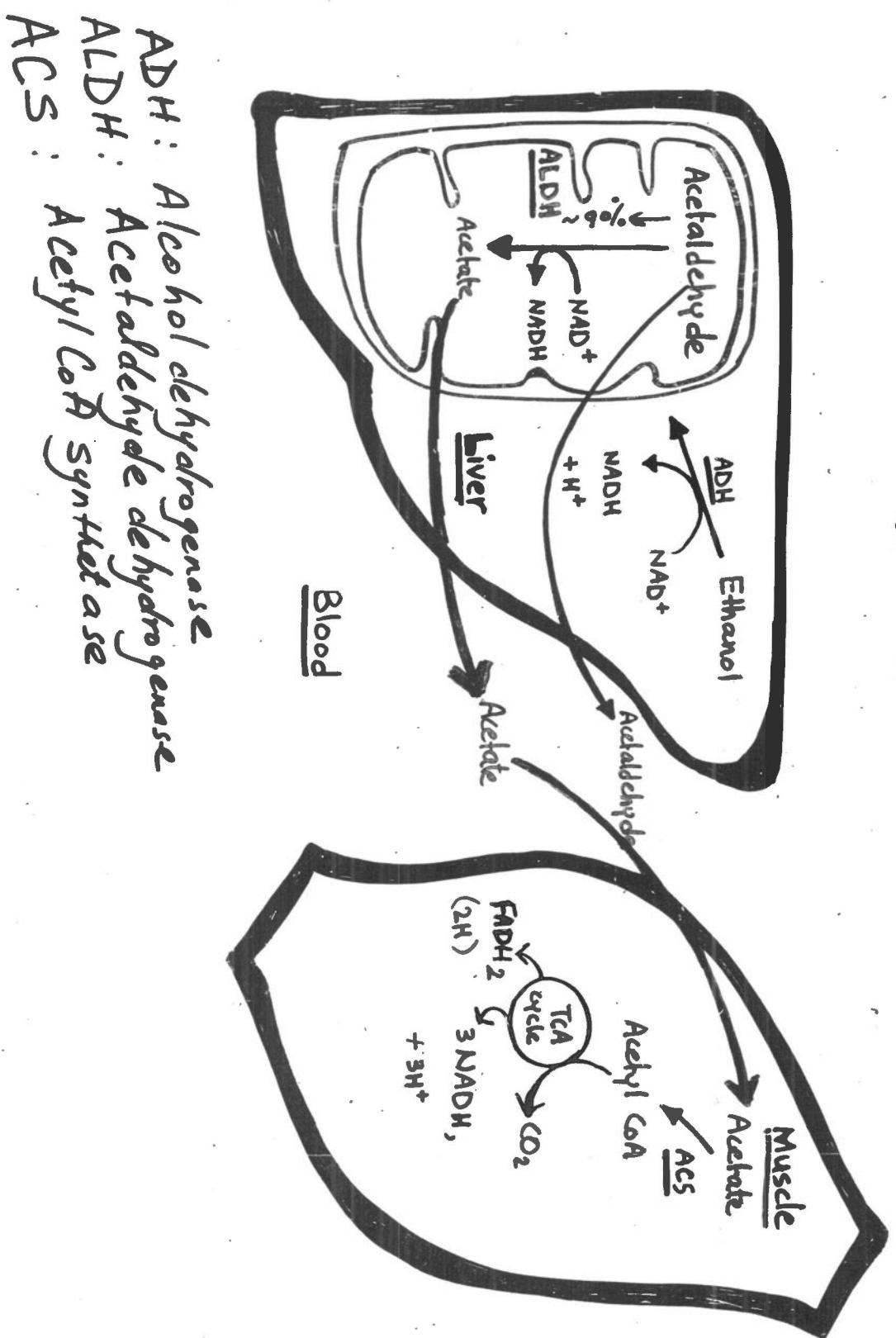


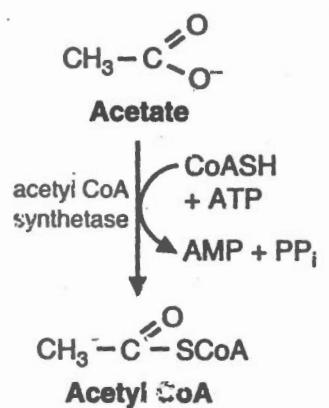
Overall Metabolism of Alcohol and Acetate



ADH : Alcohol dehydrogenase

ALDH : Acetaldehyde dehydrogenase

ACS : Acetyl CoA Synthetase



ACS Cytosolic enzyme
in muscles & other tissues
→ AcetylCoA for
Cholesterol & FA Synthesis
- ACS :

Mitochondrial ACS is
in heart & skeletal muscle
 \rightarrow TCA

Fig. 25.4. The activation of acetate to acetyl CoA

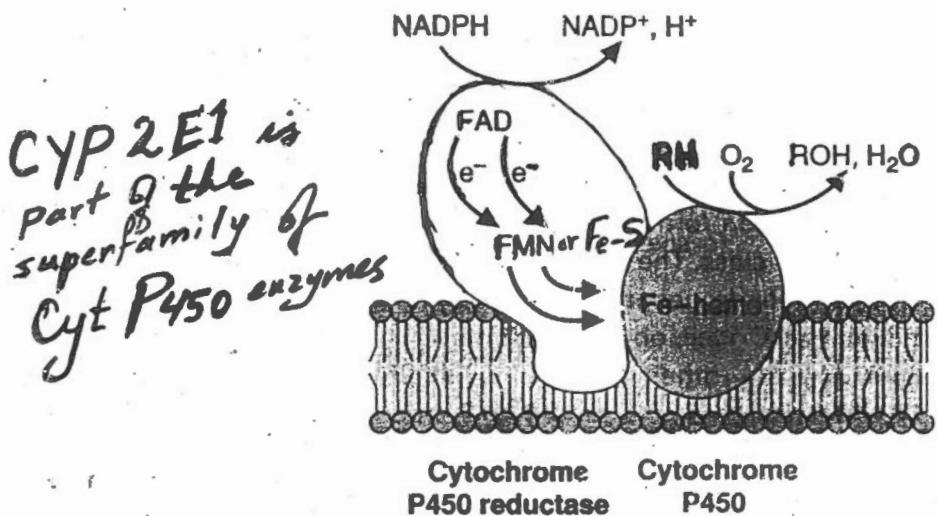


Fig. 25.5. General structure of cytochrome P450 enzymes. O₂ binds to the P450 Fe-heme in the active site and is activated to a reactive form by accepting electrons. The electrons are donated by the cytochrome P450 reductase, which contains an FAD plus an FMN or Fe-S center to facilitate the transfer of single electrons from NADPH to O₂. The P450 enzymes involved in steroidogenesis have a somewhat different structure. For CYP2E1, RH is ethanol (CH₃CH₂OH) and ROH is acetaldehyde (CH₃COH).

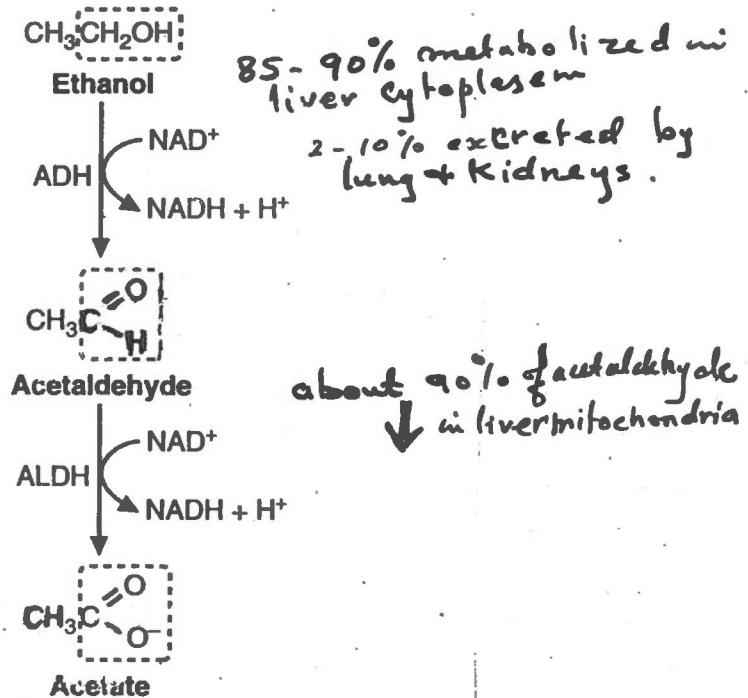


Fig. 25.2. The pathway of ethanol metabolism (ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase).

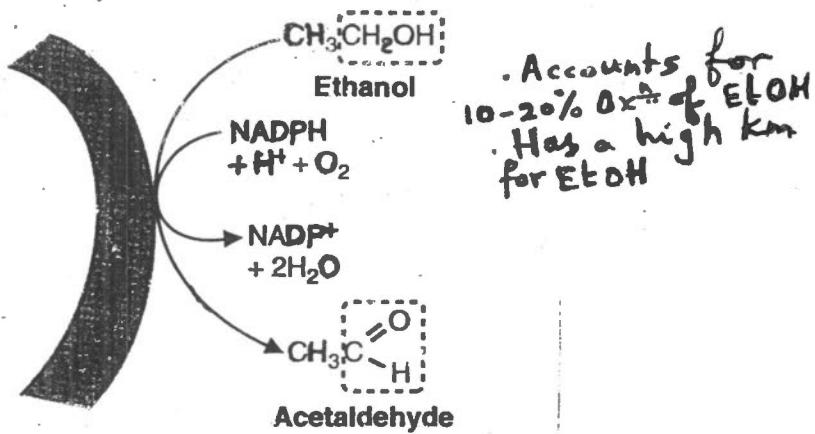


Fig. 25.3. The reaction catalyzed by MEOS (which includes CYP2E1) in the endoplasmic reticulum.

Metabolism of Ethanol

Ethanol is a dietary fuel that is metabolized to acetate principally in the liver, with the generation of NADH. The principal route for metabolism of ethanol is through hepatic alcohol dehydrogenases, which oxidize ethanol to acetaldehyde in the cytosol (Fig. 25.1). Acetaldehyde is further oxidized by acetaldehyde dehydrogenases to acetate, principally in mitochondria. Acetaldehyde, which is toxic, also may enter the blood. NADH produced by these reactions is used for adenosine triphosphate (ATP) generation through oxidative phosphorylation. Most of the acetate enters the blood and is taken up by skeletal muscles and other tissues, where it is activated to acetyl CoA and is oxidized in the TCA cycle.

Approximately 10 to 20% of ingested ethanol is oxidized through a microsomal oxidizing system (MEOS), comprising cytochrome P450 enzymes in the endoplasmic reticulum (especially CYP2E1). CYP2E1 has a high K_m for ethanol and is inducible by ethanol. Therefore, the proportion of ethanol metabolized through this route is greater at high ethanol concentrations, and greater after chronic consumption of ethanol.

