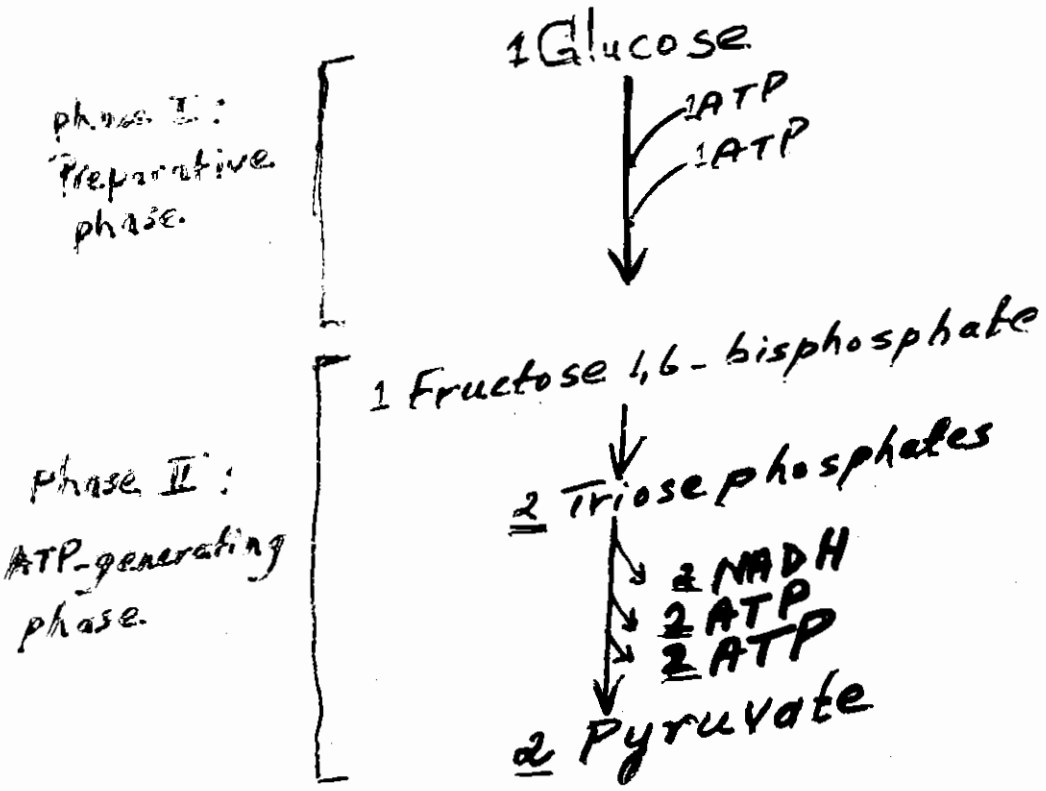




Glucose transport through the Capillary Endothelium

GLYCOLYSIS

- Universal Pathway in all cell types
- Generation of ATP with, and without, O_2
- Anabolic Pathway
  → biosynthetic precursors
- Phases of the glycolytic Pathway



GLYCOLYSIS :-

- Occurs in all Human Cells

Glucose ⟹ 2 Pyruvate —PDH→ 2-acetyl CoA

2-lactate $2CO_2$ TCA → $4CO_2$

No O_2-requirement for glycolysis - anaerobic fermentation

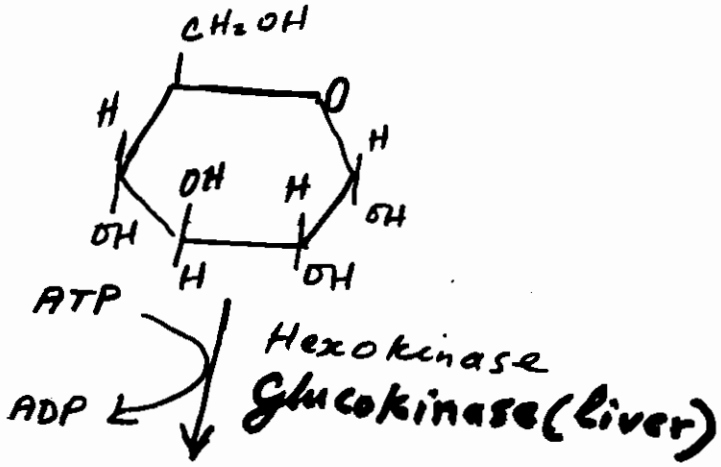
O_2-requirement for PDH & TCA activity

$Glu + 2ADP + 2Pi \rightarrow 2ATP + 2\text{-lactate}$

$Glu + 6O_2 + 38ADP + 38Pi + 38H^+ \rightarrow 6CO_2 + 6H_2O + 38ATP$

- Tissues that have an Absolute Requirement for Glucose
  - Brain
  - Red Blood cells
  - Cornea, lens and retina
  - Kidney Medulla, testis, leukocyte and white muscle fibers

