

Chapter 13

Glycolysis “Sugar splitting”

10 Reactions & some mechanisms

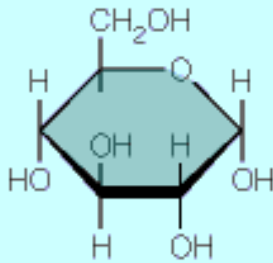
Energy

Enzymes

Regulation

Pyruvate Fate--aerobic or not?

ENERGY INVESTMENT PHASE



Glucose

Reactions 1 - 3

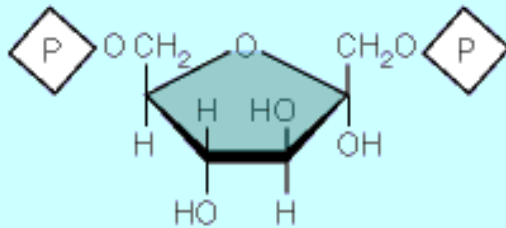
Activation by phosphorylation
2 ATPs invested

INVESTMENT
--spend ATP
--split sugars

1

2

3



Fructose-1,6-bisphosphate

Reactions 4 and 5

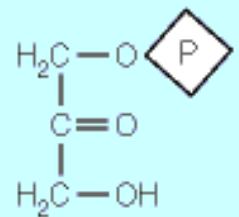
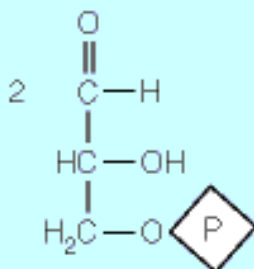
Cleavage of 1 six-carbon sugar phosphate to 2 three-sugar phosphates

4

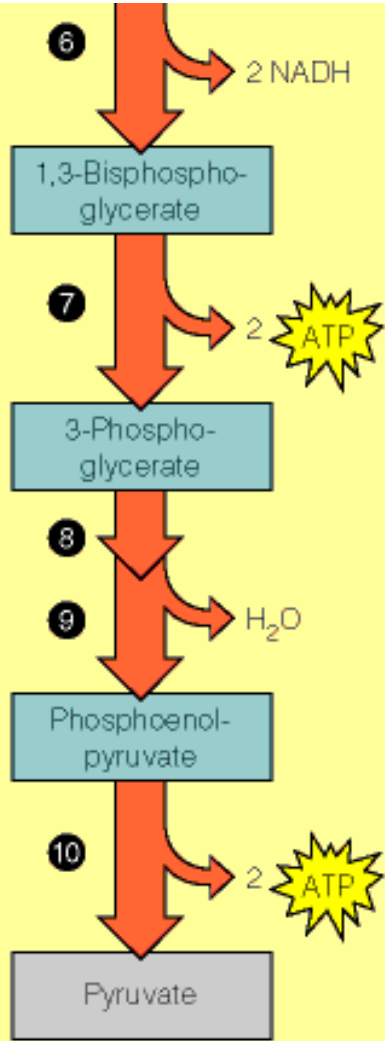
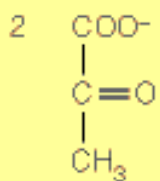
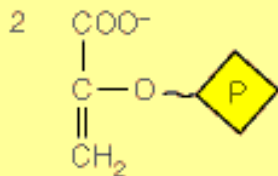
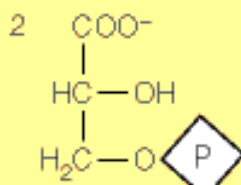
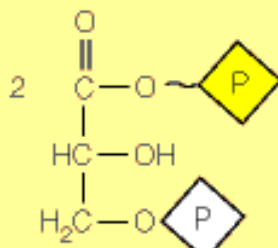
5

Glyceraldehyde-3-phosphate

Dihydroxyacetone phosphate



ENERGY GENERATION PHASE



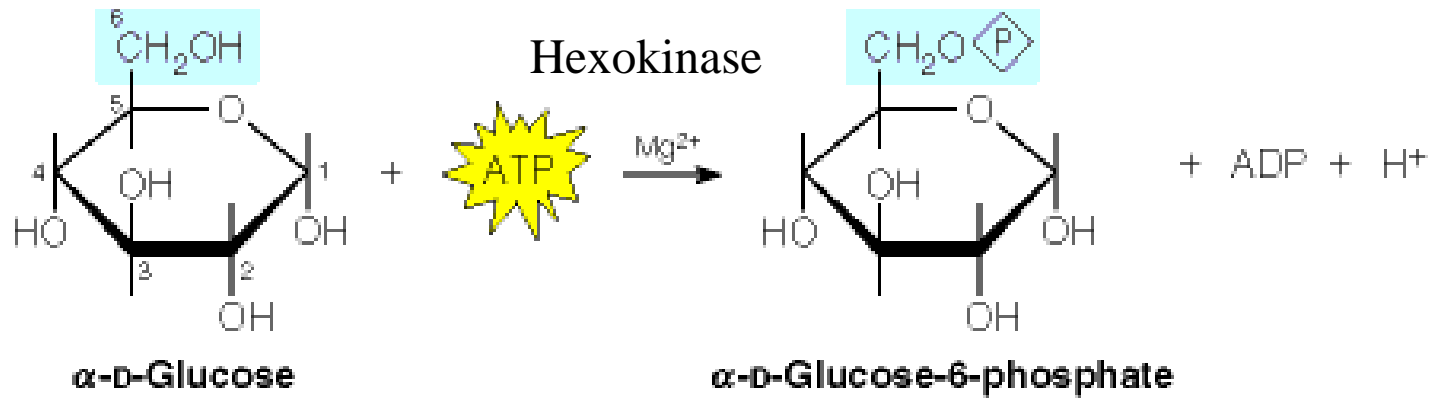
Reaction 6
Generation of 2 NADH and a super-high-energy compound

Reaction 7
Substrate-level phosphorylation
2 ATPs generated

Reactions 8 and 9
Generation of a super-high-energy compound (and water)

Reaction 10
Substrate-level phosphorylation
2 ATPs generated

THE PAY-OFF
Make ATP from
Higher Energy
Compounds



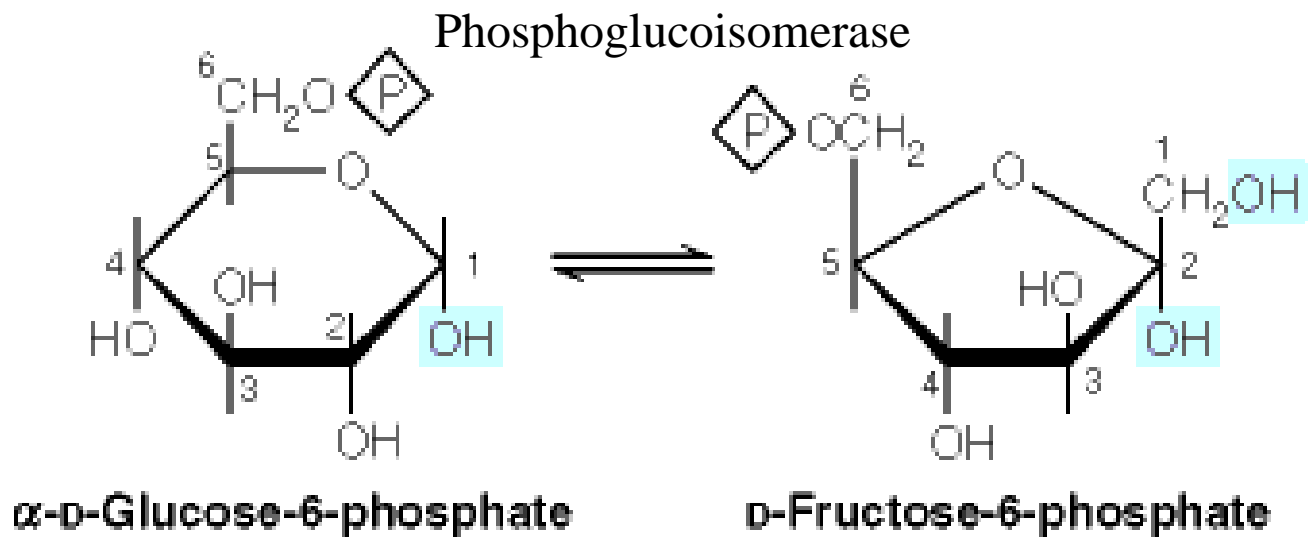
$$\Delta G^{0'} = -16.7 \text{ kJ/mol}$$

Hexokinase--

blood form low K_m --at V_{max}

Liver form high K_m --< V_{max} controls

Reaction #1--Produce G6P



$$\Delta G^{\circ'} = +1.7 \text{ kJ/mol}$$

Isomerize to fructose

Mechanism?

Linearize to aldose (C1), endiol (C1+C2), ketose (C2), recyclize

Phosphofructokinase

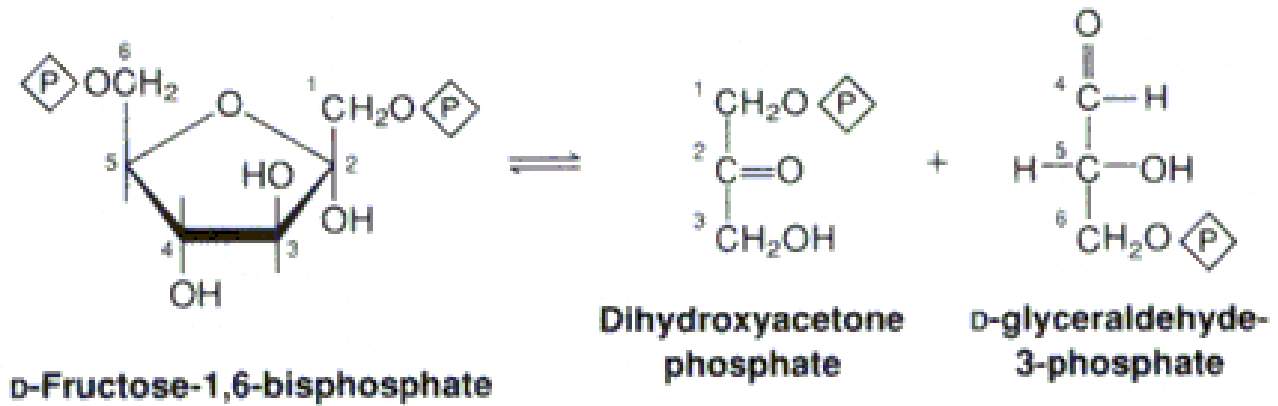


$$\Delta G^{\circ, \prime} = -14.2 \text{ kJ/mol}$$

Reaction #3

ATP investment to make
“symmetrical” phosphorylated fructose.