- Distribution of PGlucose:

free glucose in E.C.F. = $20 \text{ gr} \equiv 80 \text{ Cal}$

= $\text{mglycogen in liver} = \sim 75 \text{ g} \pm 100 \text{ g}$

" " " " = muscle = $\sim 400 \text{ gr}$

- Liver glycogen maintains blood glucose $\approx 16 \text{ hr}$

- Brain uses $\sim 120 \text{ gr}$ of glucose / day

- 70 kg man has $\sim 15 \text{ Kg fat} \equiv 130,000 \text{ Kcal}$

" supply energy $\rightarrow 60 - 90 \text{ days}$

- Conc of ATP in muscle $\sim 5 \text{ mM}$

" " Creatine phosphate = $\sim 20 \text{ mM}$

Upon vigorous exercise

ATP \rightarrow 2 to 4 sec

CP \rightarrow 20 sec

- Post-absorptive resting muscle or
with moderate exercise \rightarrow F.A. main source
80% of glucose is utilized by brain & rbc

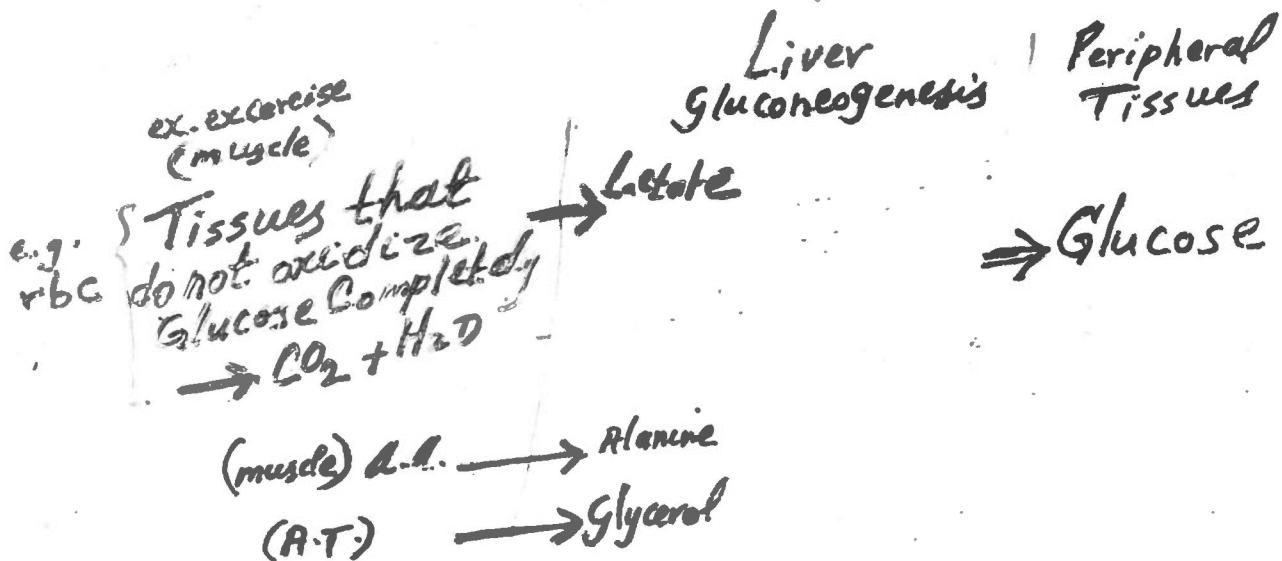
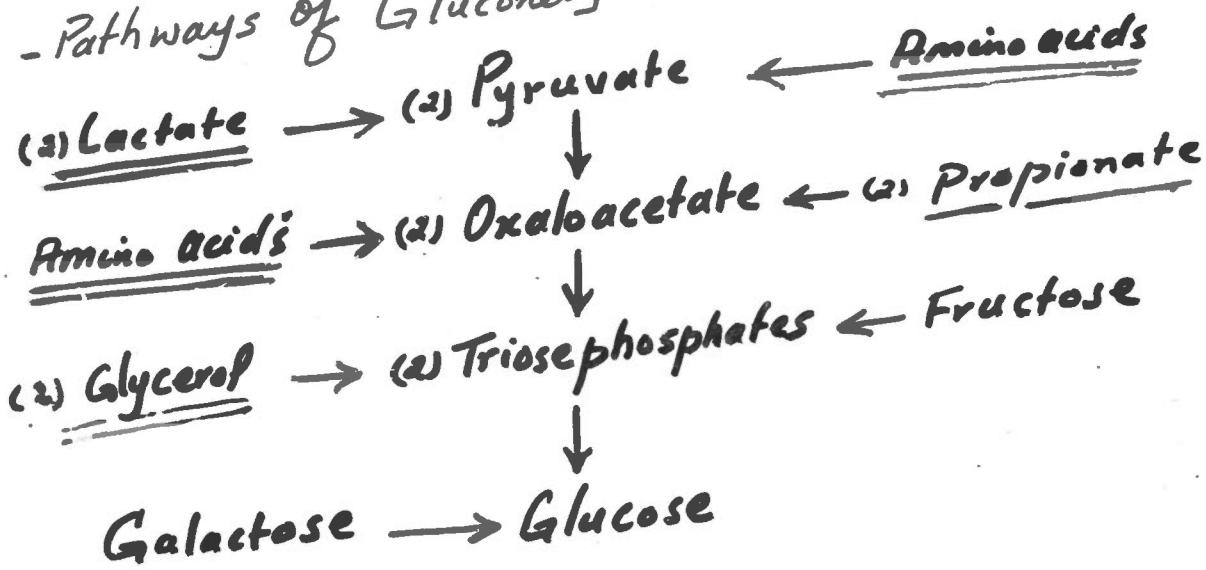
- During prolonged fasting, utilization of
F.A. by all tissues (except brain & rbc) is increased
4 to 5 times & ketone bodies by more
than 100-times

GLUCONEOGENESIS

1

- Glucose Synthesis is Required for Survival

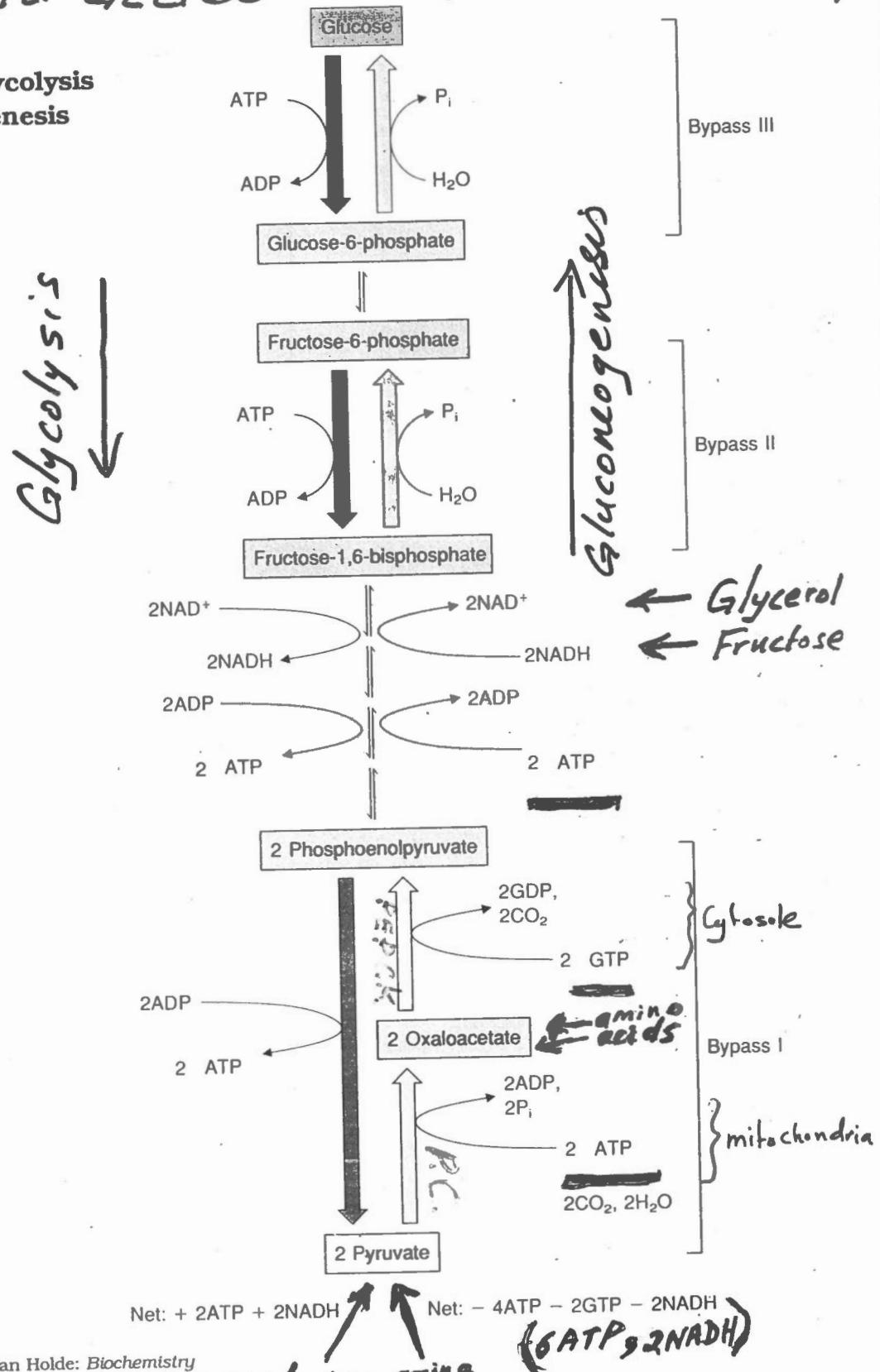
- Pathways of Gluconeogenesis



ENERGY For GLUCONEOGENESIS 2

Reactions of glycolysis and gluconeogenesis

Figure 16.3



From Mathews and van Holde: *Biochemistry*
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Energy Requirements of Gluconeogenesis