Glucose-6-phosphate Metabolism

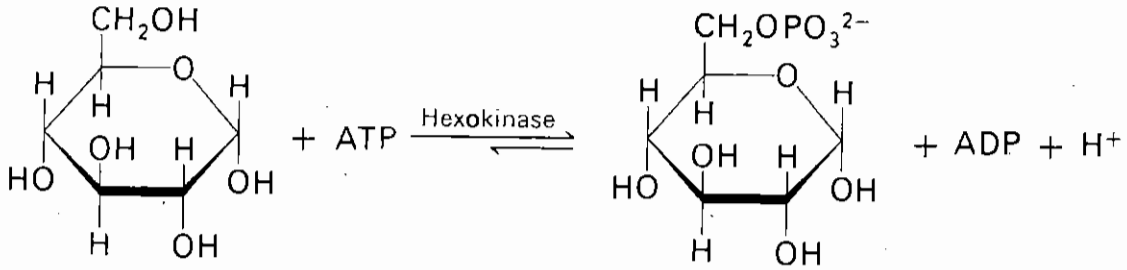


Glu-6-P

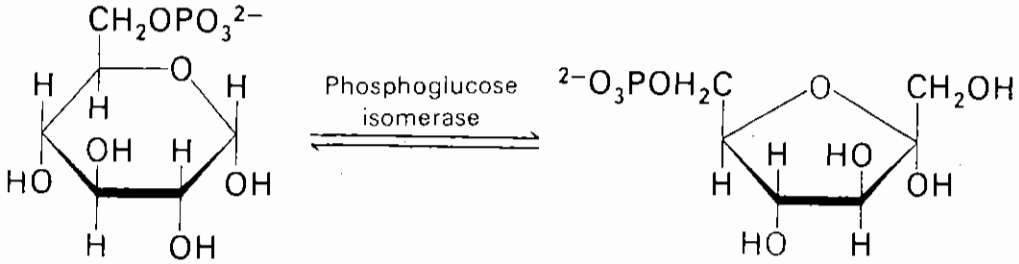
- Other Pathways
- Glycolysis
- Pentose phosphate pathway
- Glycogen synthesis

	HK	GK in Liver
Occurance	in all tissues	
Km	<0.02 mM	10 – 20 mM
Sp.	Glu, Fru, Man, Gal	Glu + others
Induction	Not induced	↑ insulin, Glu
Function	Even low blood Glu	only > 100 mg/dl