aldolase



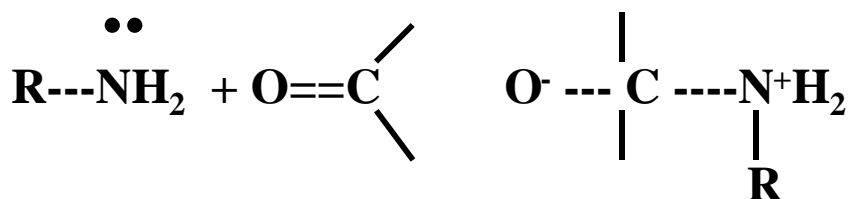
$$\Delta G^{o'} = +23.9 \text{ kJ/mol}$$

Reaction #4
Sugar splitting is energetically uphill

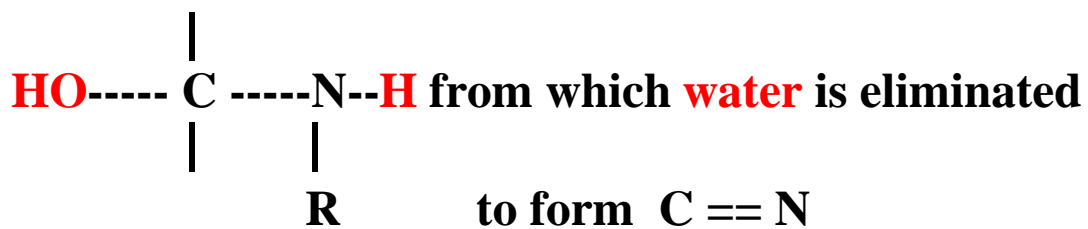
Mechanism--Schiff base

Schiff Base Mechanism:

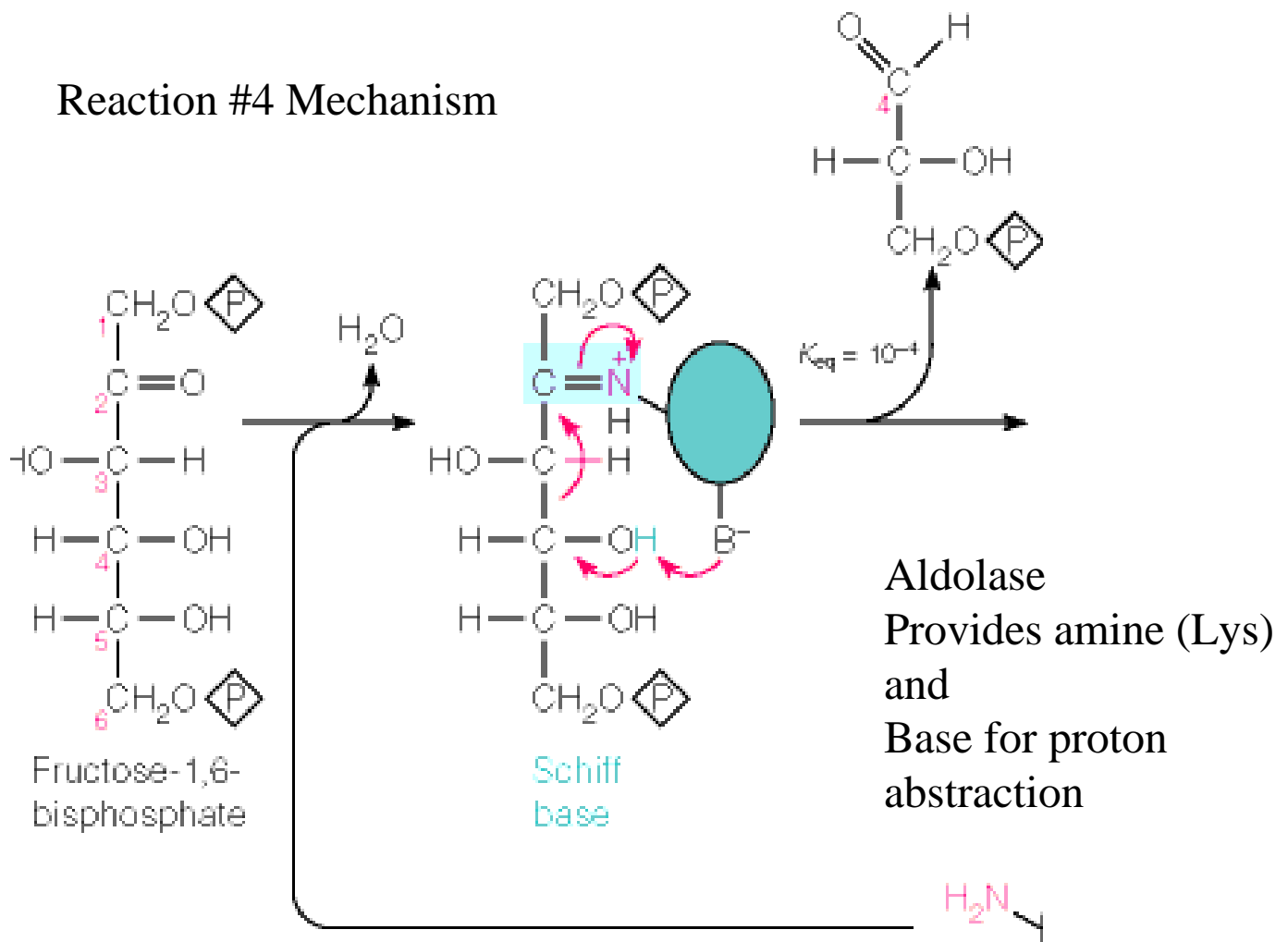
Amine + ketone or aldehyde \longrightarrow water + imine (C=N)



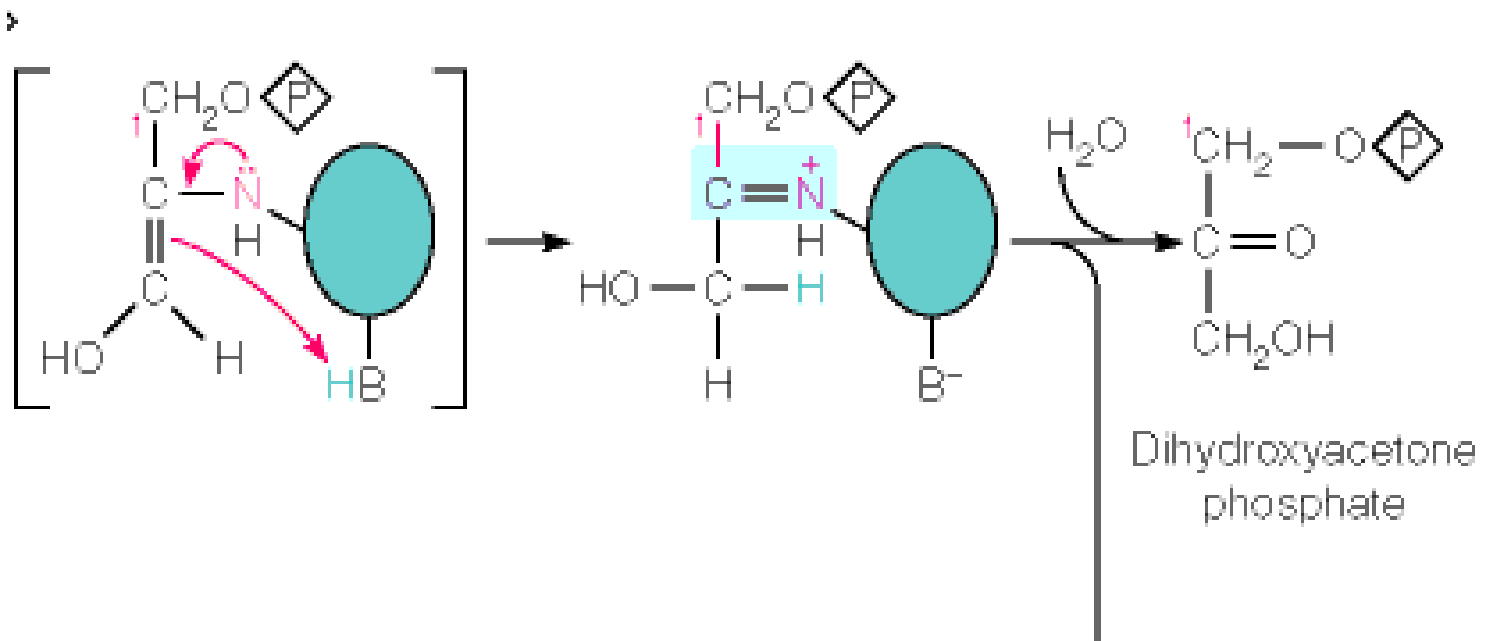
Which tautomerizes to:



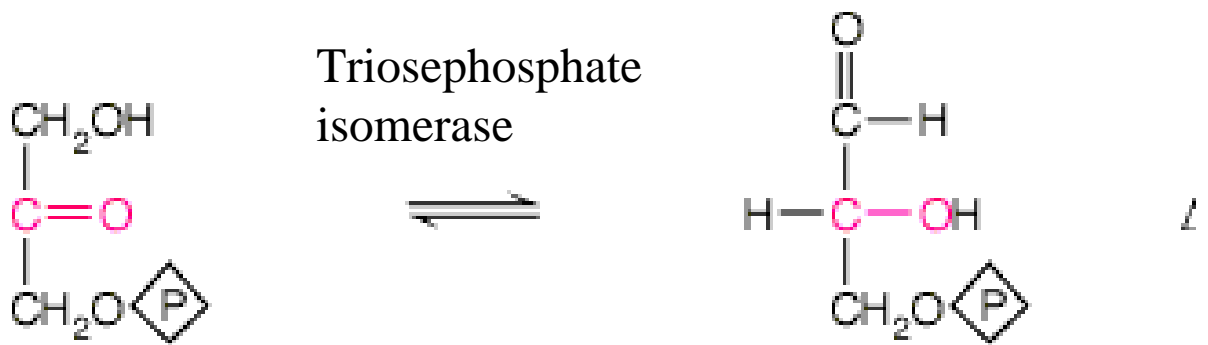
Reaction #4 Mechanism



Glyceraldehyde-3-phosphate



Reaction #4 Mechanism Part 2



Dihydroxyacetone phosphate

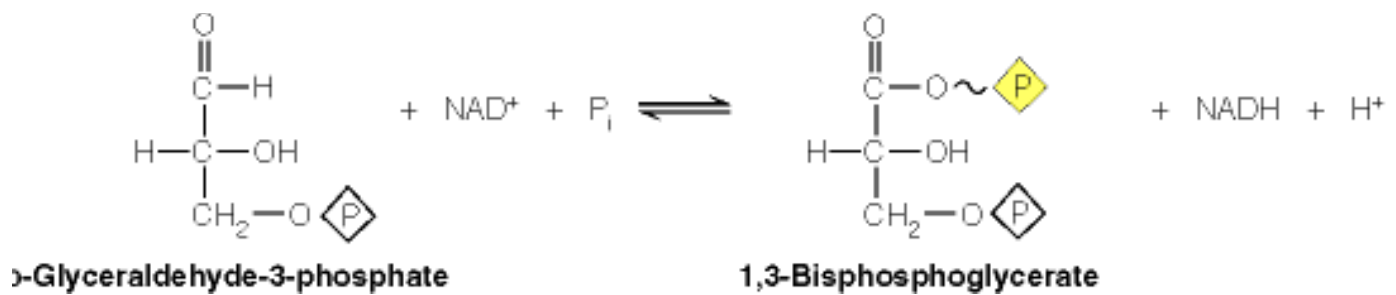
D-Glyceraldehyde-3-phosphate

$$\Delta G^{\circ r} = +7.6 \text{ kJ/mol}$$

Enediol intermediate

Reaction #5

Glyceraldehyde-3-phosphate dehydrogenase



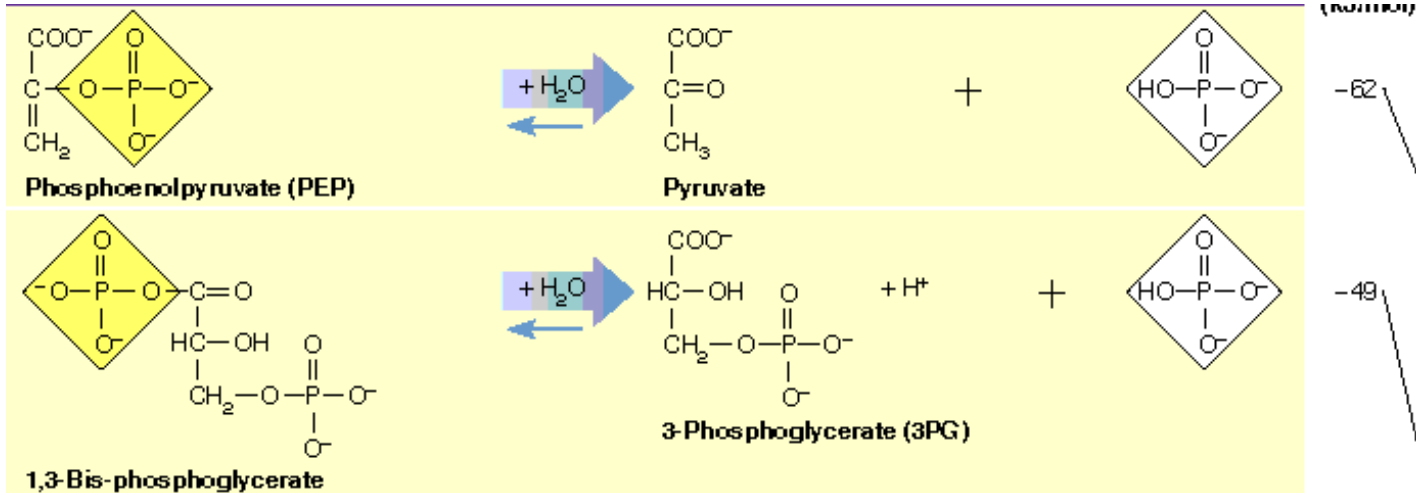
$$\Delta G^{\circ'} = +6.3 \text{ kJ/mol}$$

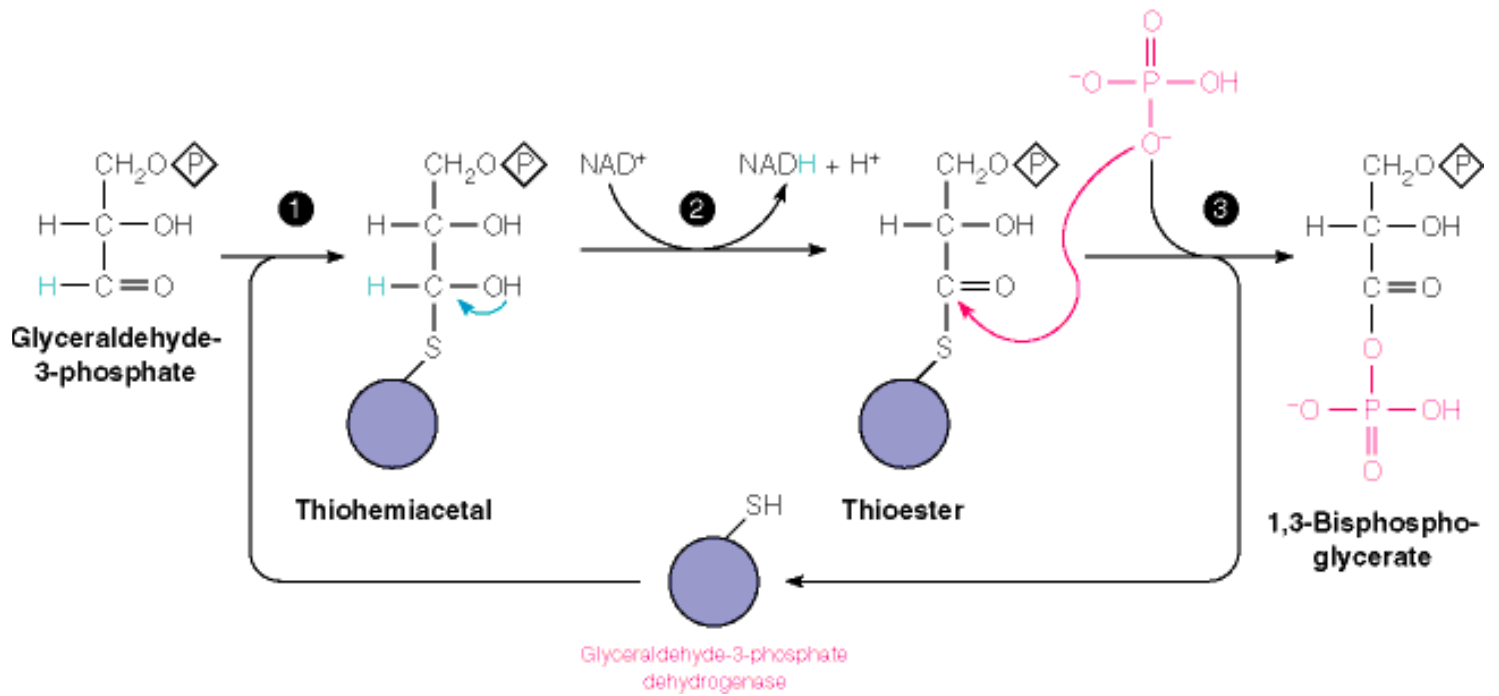
Reaction #6

Redox!!!!

Historical experiment--addition of inorganic phosphate stimulates glycolysis.