36

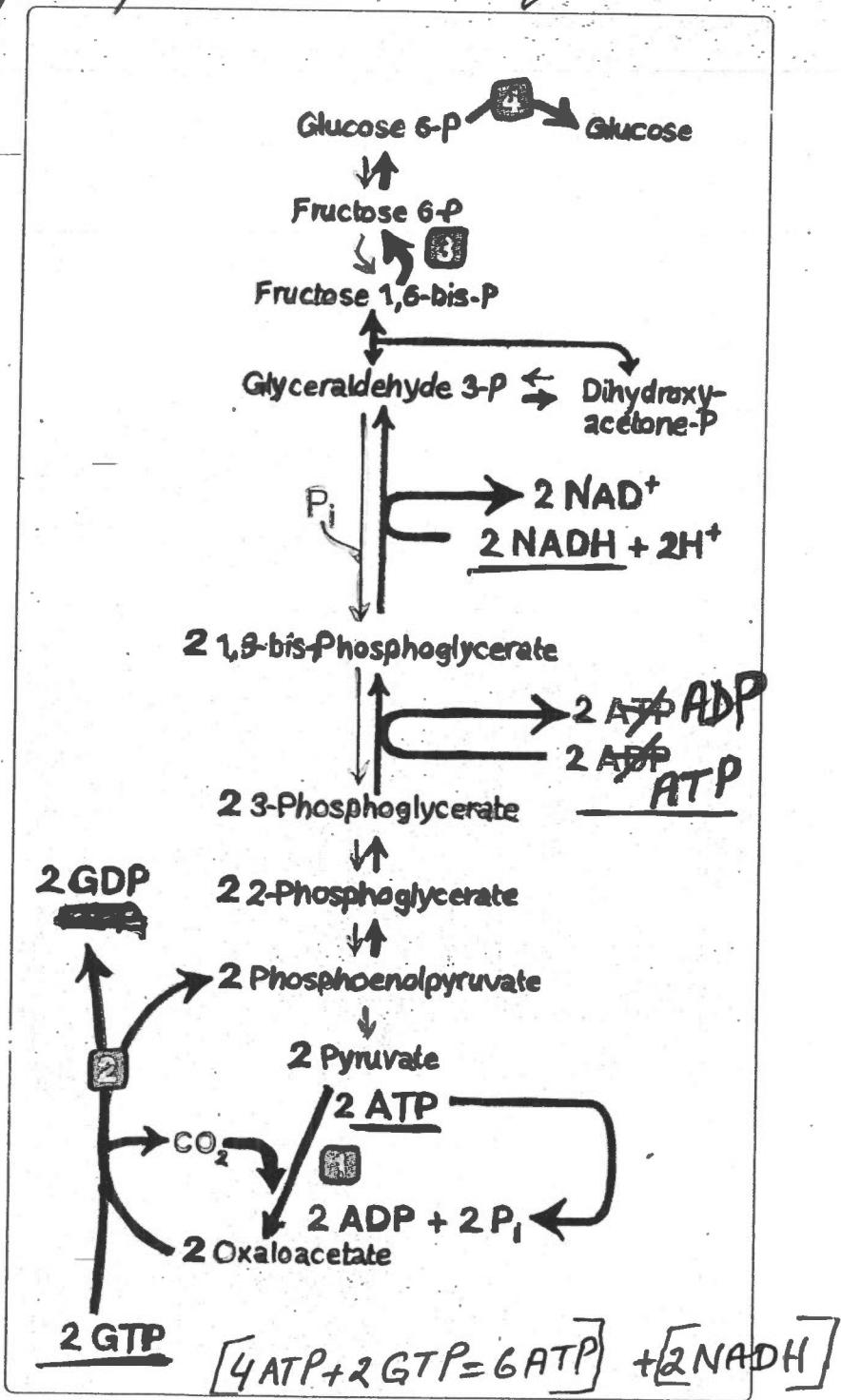
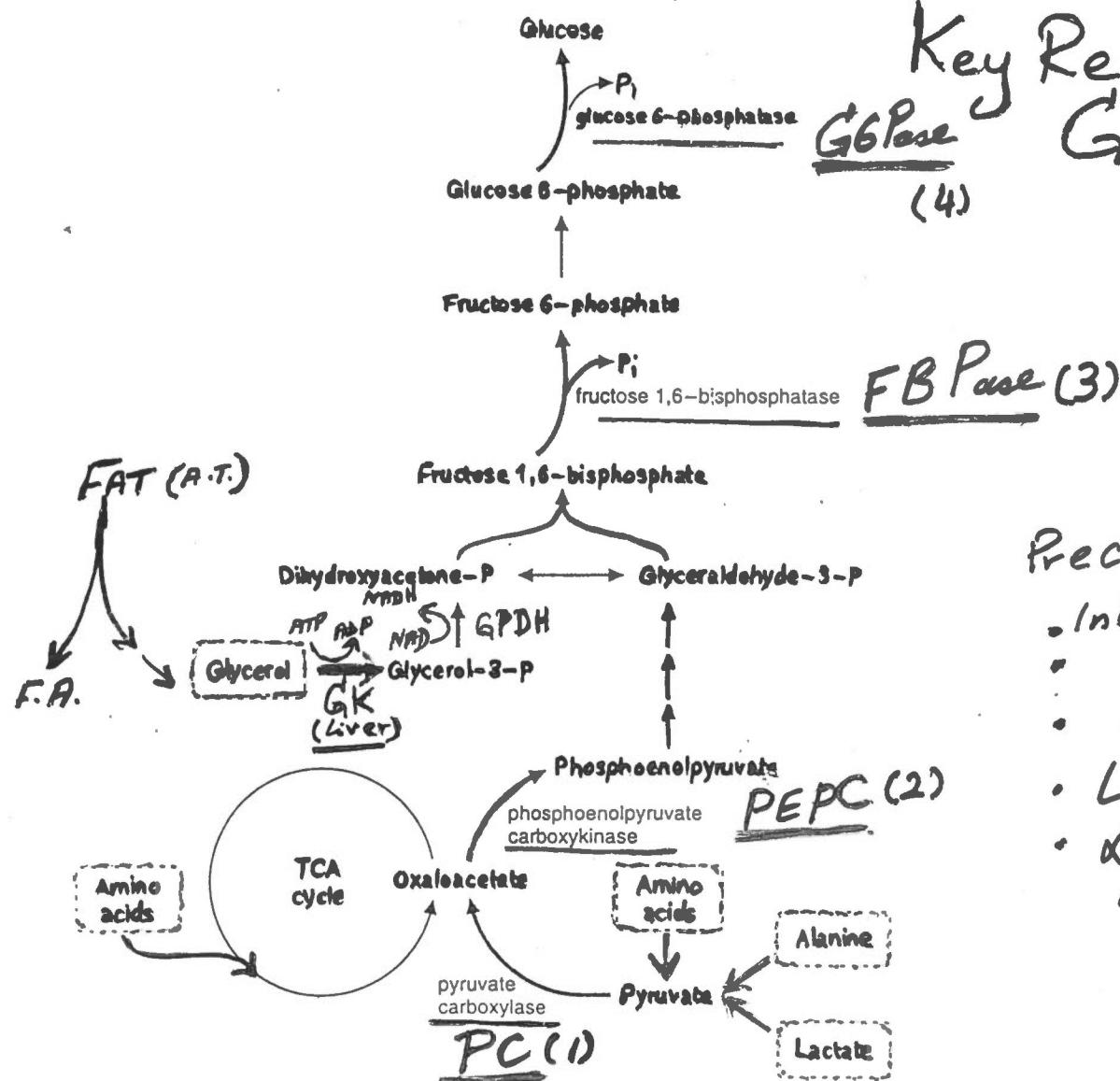


Figure 10.7

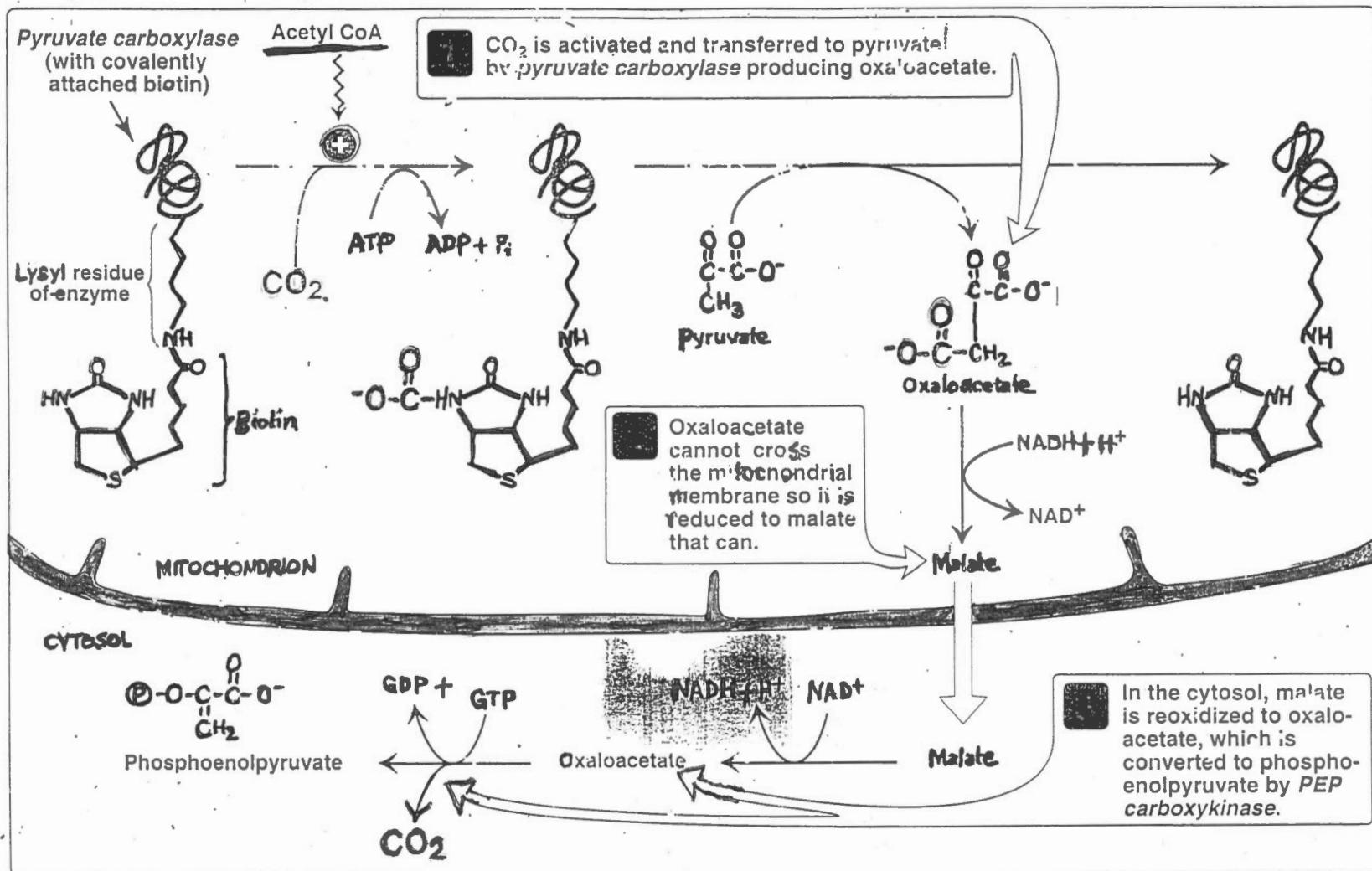
Summary of the reactions of glycolysis and gluconeogenesis, showing the energy requirements of gluconeogenesis.



- Precursors of Gluconeogenesis
- Intermediates of Glycolysis
 - " " " TCA
 - Glycerol during hydrolysis of fat
 - Lactate
 - α -Keto acids from glucogenic amino acids

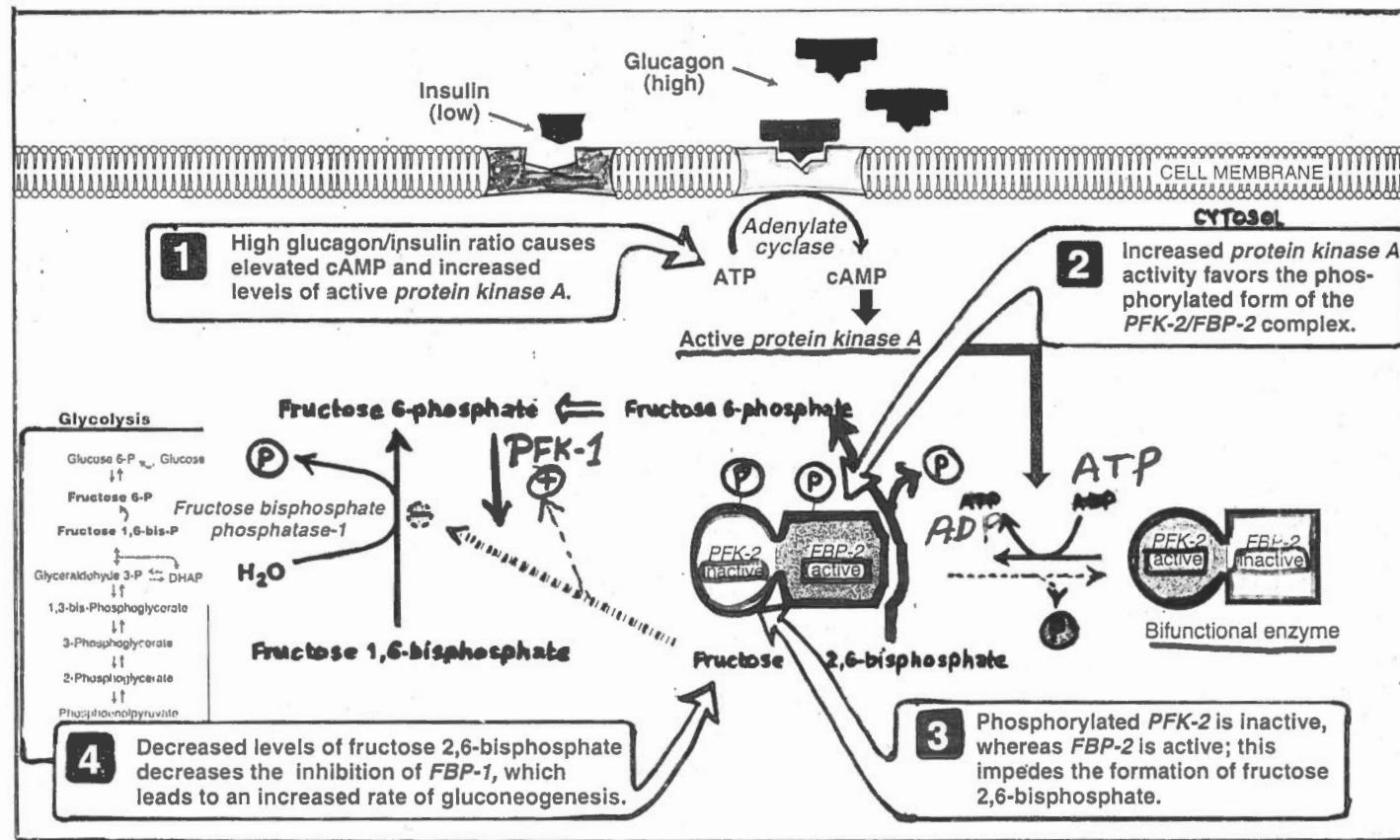
Fig. 27.6. Key reactions of gluconeogenesis. The precursors are amino acids (particularly alanine), lactate, and glycerol. Heavy arrows indicate steps that differ from those of glycolysis.