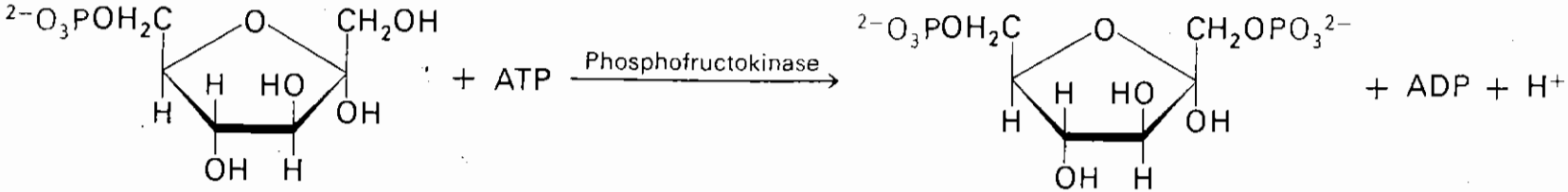
Reactions of GLYCOLYSIS



Glucose **Glucose 6-phosphate**

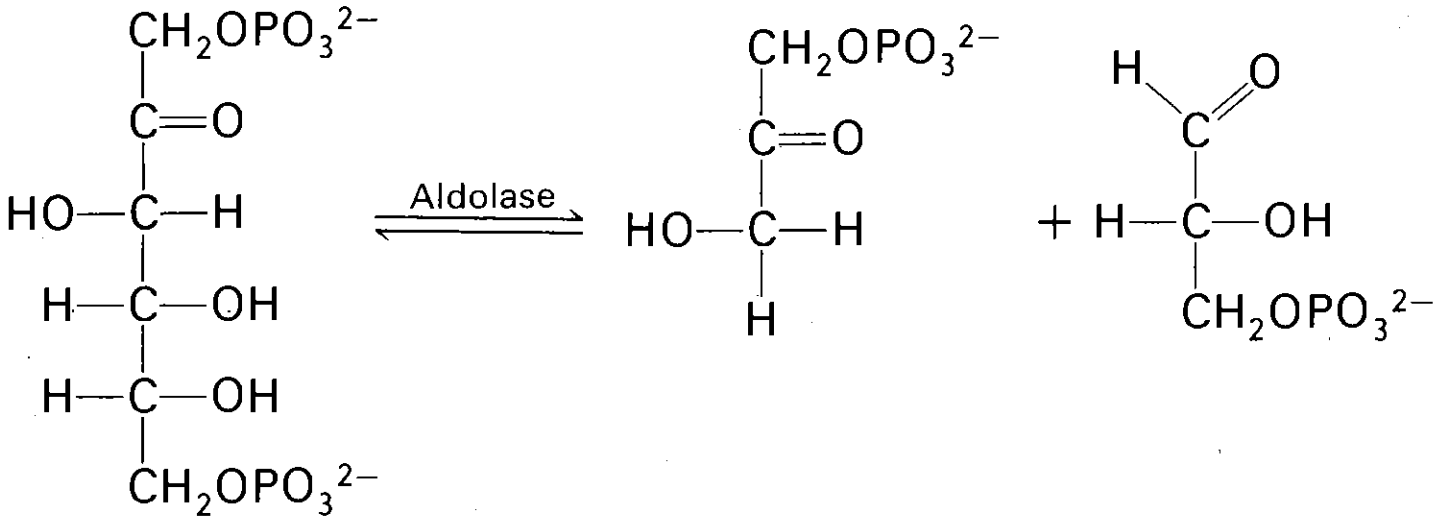


Glucose 6-phosphate **Fructose 6-phosphate**



Fructose 6-phosphate **Fructose 1,6-bisphosphate**

Assorted figures from pages 486 and 487



Fructose 1,6-bisphosphate | **Dihydroxyacetone phosphate** | **Glyceraldehyde 3-phosphate**

Bottom figure, page 487

Glyceraldehyde 3-P dehydrogenase

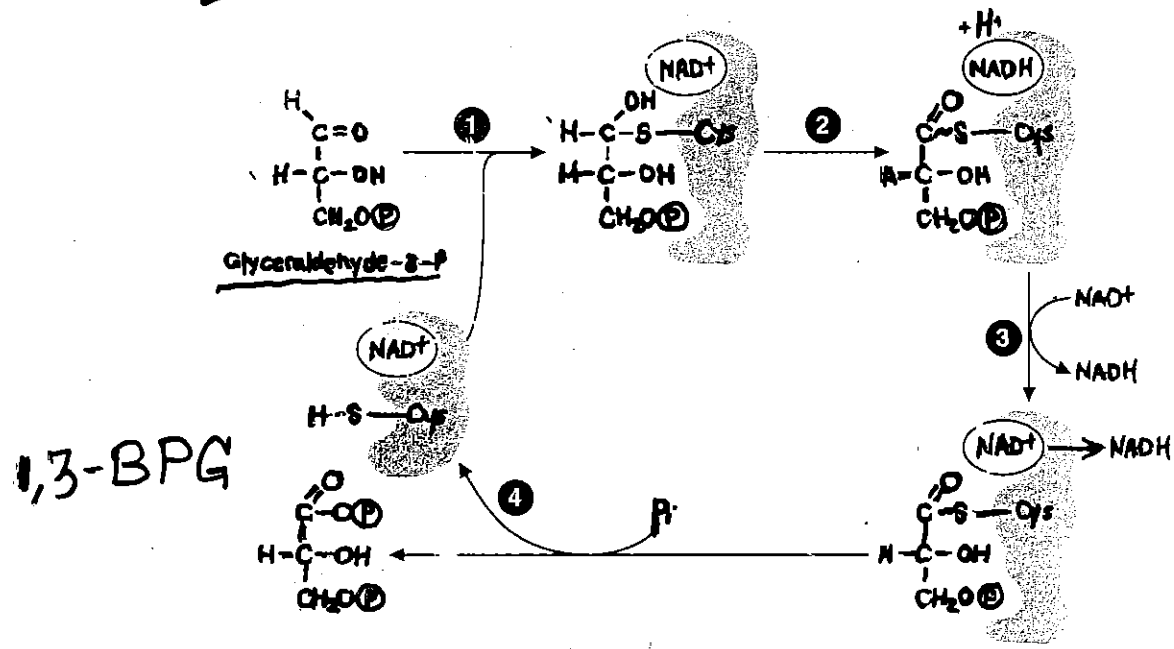
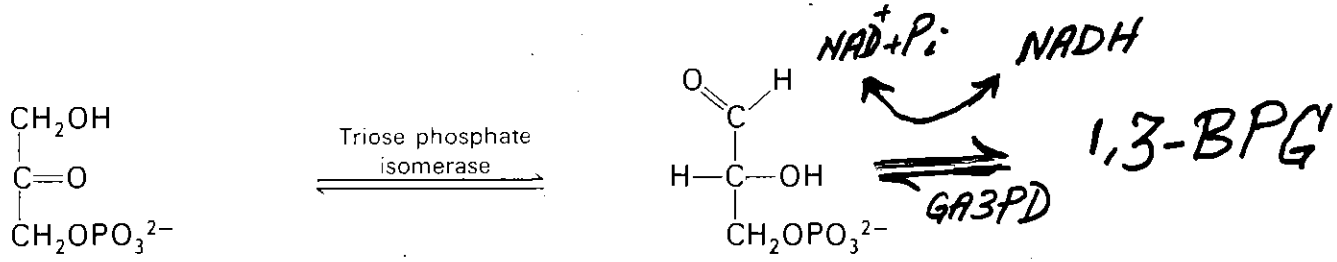