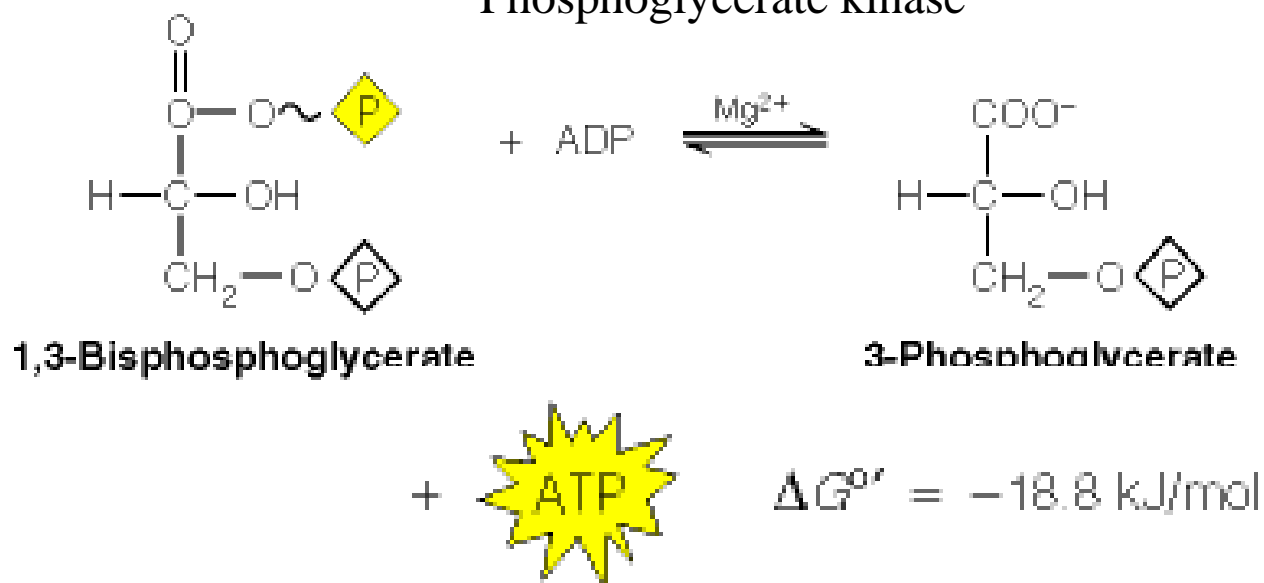
“Super” High Energy Compounds





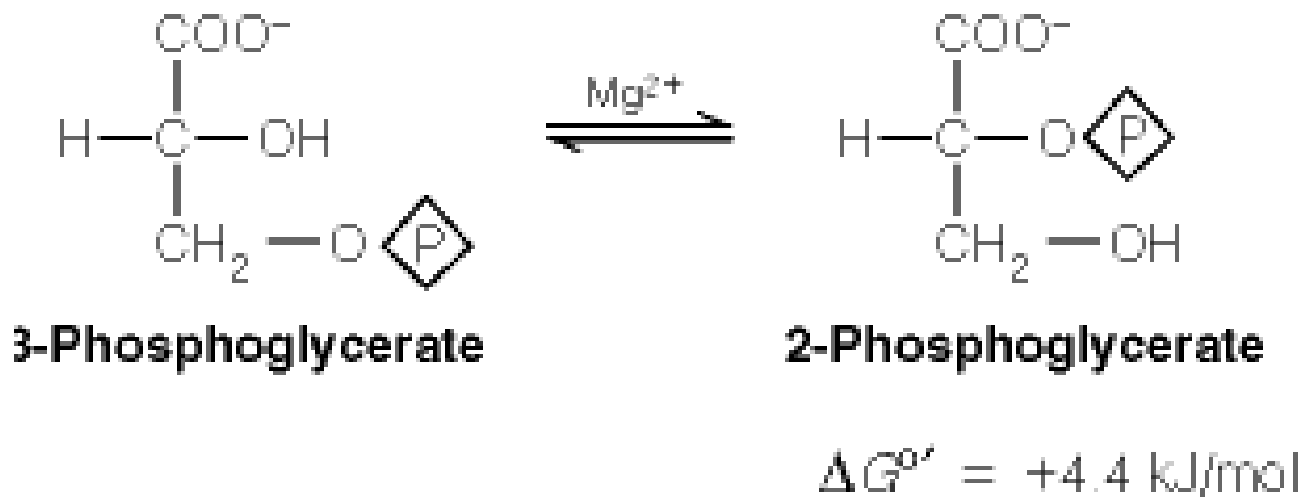
Mechanistic Clues--this reaction is inhibited by iodoacetate and mercury.

Phosphoglycerate kinase

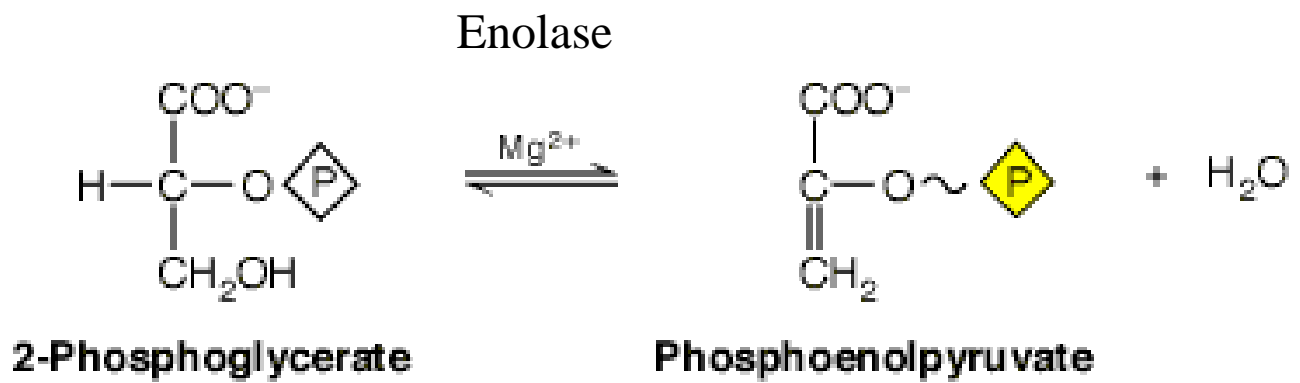


Reaction #7--ATP production

Phosphoglycerate mutase

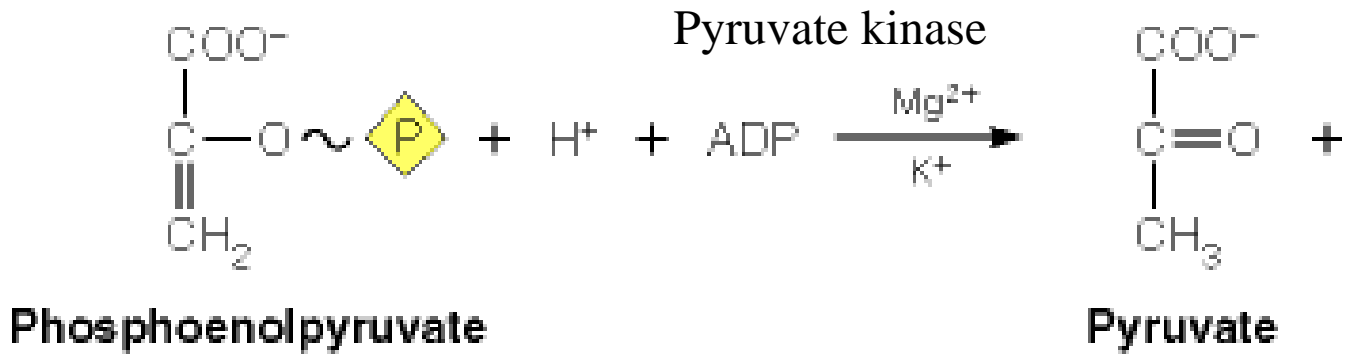


Reaction #8



$$\Delta G^{\circ'} = +1.7 \text{ kJ/mol}$$

Reaction # 9

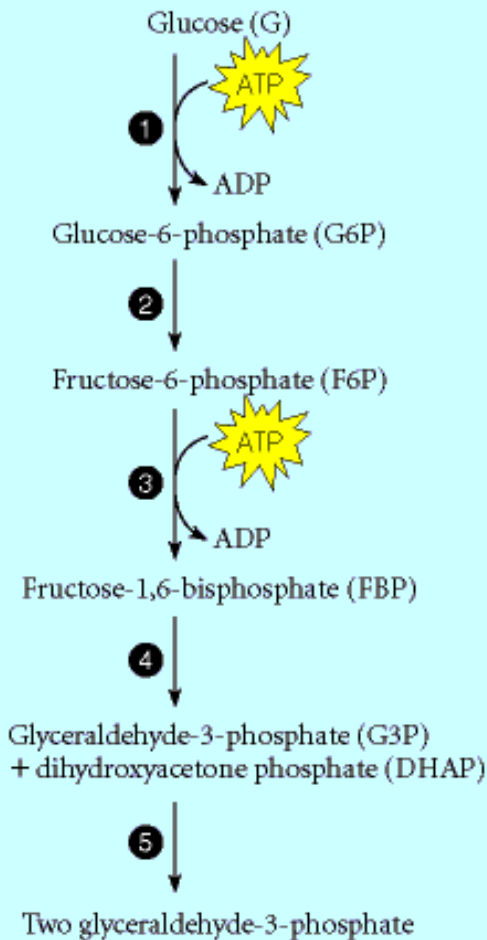


$$\Delta G^{0'} = -31.4 \text{ kJ/mol}$$

Reaction #10--More ATP

But net oxidation of 3C/ reduction of NAD⁺

ENERGY INVESTMENT PHASE



Hexokinase (HK)

-1

-16.7

-33.5

Phosphoglucoisomerase (PGI)

+1.7

-2.5

Phosphofructokinase (PFK)

-1

-14.2

-22.2

Aldolase (ALD)

+23.9

-1.3

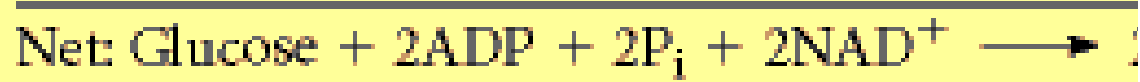
Triose phosphate isomerase (TP)

+7.6

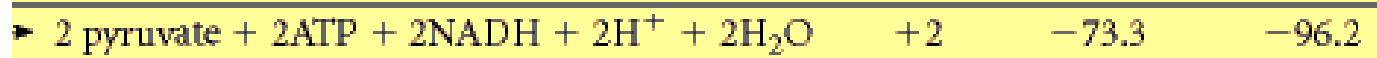
+2.5

ENERGY GENERATION PHASE

<p>6</p> <p>$2\text{NAD}^+ + 2\text{P}_i$</p> <p>$2\text{NADH} + 2\text{H}^+$</p>	<p>Glyceraldehyde-3-phospho dehydrogenase (G3PDP)</p>	<p>+12.6</p>	<p>-3.4</p>	
<p>Two 1,3-bisphosphoglycerate (BPG)</p>				
<p>7</p> <p>2ADP</p> <p>2 ATP</p>	<p>Phosphoglycerate kinas</p>	<p>+2</p>	<p>-37.6</p>	<p>+2.6</p>
<p>Two 3-phosphoglycerate (3PG)</p>				
<p>8</p>	<p>Phosphoglycerate muta</p>	<p>+8.8</p>	<p>+1.6</p>	
<p>Two 2-phosphoglycerate (2PG)</p>				
<p>9</p> <p>$2\text{H}_2\text{O}$</p>	<p>Enolase (ENO)</p>	<p>+3.4</p>	<p>-6.6</p>	
<p>Two phosphoenolpyruvate (PEP)</p>				
<p>10</p> <p>2ADP</p> <p>2 ATP</p>	<p>Pyruvate kinase (PK)</p>	<p>+2</p>	<p>-62.8</p>	<p>-33.4</p>
<p>Two pyruvate (Pyr)</p>				