Pyruvate Carboxylase :-

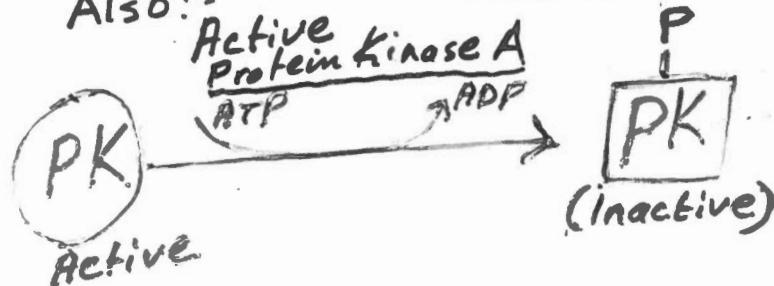


Deinhibition of fru-1,6-bisphatase

4c



Also:-



Net results:

- Inhibition of glycolysis $\text{FFK} \downarrow$
 $\text{PK} \downarrow$

- Removal of inhibition of
 (Deinhibition)
 gluconeogenesis



Regulation of Gluconeogenesis and Glycolysis

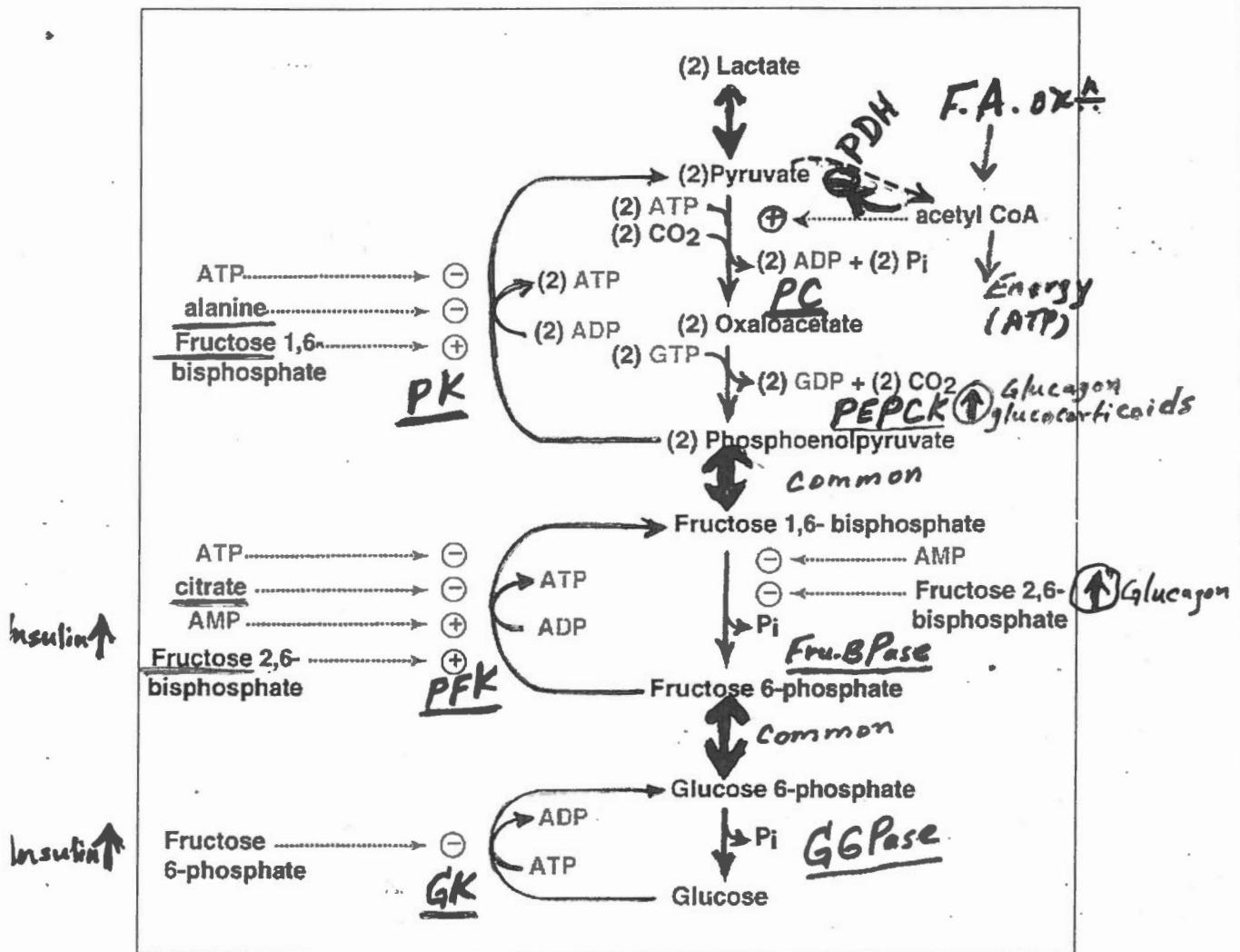


Figure: 07_45

Important allosteric regulatory features of the gluconeogenic pathway.

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CORI CYCLE

5a

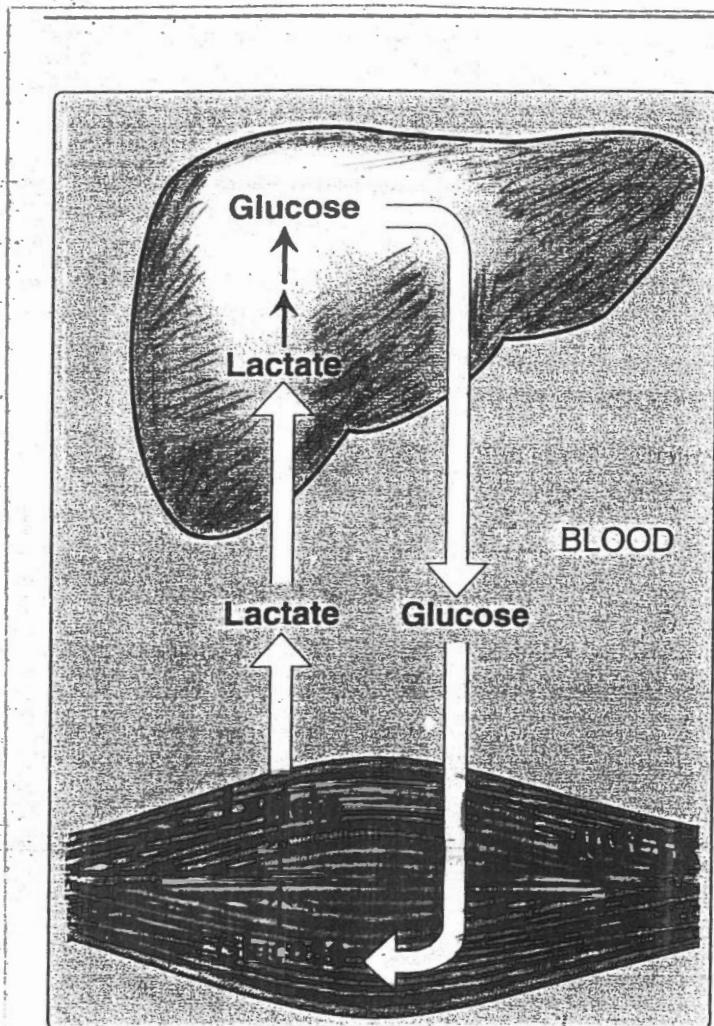
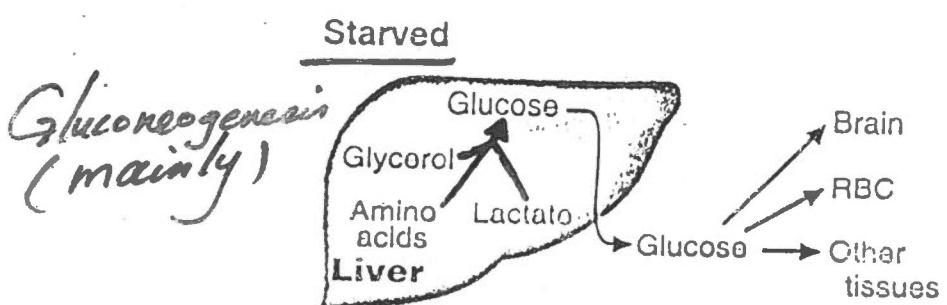
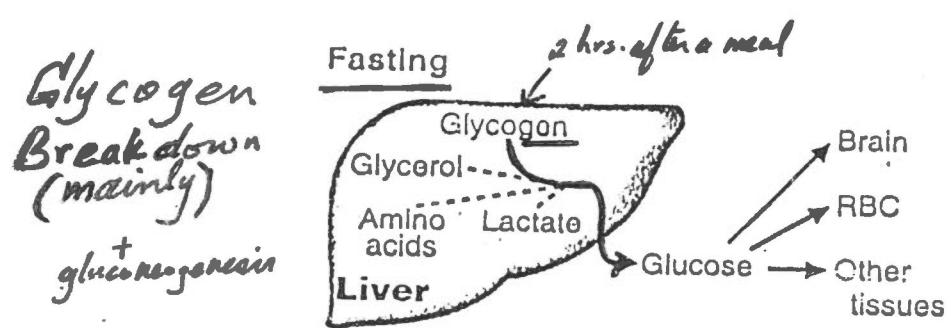
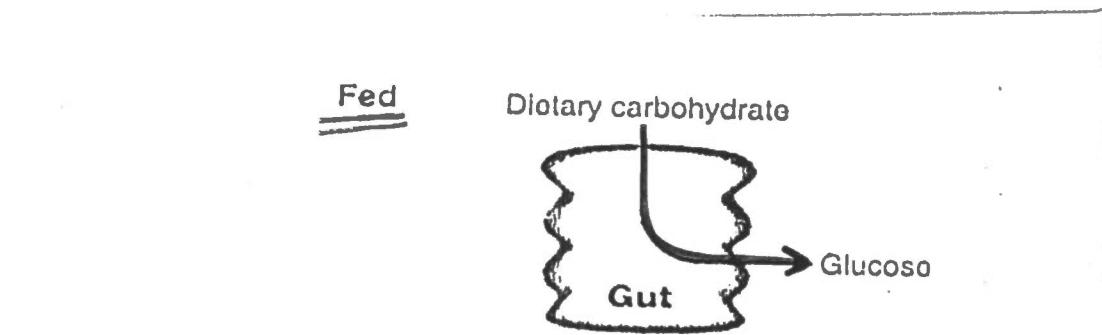


Figure 10.2
The Cori cycle.