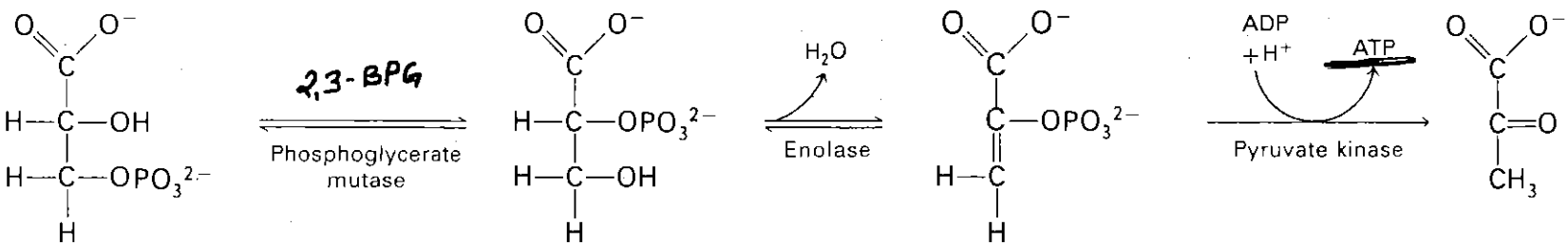
Fig. 22.17. Mechanism of the glyceraldehyde 3-phosphate dehydrogenase reaction. 1. The enzyme forms a covalent linkage with the substrate, using a cysteine group at the active site. The enzyme also contains bound NAD^+ close to the active site. 2. The substrate is oxidized, forming a high-energy thioester linkage (in blue), and NADH. 3. NADH has a low affinity for the enzyme and is replaced by a new molecule of NAD^+. 4. Inorganic phosphate attacks the thioester linkage, releasing the product 1,3 bisphosphoglycerate, and regenerating the active enzyme in a form ready to initiate another reaction.



Dihydroxyacetone phosphate
(A ketose)

Glyceraldehyde 3-phosphate
(An aldose)