Net ΔG° ' **Net ΔG '**



Net ATP

Glycolysis II

Pyruvate Fates--TPP Mechanism

Regulation and Enzymes

Other Sugars and Pathways

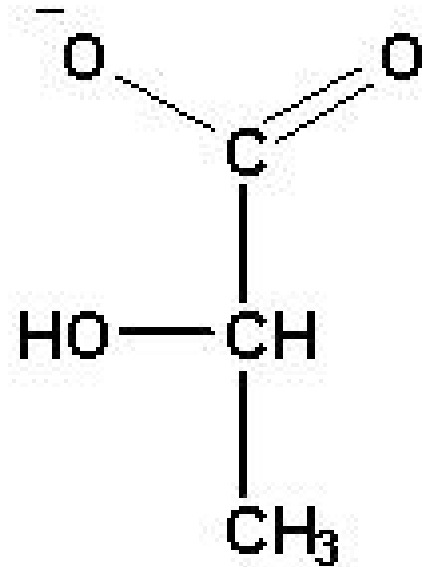
Pyruvate fates

Aerobic---On to citric acid cycle

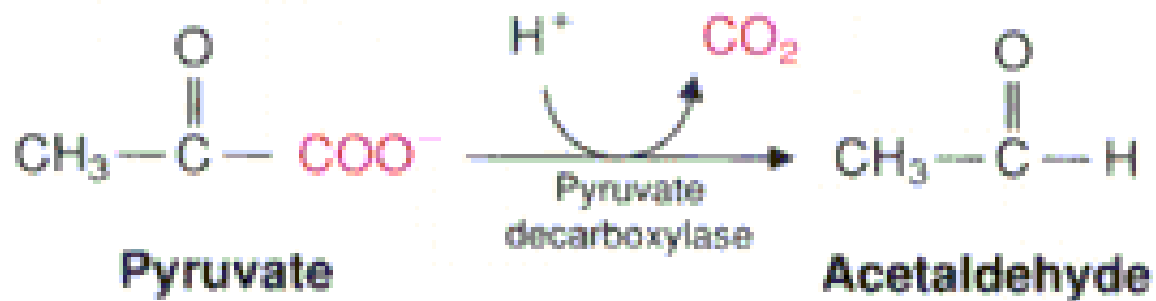
Anaerobic--fermentation

In yeast--fermentation to ethanol & release of CO₂

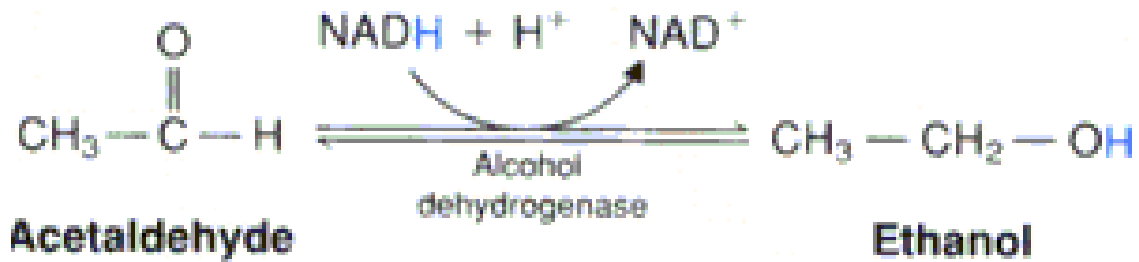
In animals--reduction to lactate & regeneration of NAD⁺



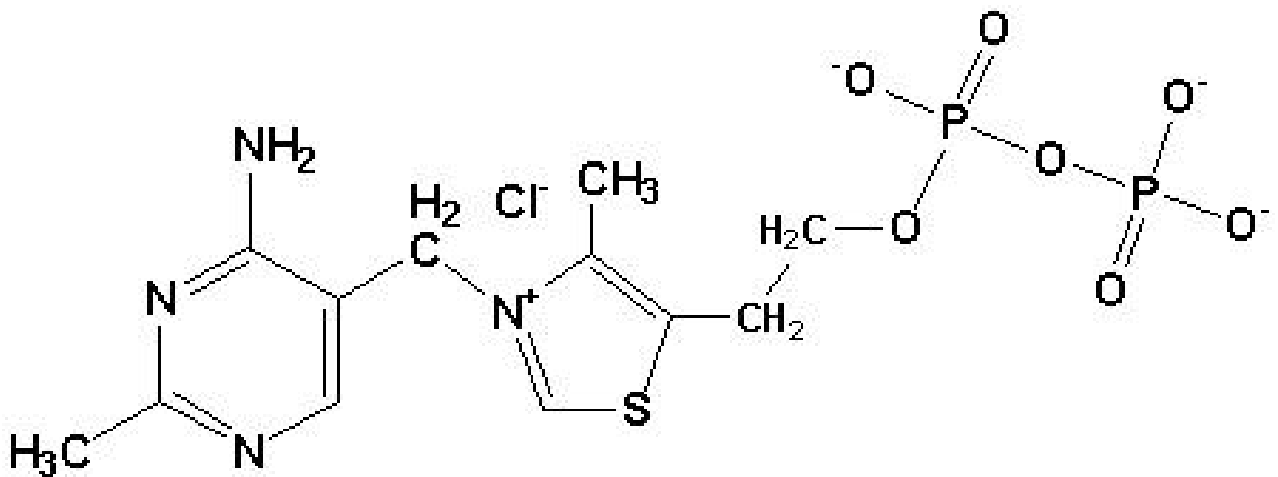
L-Lactate



Non-oxidative decarboxylation



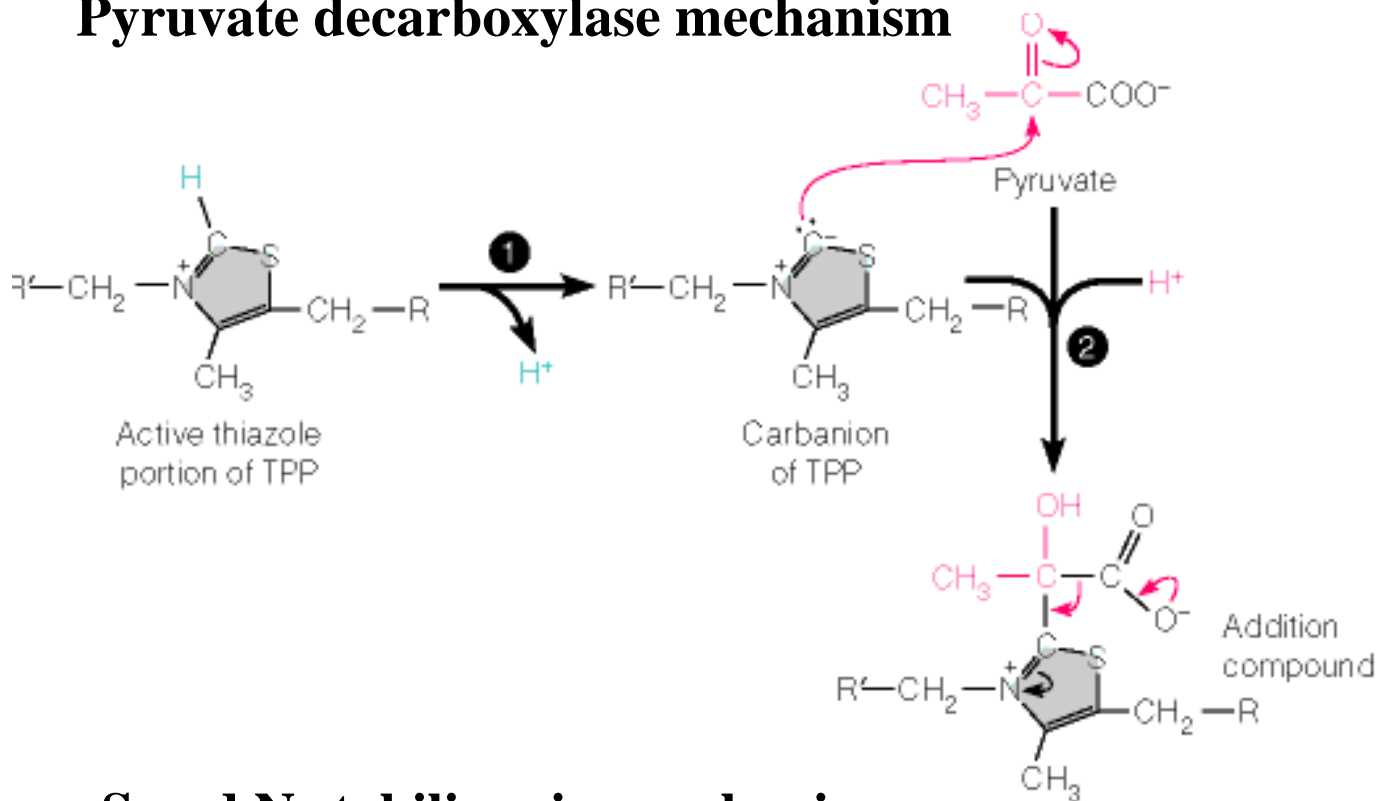
The reverse reaction occurs on alcohol consumption.
 The aldehyde and NAD⁺ depletion contribute to hangovers.



Thiamine pyrophosphate

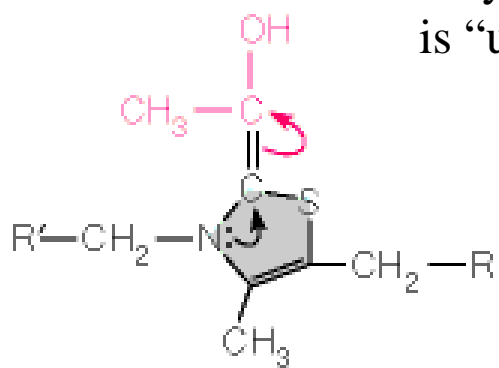
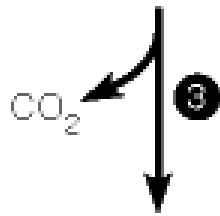
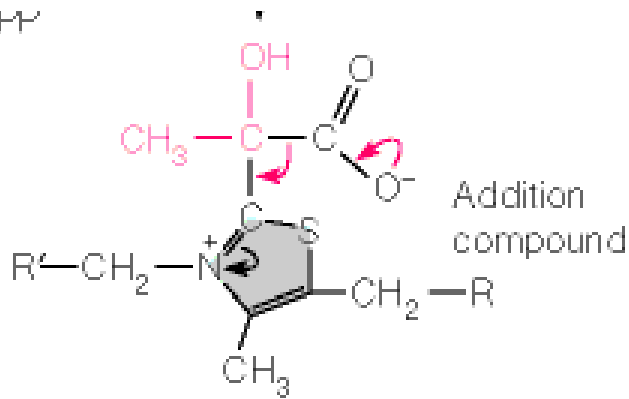
TPP-co-factor in pyruvate decarboxylase

Pyruvate decarboxylase mechanism

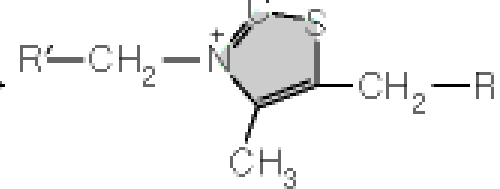
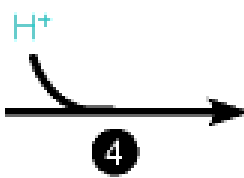