Maintainance of Blood Glucose

5s

Sources of Blood Glucose:-



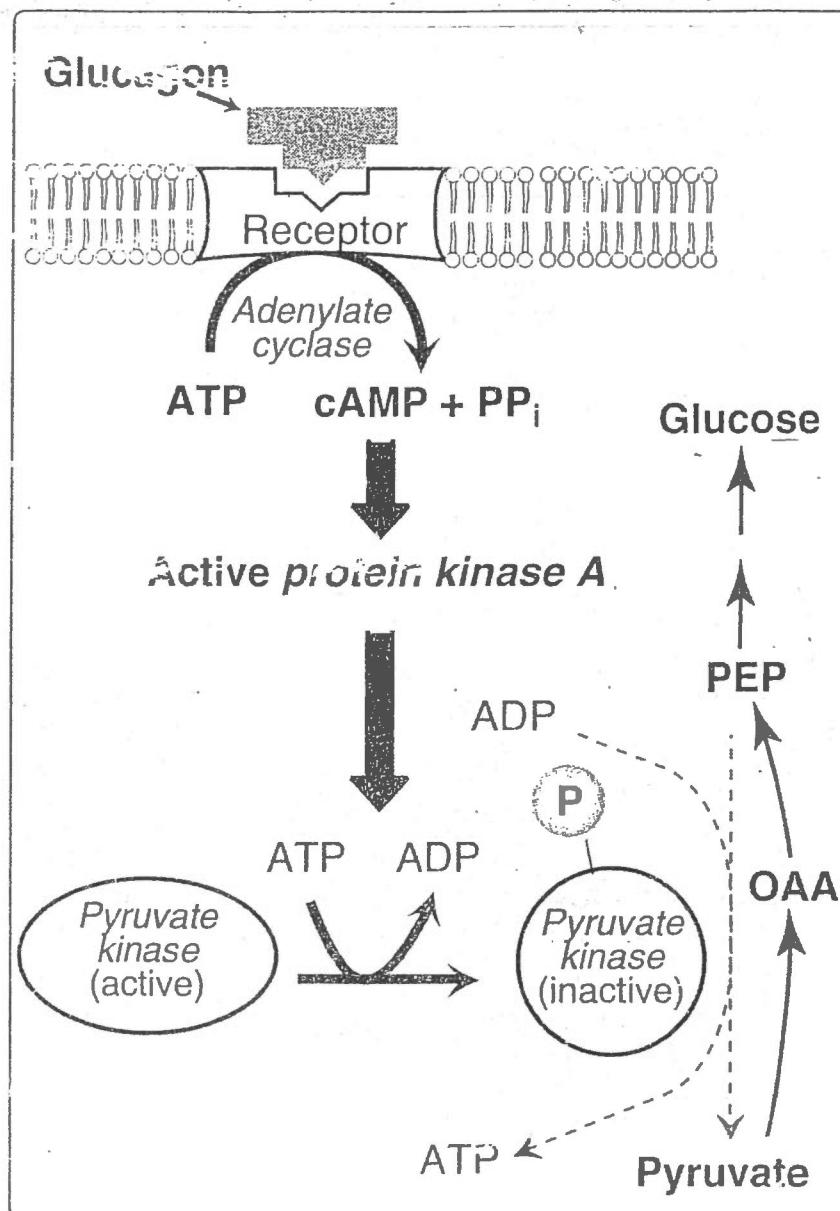
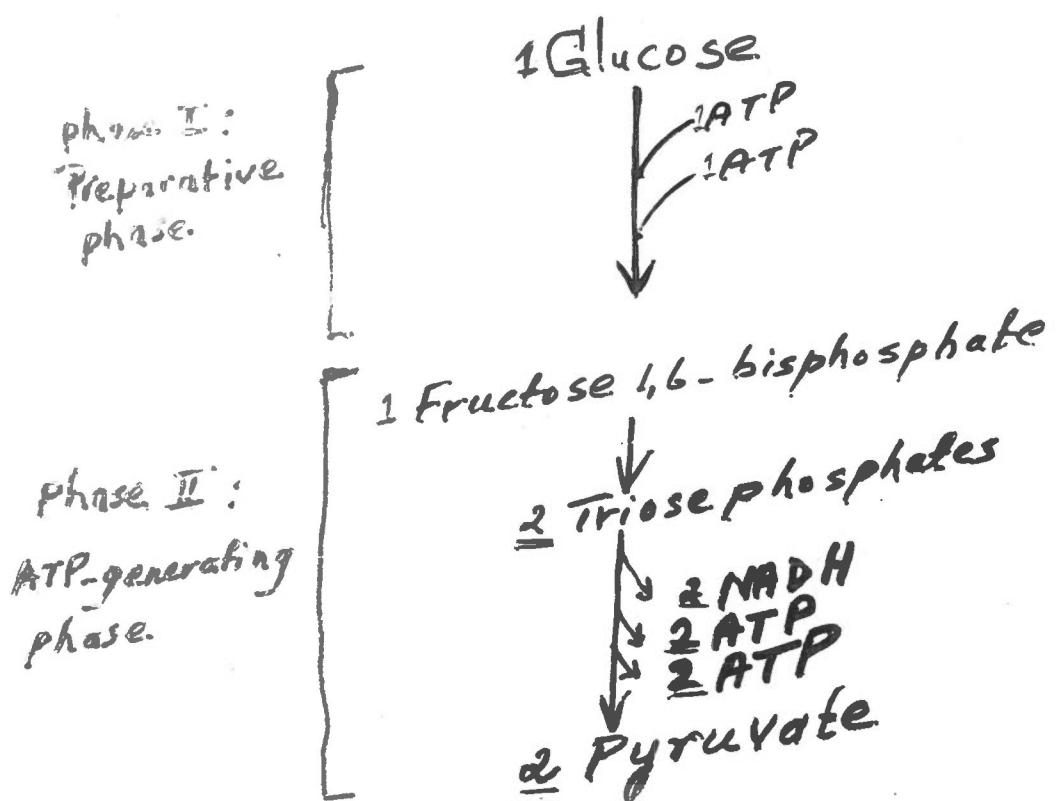


Figure 10.8
Covalent modification of *pyruvate kinase* results in inactivation of the enzyme. OAA = oxaloacetate.

GLYCOLYSIS

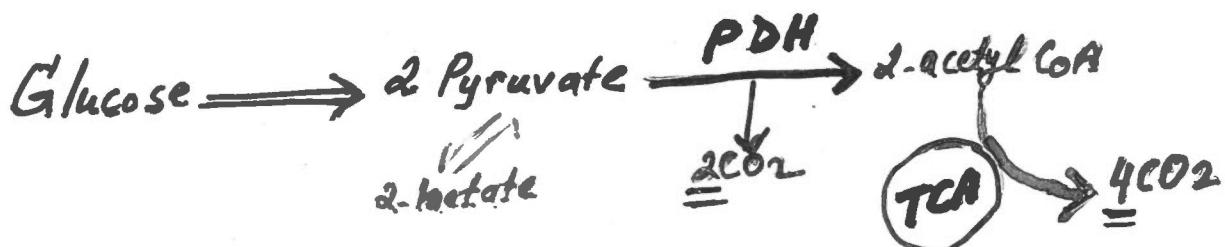
- Universal Pathway in all cell types.
- Generation of ATP with, and without, O_2
- Anabolic Pathway
→ biosynthetic precursors
- Phases of the glycolytic Pathway