1,3 BPG + ADP ⇌ (PGK) 3-phosphoGlycerate + ATP

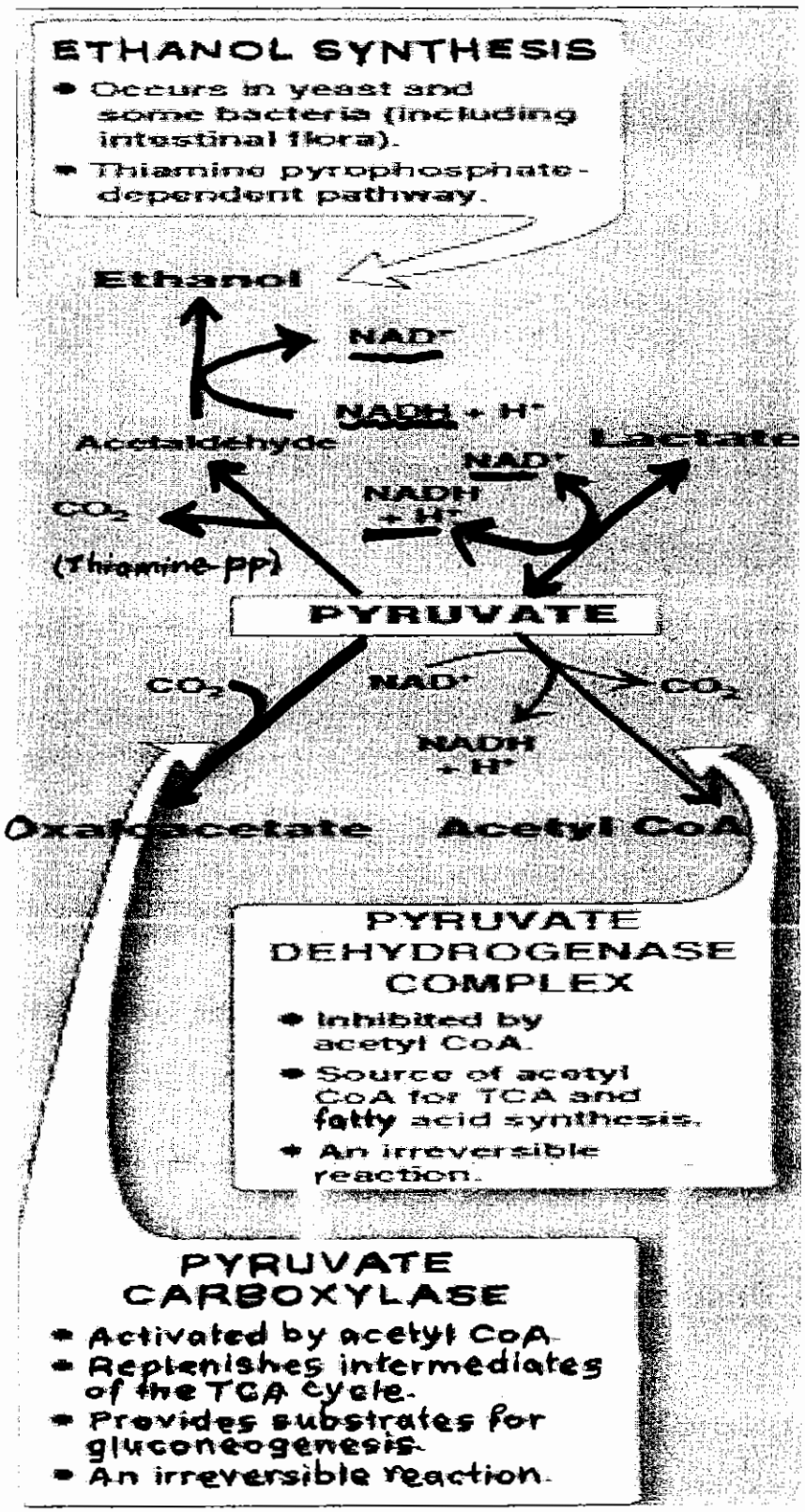


3-Phosphoglycerate **2-Phosphoglycerate** **Phosphoenolpyruvate** **Pyruvate**

Glycolytic reactions, pages 488, 489

Stryer: *Biochemistry*, Fourth Edition

Summary of Metabolic fates of Pyruvate



Lactate is produced anaerobically to meet the following demands

1. Cells with low energy demand

2. To cope with increased energy demands in vigorously exercising muscle

   Lactate level is increased 5 to 10-fold

3. Hypoxia

   to survive brief episodes of hypoxia

   -but mixed blessings

Lactic Acidosis:- → lactate > 5 mM (0.4 – 1.8 mM) Ref. range
→ pH < 7.2 (7.35 – 7.45)

is the most common cause of metabolic acidosis

→ • increased production of lactic acid
• decreased utilization " " "

Most common cause is impairment of oxidative metabolism resulting from Collapse of Circulatory System:-

- Impaired O_2 transport
  e.g. myocardial infarction
- Respiratory Failure
  e.g. Pulmonary embolism

- Uncontrolled hemorrhage
- Direct inhibition of Oxidative-phosphorylation

Other Causes :-

- Hypoxia in any tissue
- Alcohol intoxication → ↑↑ NADH/NAD

v. rare

- ↓ gluconeogenesis
- ↓ Pyruvate dehydrogenase
  e.g. inheritted deficiency
  thiamine deficiency
- ↓ TCA activity
- ↓ Pyruvate Carboxylase deficiency