S and N stabilize ring carbanion

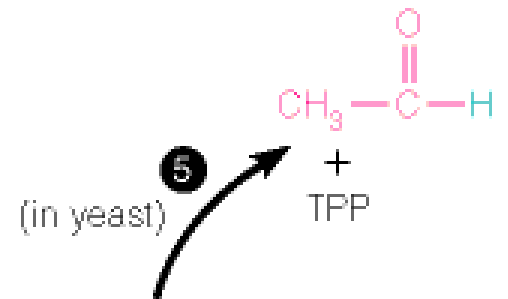
of TPP



TPP-
only a small portion
is "useful"

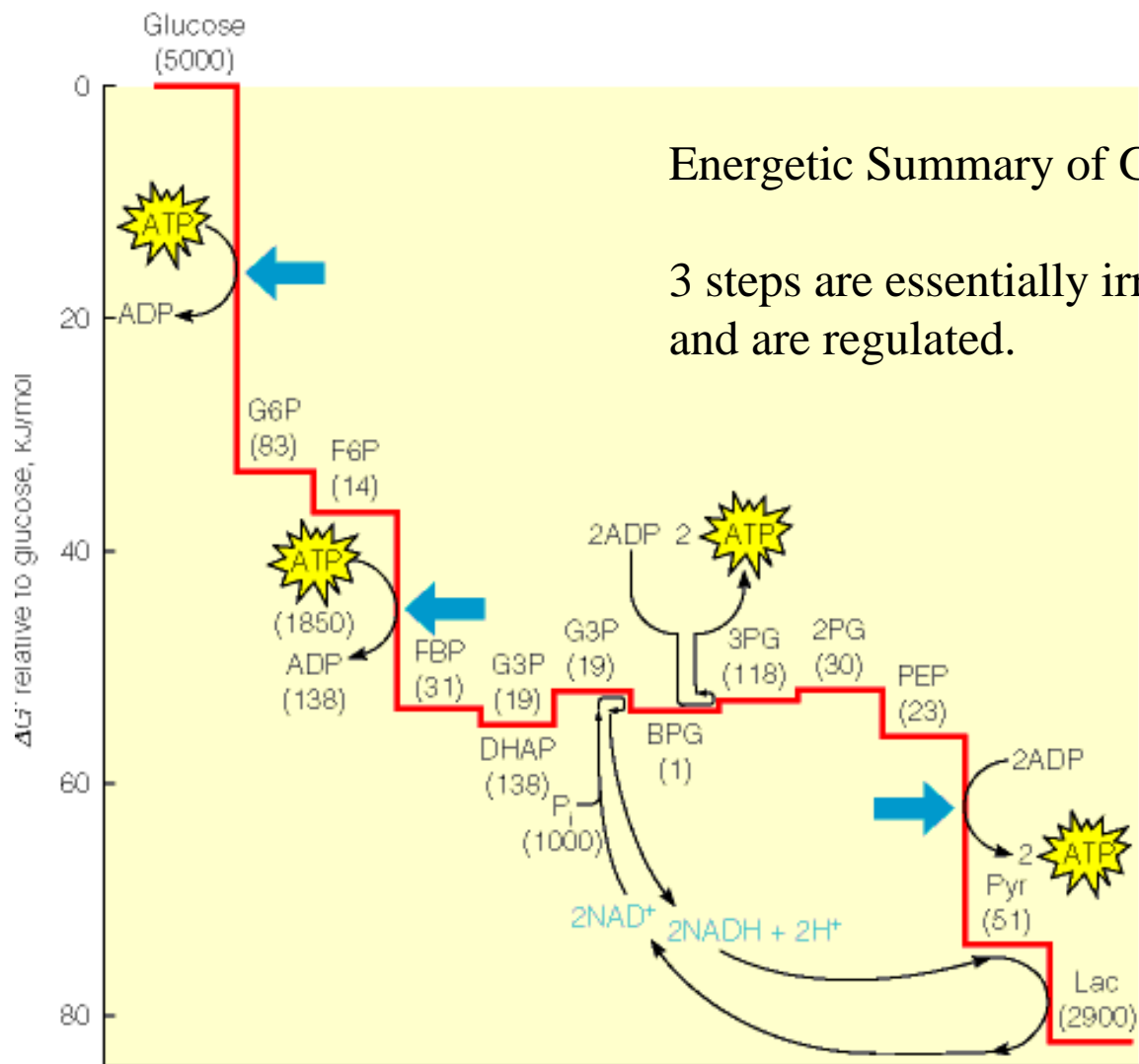


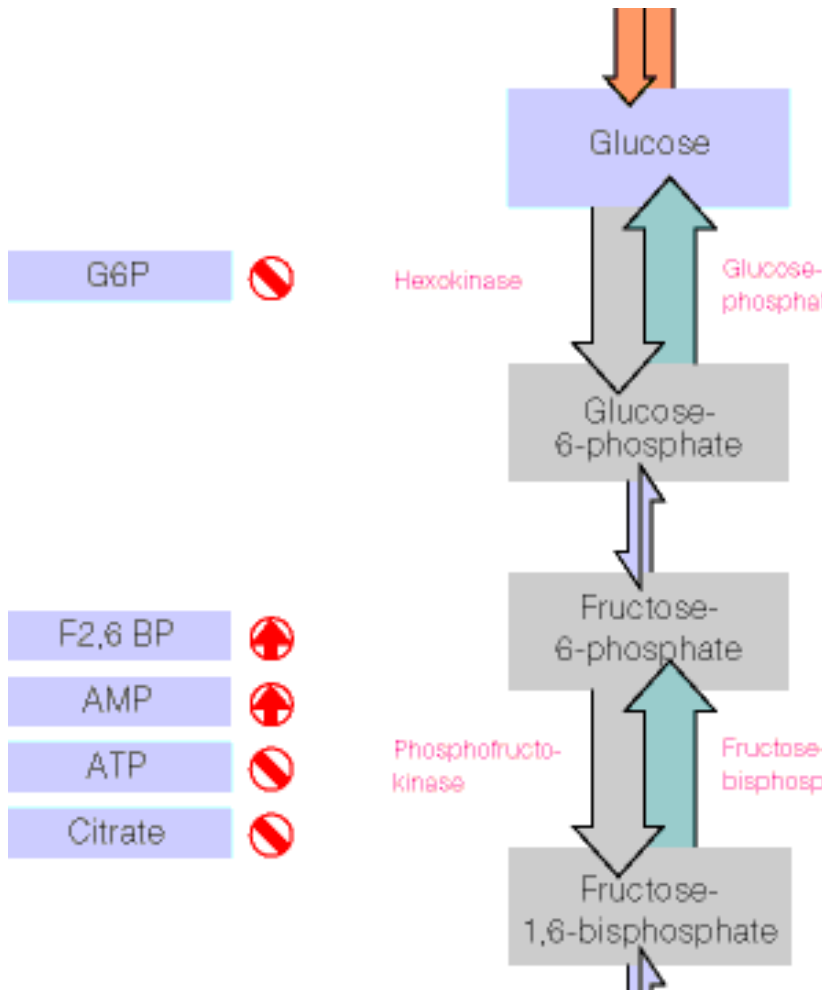
Acetaldehyde in yeast



Energetic Summary of Glycolysis

3 steps are essentially irreversible and are regulated.





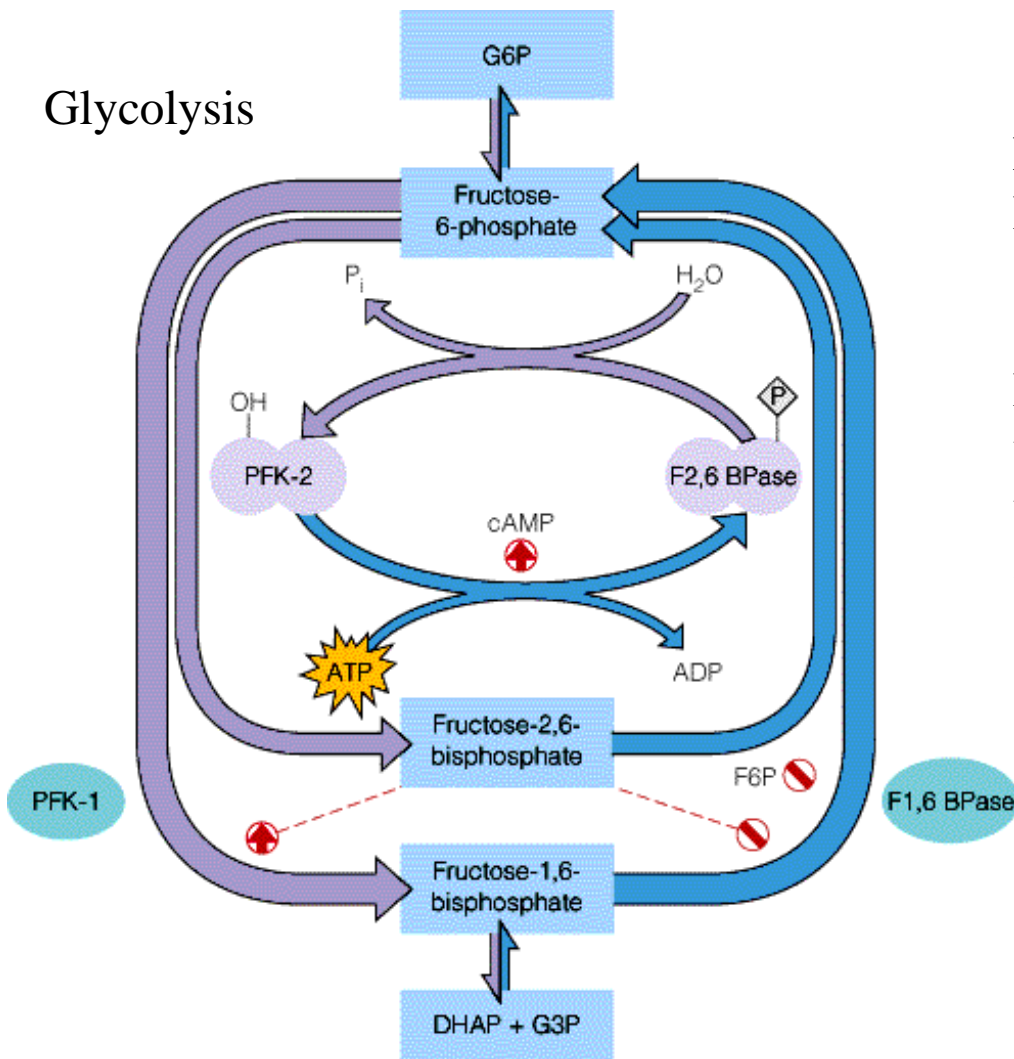
Hexokinase
Product inhibited

Phosphofruktokinase (PFK)