GLYCOLYSIS :-

1a

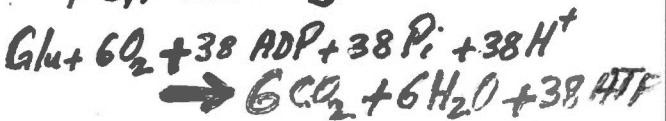
- Occurs in All Human Cells



No O_2 -requirement for glycolysis - anaerobic fermentation



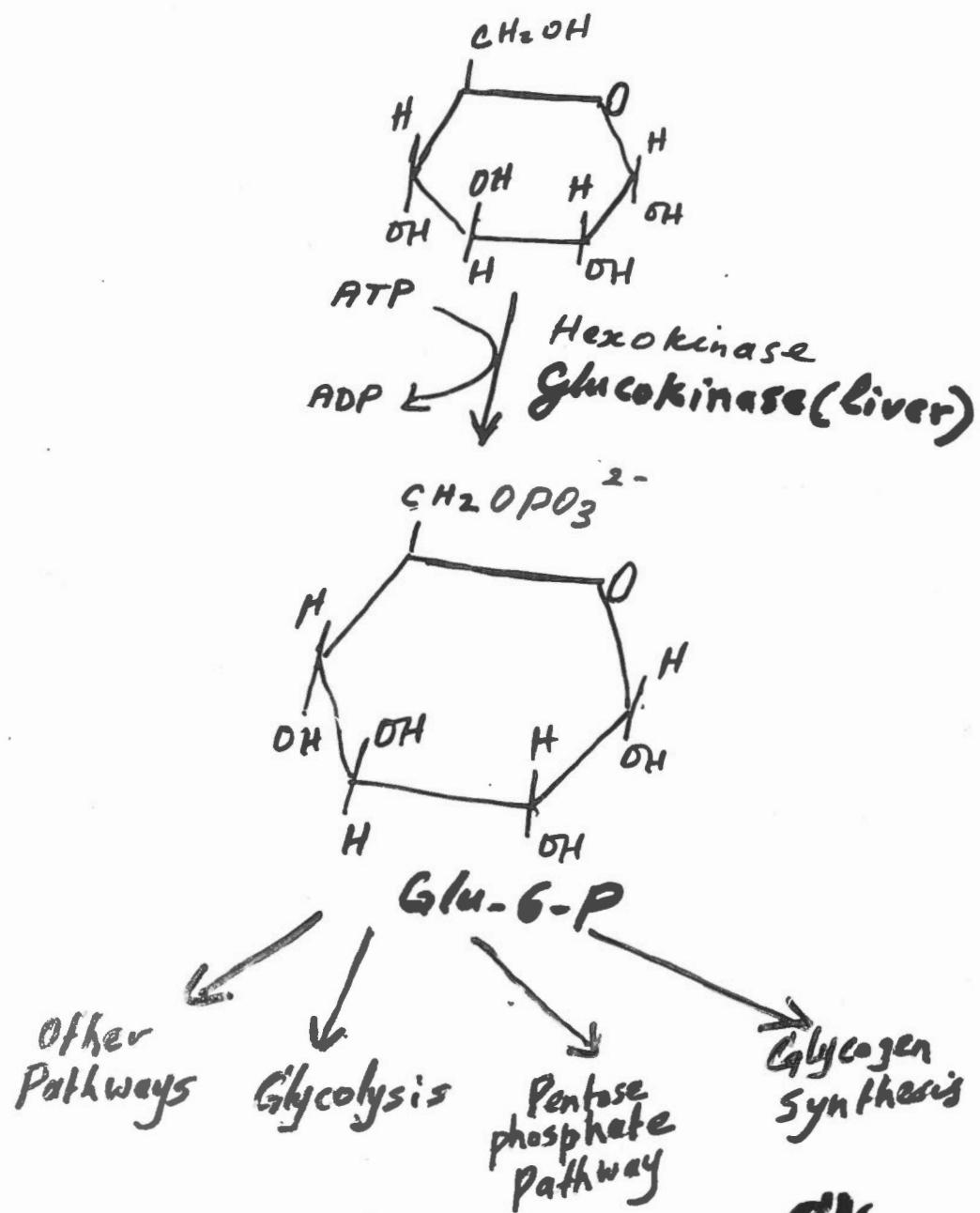
O_2 -requirement for PDH & TCA activity



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

1b

Glucose-6-phosphate Metabolism



Occurrence in all tissues

Km 0.02 mM

Sp. Glu, Fru, Man, Gal

Induction Not induced

Function Even low blood Glu only > 100 mg/dL

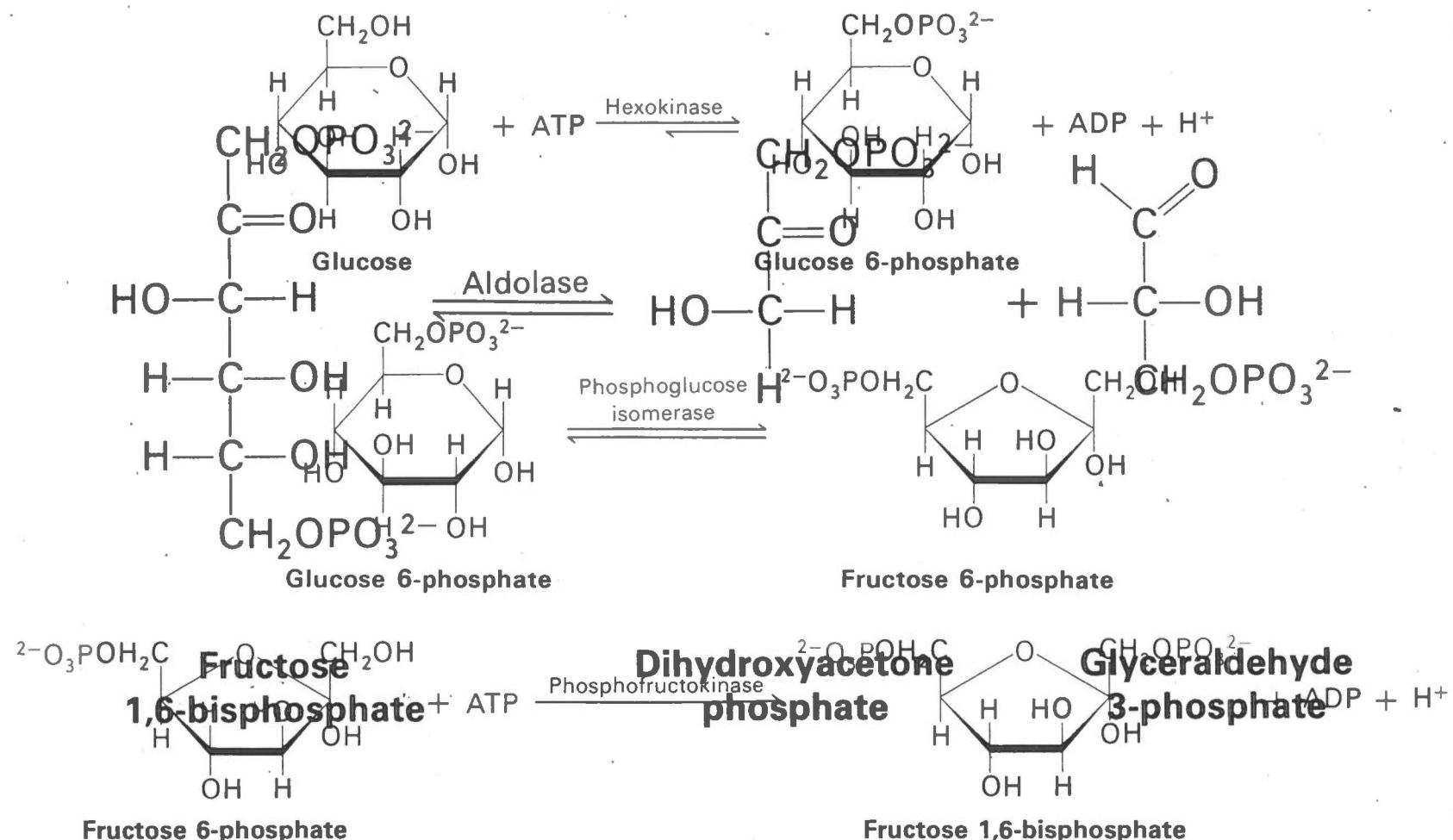
GK
in Liver

10 - 20 mM

Glu + others
↑ insulin, Glu

Reactions of GLYCOLYSIS

1dc



Associated figures, pages 486 and 487

Stryer: Biochemistry, Fourth Edition
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T-58

Set I

Glyceraldehyde 3-P dehydrogenase

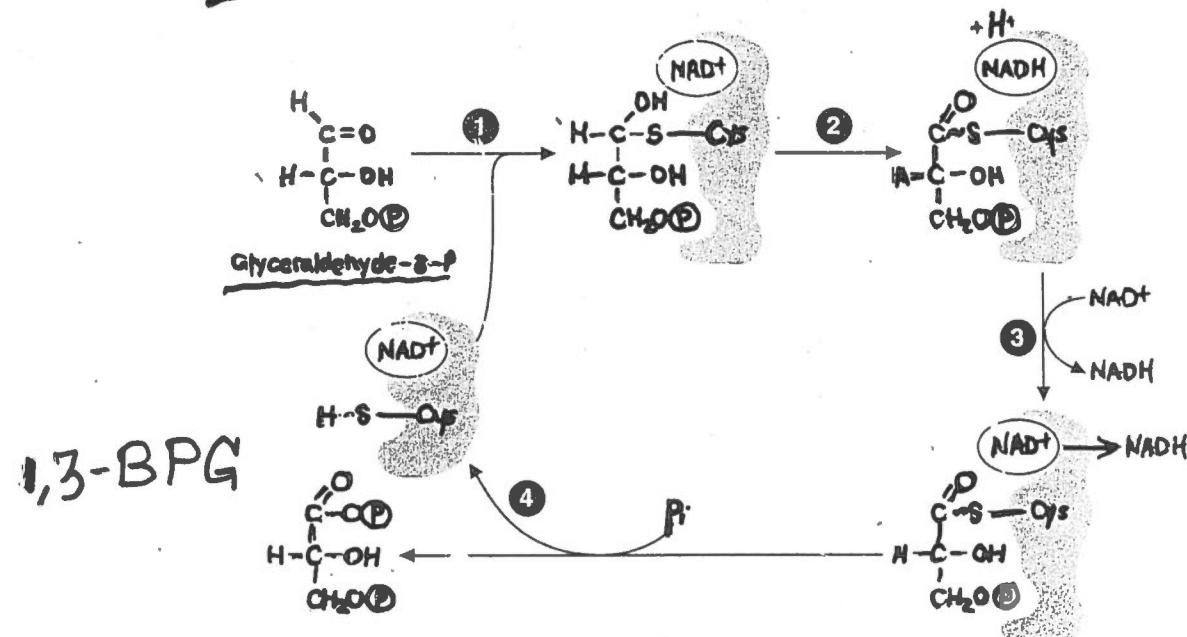
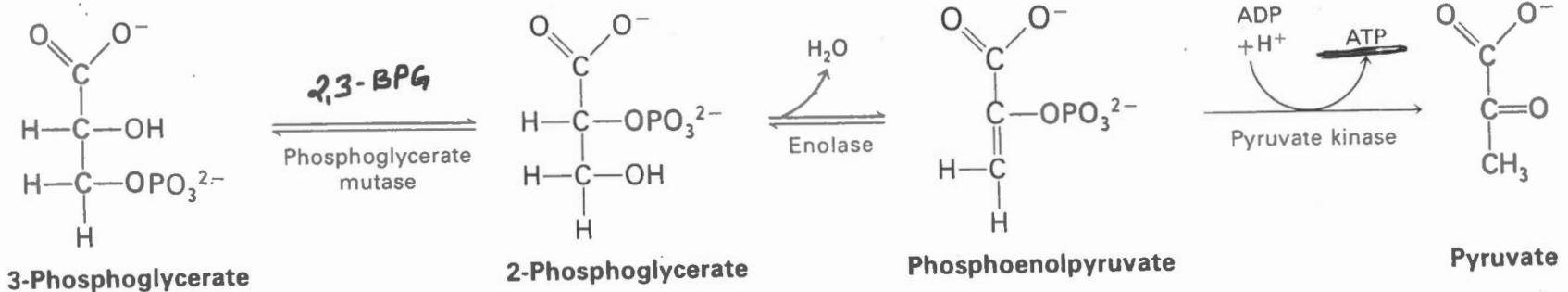
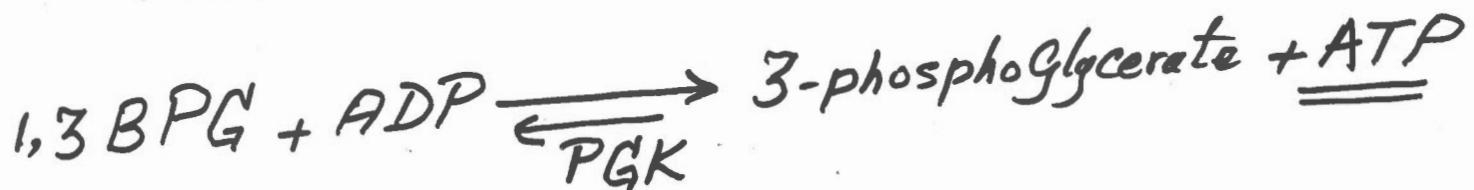
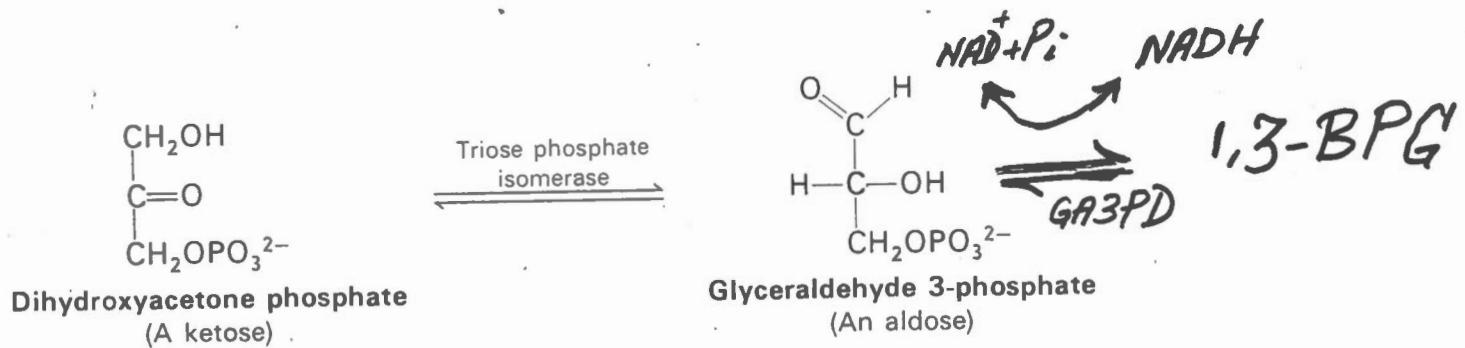


Fig. 22.17. Mechanism of the glyceraldehyde 3-phosphate dehydrogenase reaction. 1. The enzyme forms a covalent linkage with the substrate, using a cysteine group at the active site. The enzyme also contains bound NAD⁺ close to the active site. 2. The substrate is oxidized, forming a high-energy thioester 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.

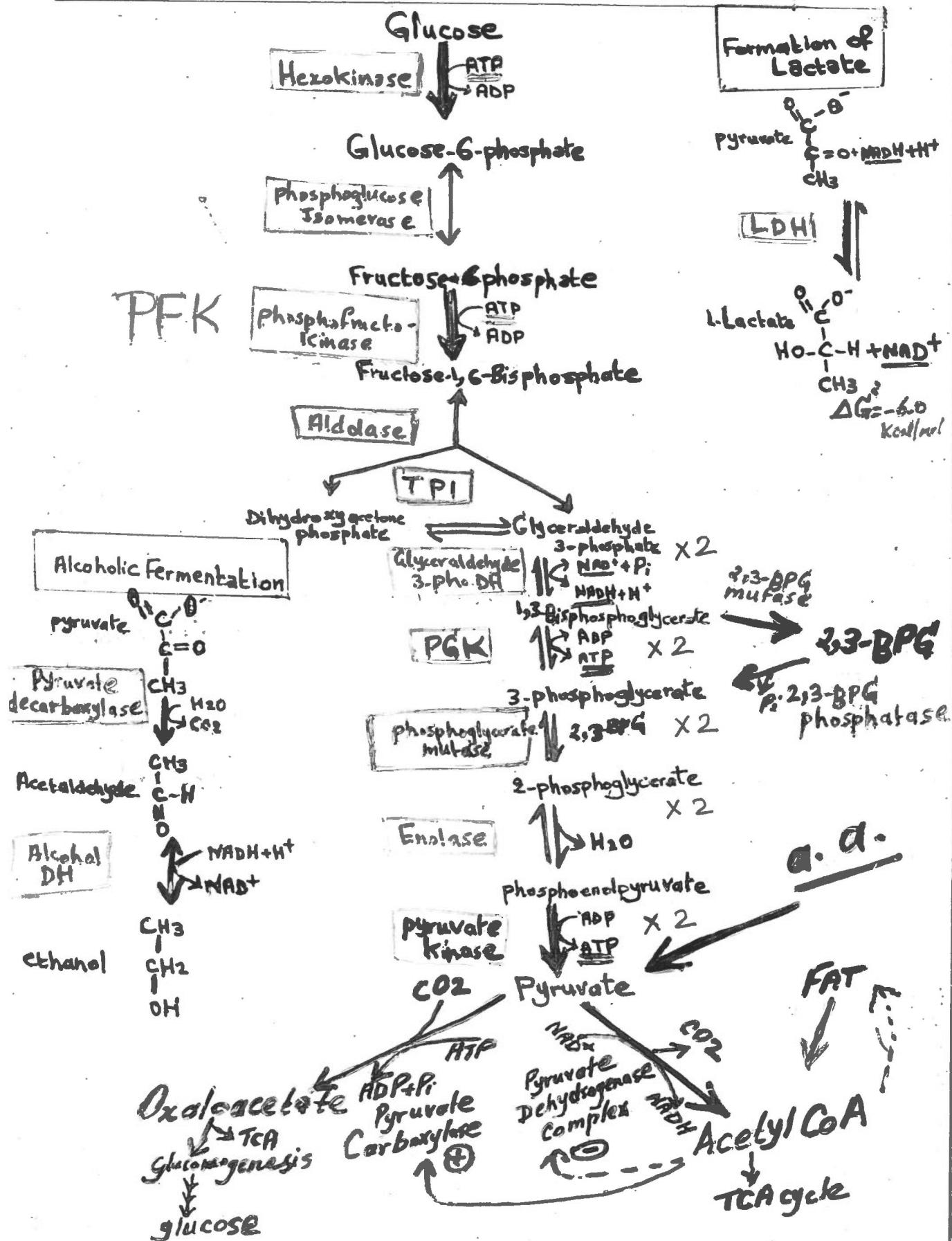
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1e



The Glycolytic Pathway

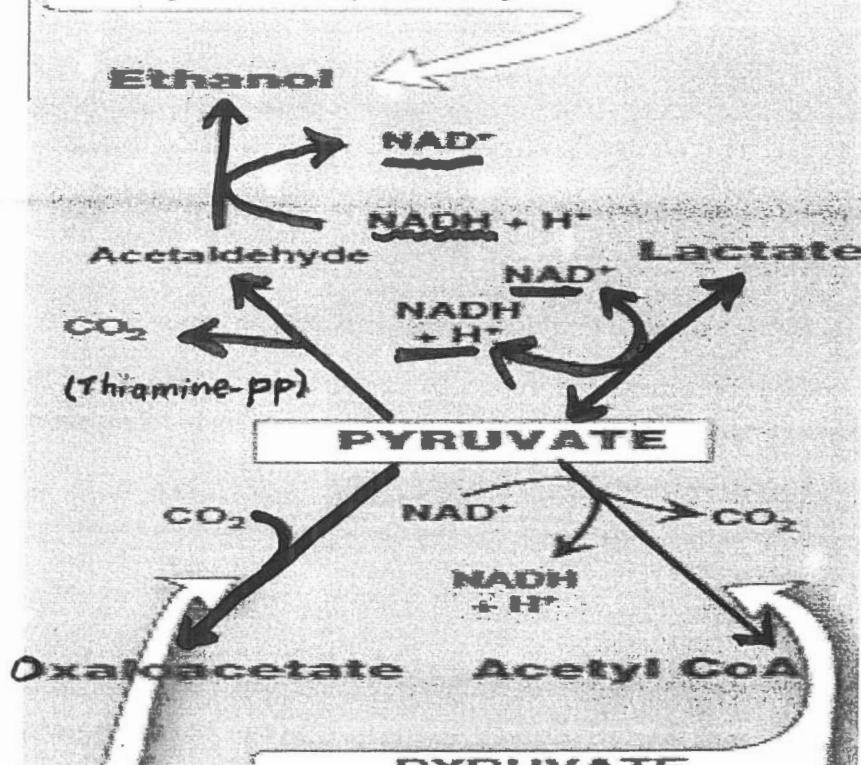
Ig



Summary of Metabolic fates of Pyruvate

ETHANOL SYNTHESIS

- Occurs in yeast and some bacteria (including intestinal flora).
- Thiamine pyrophosphate-dependent pathway.



PYRUVATE DEHYDROGENASE COMPLEX

- Inhibited by acetyl CoA.
- Source of acetyl CoA for TCA and fatty acid synthesis.
- An irreversible reaction.

PYRUVATE CARBOXYLASE

- Activated by acetyl CoA.
- Replenishes intermediates of the TCA cycle.
- Provides substrates for gluconeogenesis.
- An irreversible reaction.

Lactate is produced anaerobically
to meet the following demands

3

1. Cells with low energy demand
2. To cope with increased energy demands in vigorously exercising muscle
3. Hypoxia
to survive brief episodes of hypoxia
-but mixed blessings

$\text{Lactate} > 5 \text{ mmol/L}$ (0.4 - 1.8 mmol/L)
Ref range
 $\text{pH} < 7.2$ (7.35 - 7.45)
Lactic Acidosis:
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

$\rightarrow \uparrow\uparrow \text{NADH}/\text{NAD}$

rare

↓ gluconeogenesis

↓ Pyruvate dehydrogenase
e.g. in heritted deficiency
thiamine deficiency

↓ TCA activity

↓ Pyruvate Carboxylase deficiency

Regulation of the Glycolytic Pathway

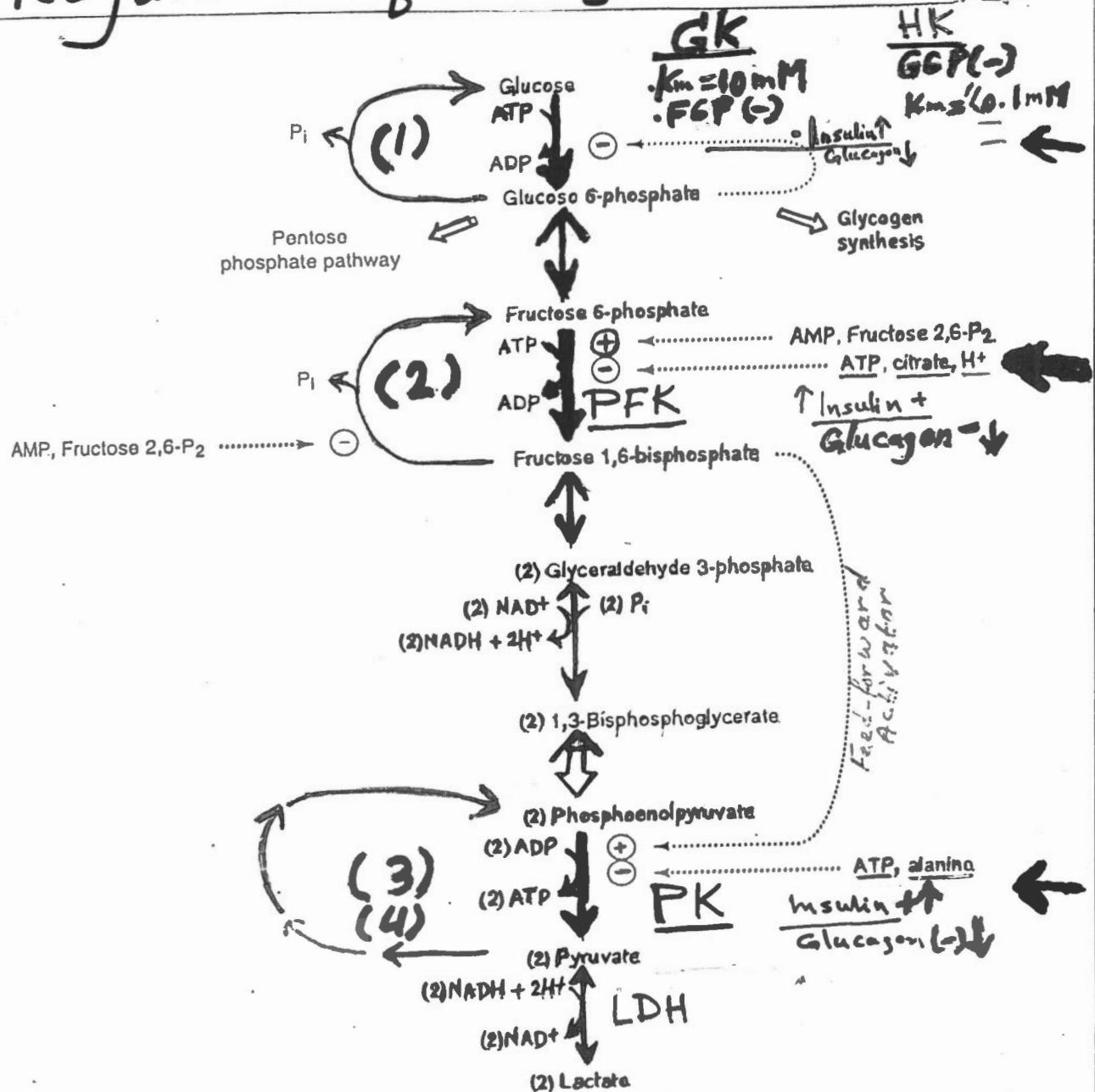


FIGURE 7.13

Important regulatory features of the glycolytic pathway.

Because of differences in isoenzyme distribution, not all tissues of the body have all of the regulatory mechanisms shown here.

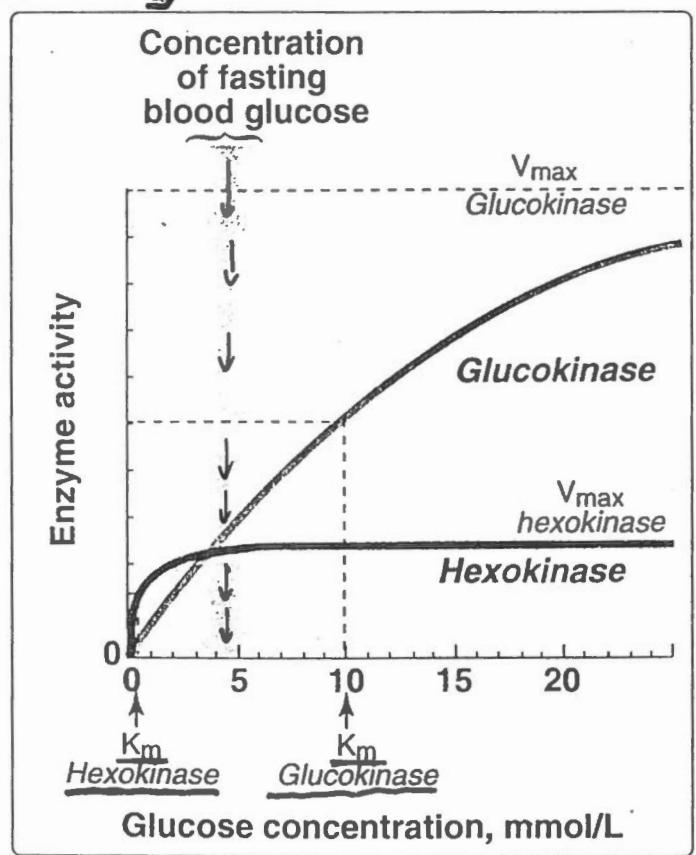
- Regulation of Liver PK

by phosphorylation - Dephospho-

Insulin ↑ PK — PK-P Inactive Insulin ↓
Glucagon ↓ Active

Effect of [Glucose] on HK and GK

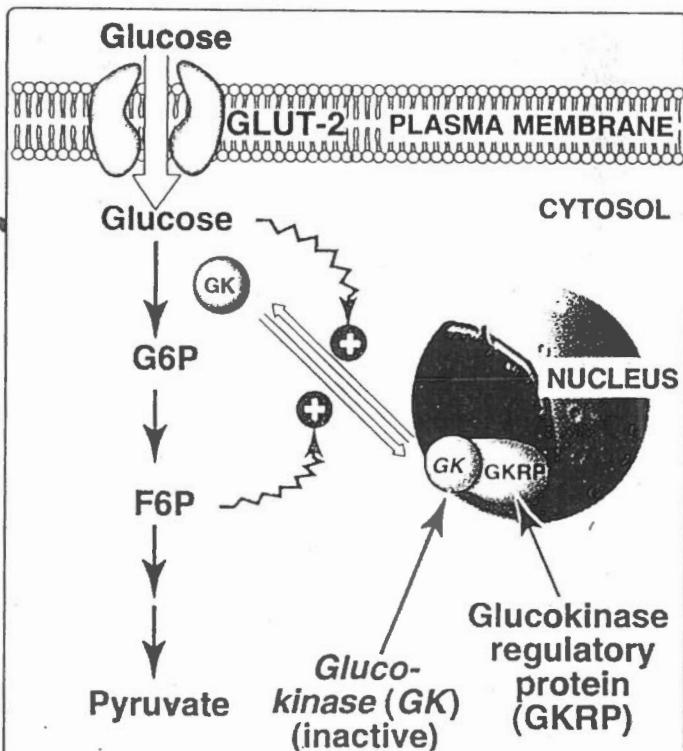
7.