Stimulated
F26BP & AMP

Inhibited
ATP & Citrate

Glycolysis



F26BP stimulates PFK

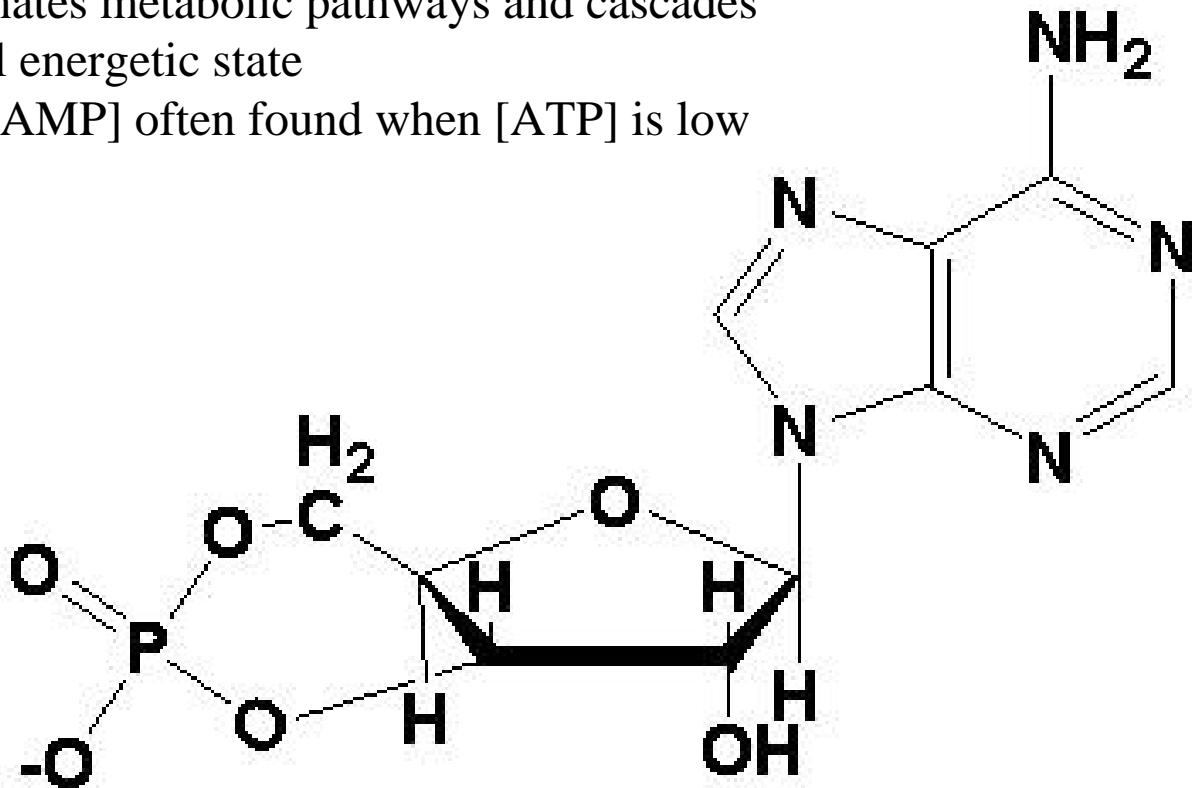
Synthesis of F26BP Requires PFK-2 which is present when cAMP levels are low.

cAMP

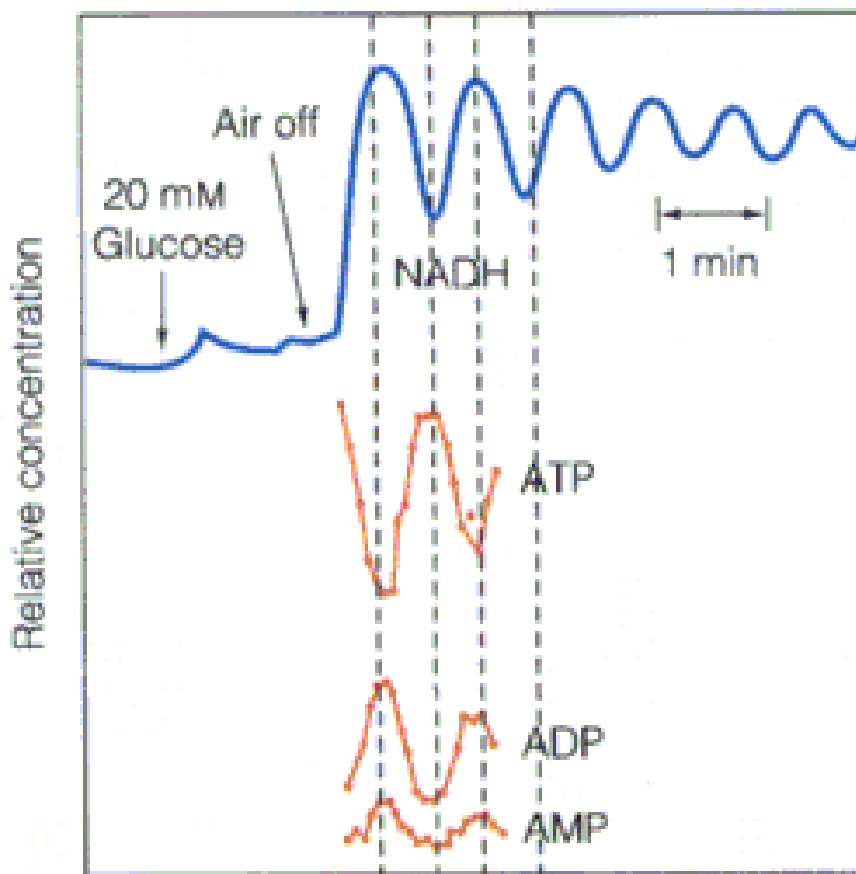
Coordinates metabolic pathways and cascades

General energetic state

High [cAMP] often found when [ATP] is low



Cyclic adenosine monophosphate (cAMP)

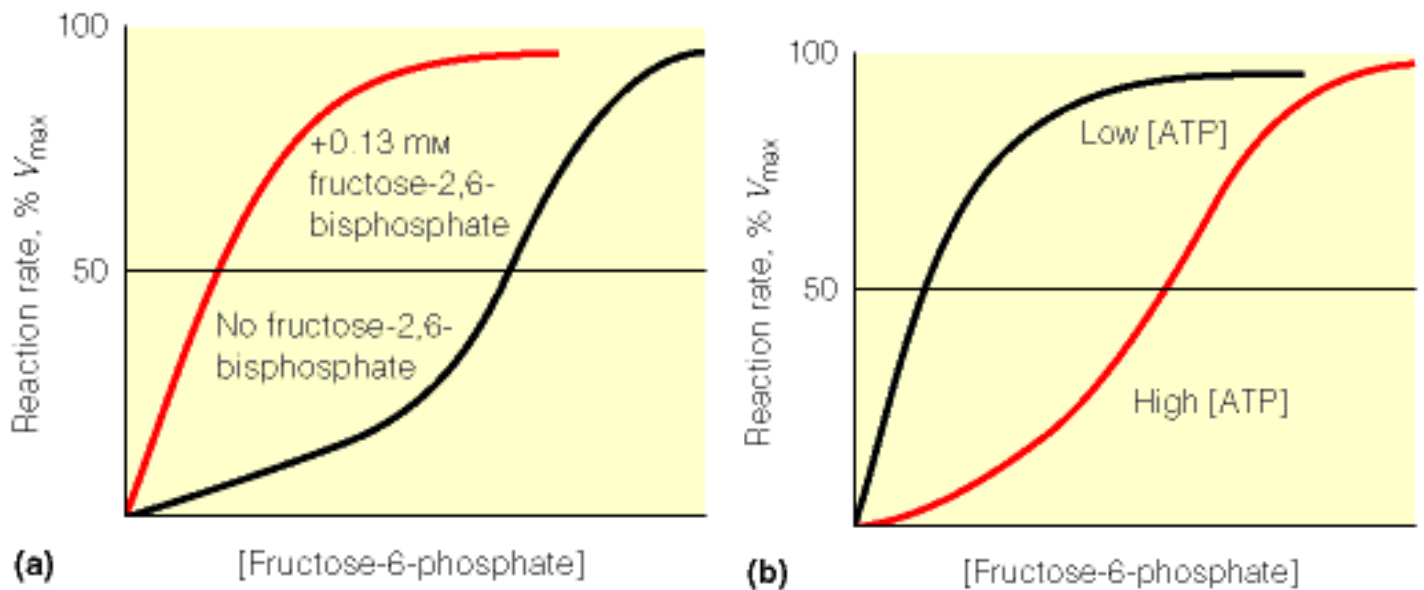


**Pasteur Effect--
O₂ represses glycolysis
(and stimulates
Aerobic pathways)**

**Removal of O₂
stimulates glycolysis.**

**High ATP represses
PFK activity so NAD⁺
levels remains high.**

**Oscillatory behavior is
characteristic of feedback
regulation.**

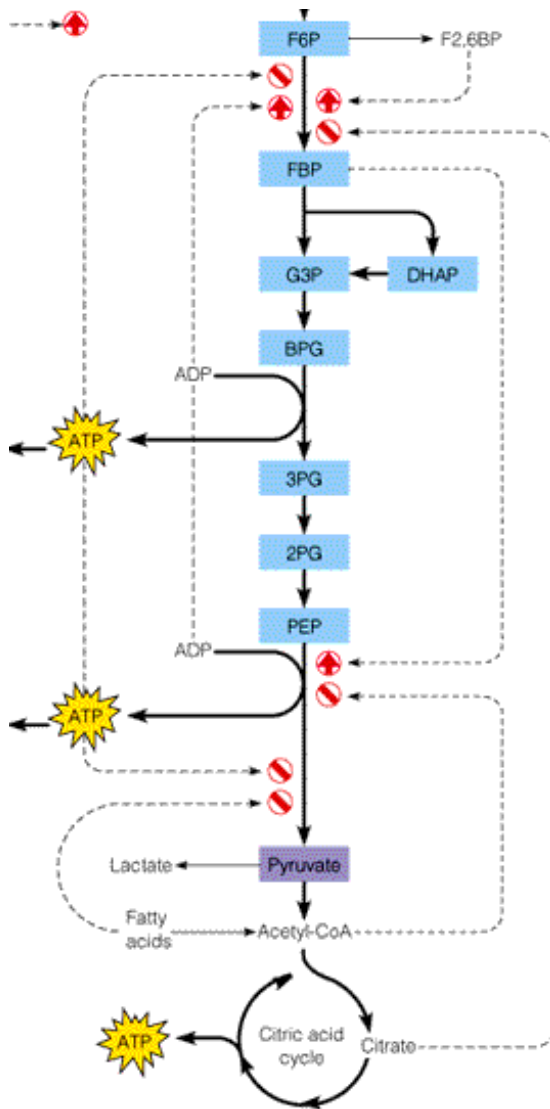


PFK regulation

F26BP--ties in to gluconeogenesis (glucose synthesis)

ATP--feedback inhibited (allosteric). ATP is also a substrate!