Regulation of GK by "GKRP"

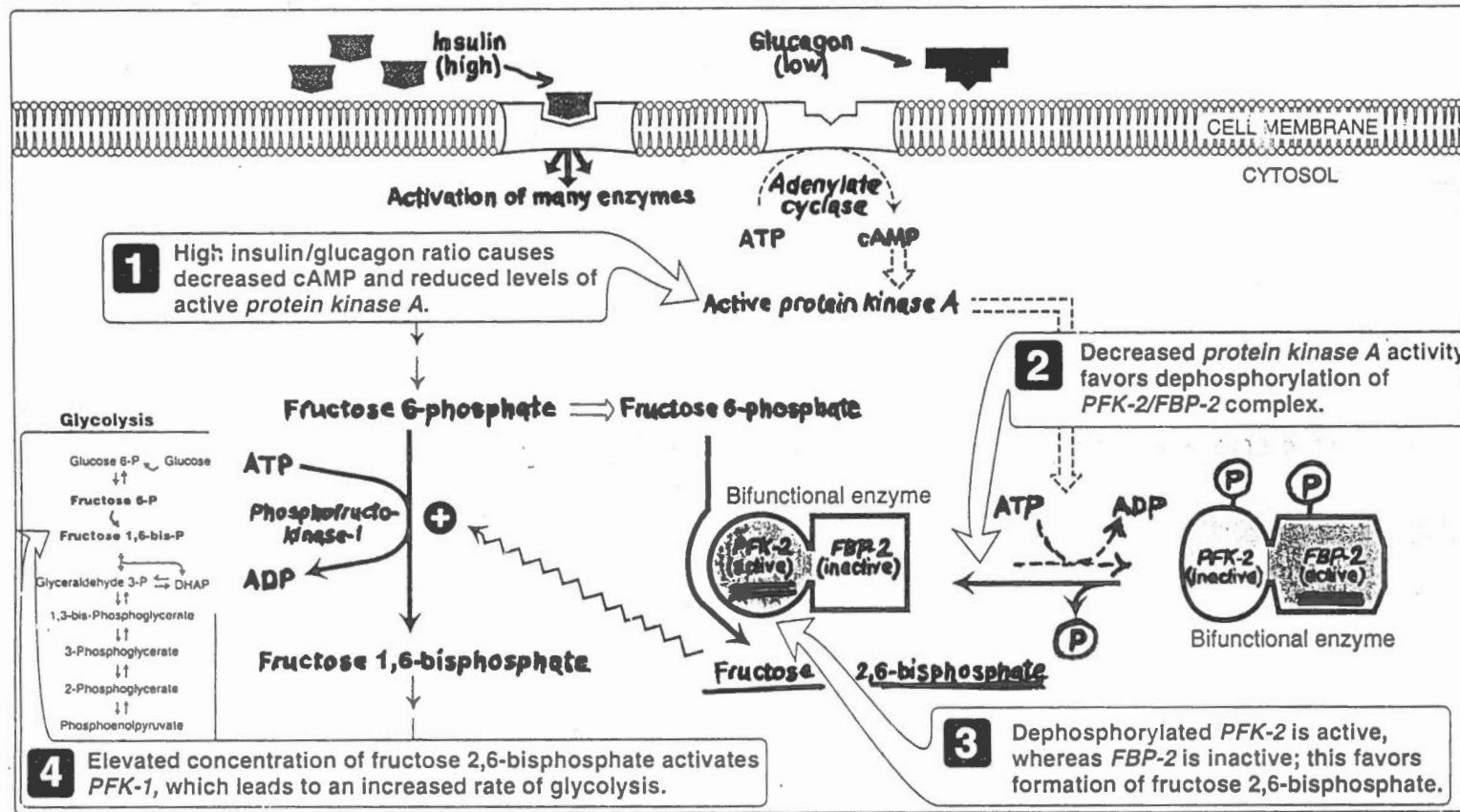
2)

Insulin \rightarrow ↑ GK transcription



- Regulation of Fru-2,6-BP Level by Hormones

8

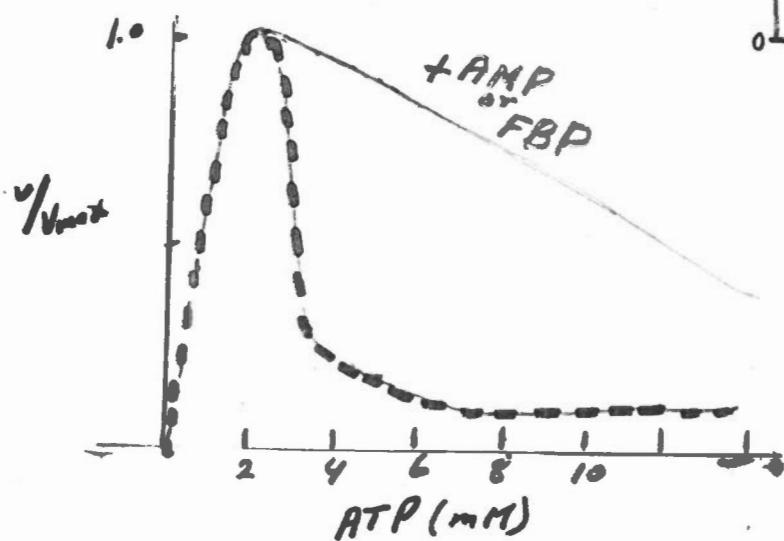
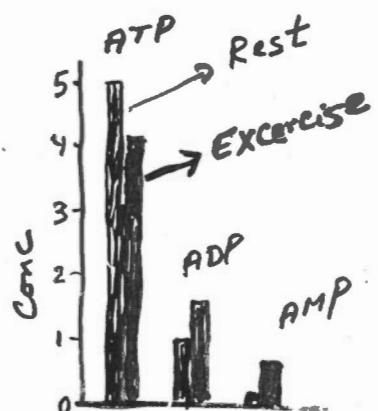
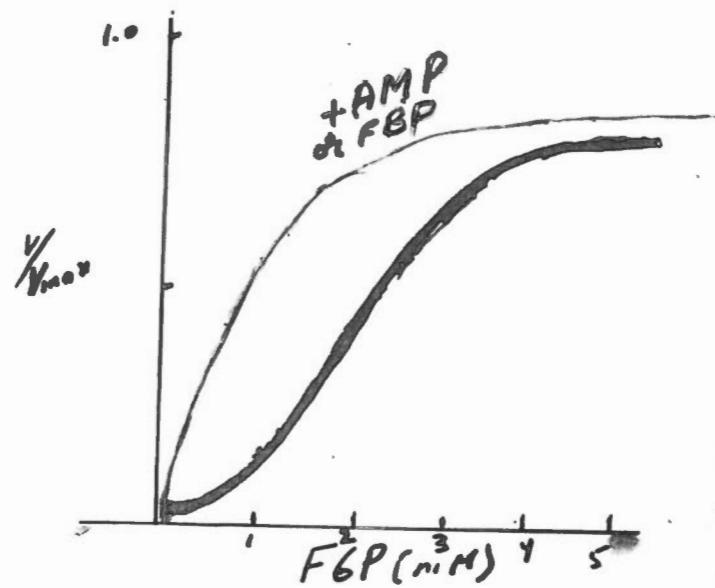


- Regulation of PK by phosphorylation - Dephospt
in the liver.



8a

- Regulation of PFK by AMP and ATP
and Fru-2,6-BP(FBP)



Inorganic inhibitors of Glycolysis:-

- Fluoride inhibits Enolase

Fluoridated water inhibits bacterial enolase to prevent Dental Caries

- Arsenic Poisoning

(1) Pentavalent arsenic (Arsenate)
prevent net ATP and NADH production by glycolysis
(Compete with Pi as a substrate for G3PD)

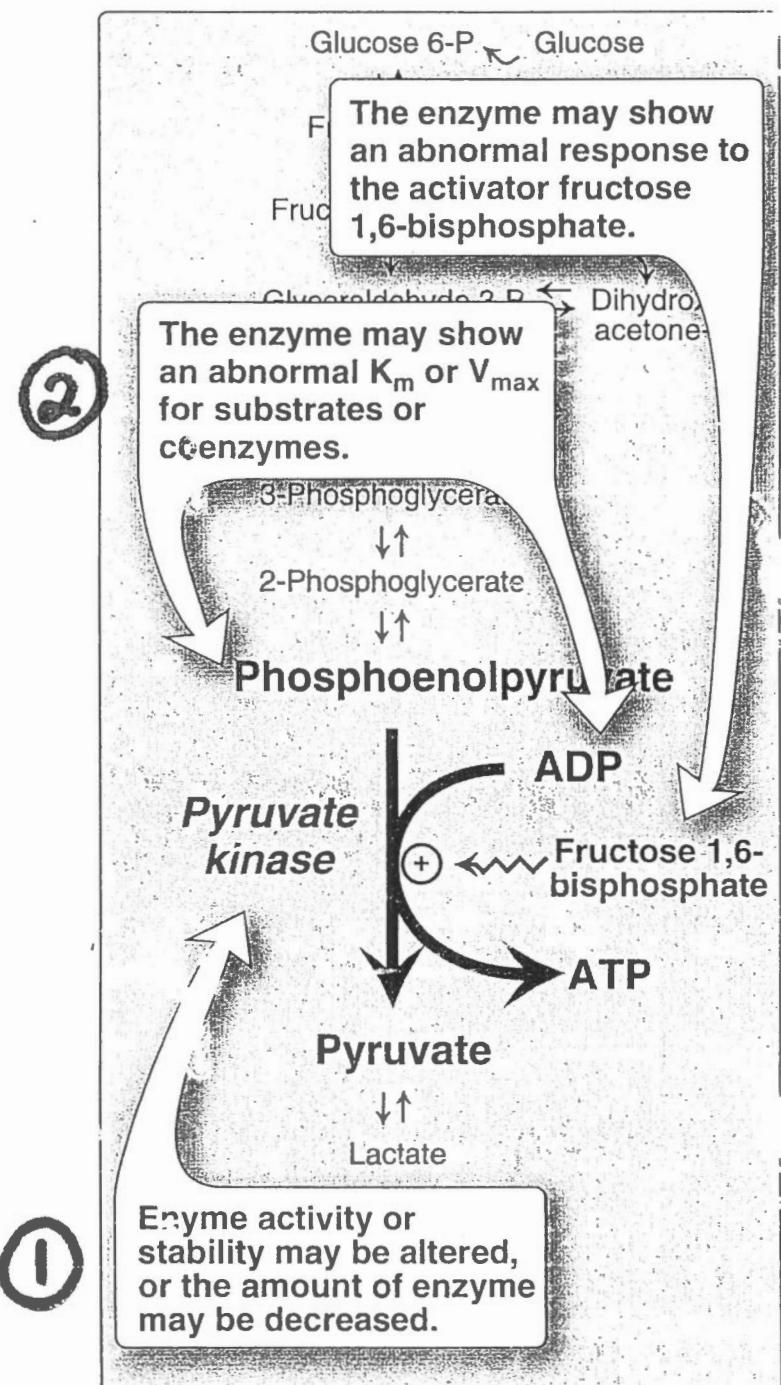
(2) Trivalent arsenic (arsenite)
• form stable complex with -SH of lipoic acid
inhibiting .PDH complex

- α -Ketoglutarate dehydrogenase
- branched-chain α -keto acid dehydrogenase

- cause neurological disturbances of death

- Pyruvate Kinase Deficiency

95% of glycolytic enzyme deficiency cases



- Severe deficiency requires blood transfusion

→ ↑ 2,3-BPG

→ ↓ ATP

- PGI (4% of glycolytic cases)