ADP stimulates and citrate inhibits.







PFK regulation

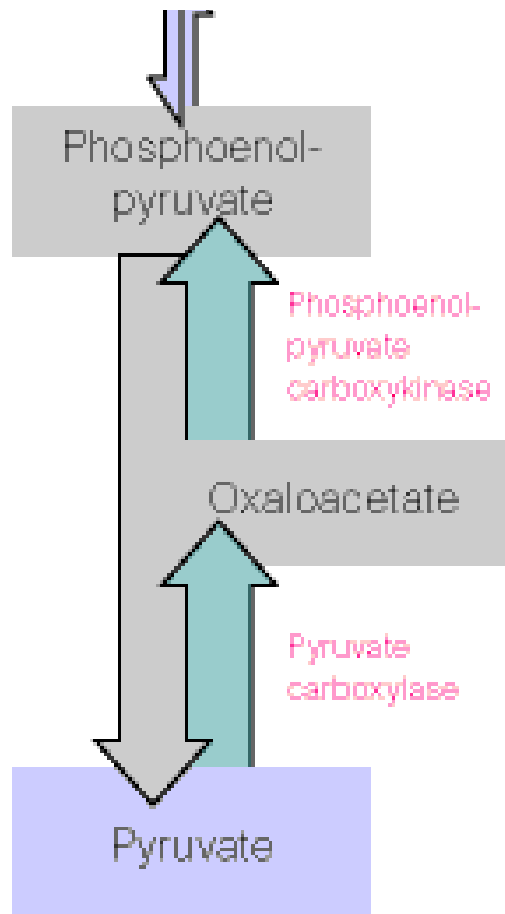
Pyruvate Kinase Regulation

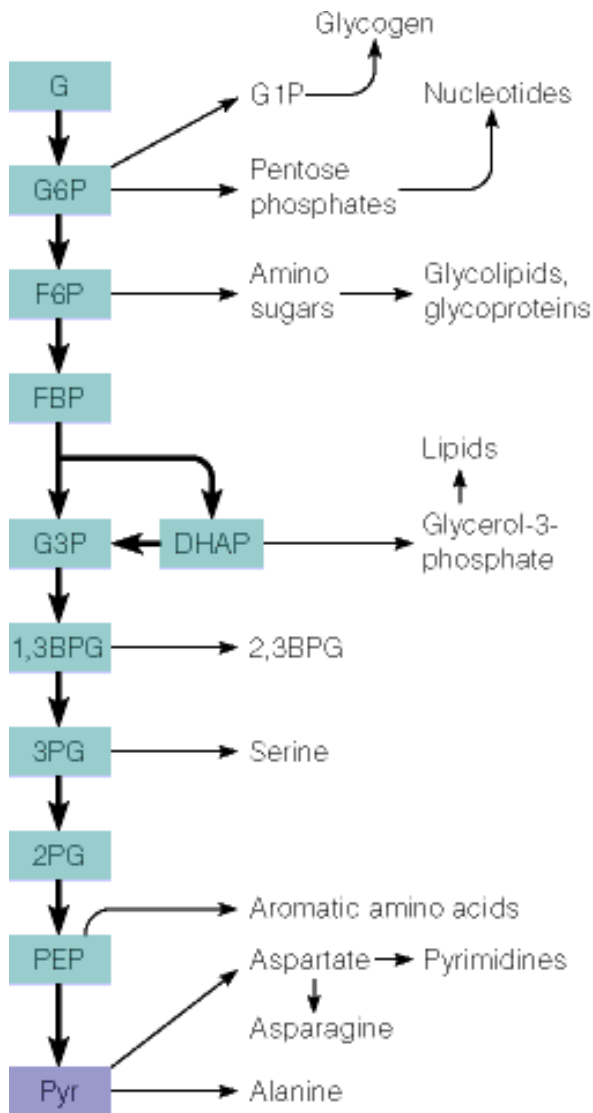
FBP “feed forward”

Acetyl Co-A inhibition

Both enzymes are large, multi sub-unit allosterically regulated enzymes.

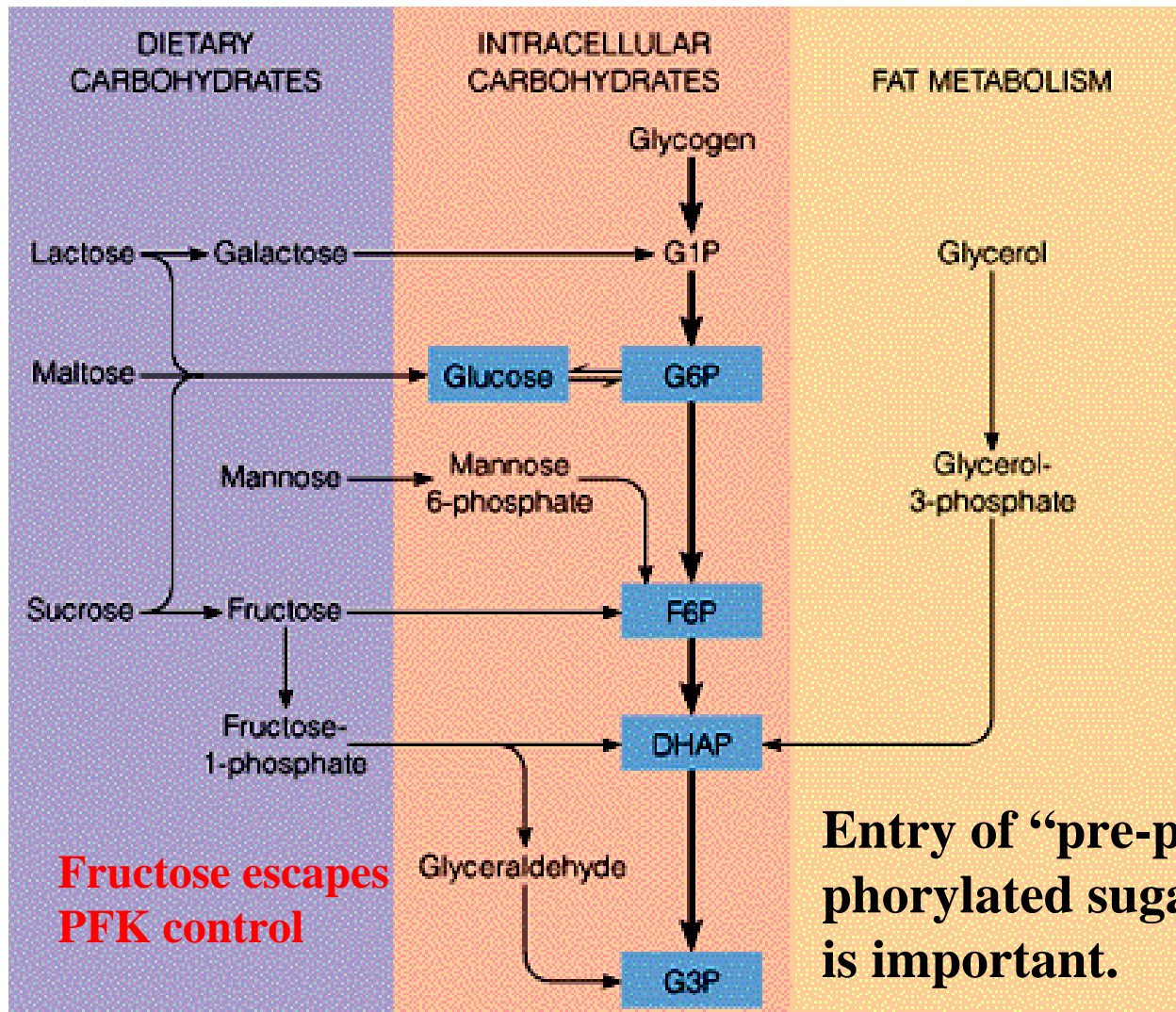
- F1,6 BP 
- Acetyl-CoA 
- ATP, alanine 
- cAMP-dependent phosphorylation 





Multiple regulatory points are needed to control the flux to other pathways.

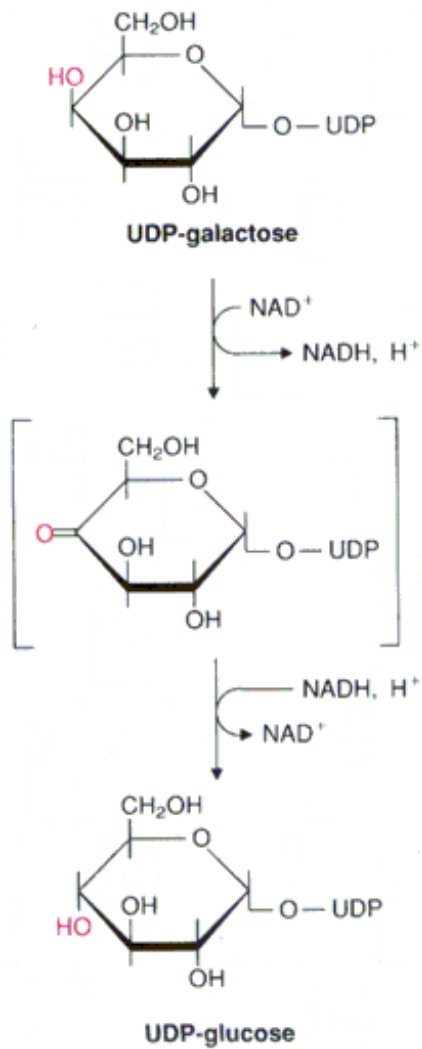
Many sugars feed into the pathway at G6P, so hexokinase is not a major regulatory point.



**Disacharides are broken down enzymatically and
Generally converted to glycolytic products.**



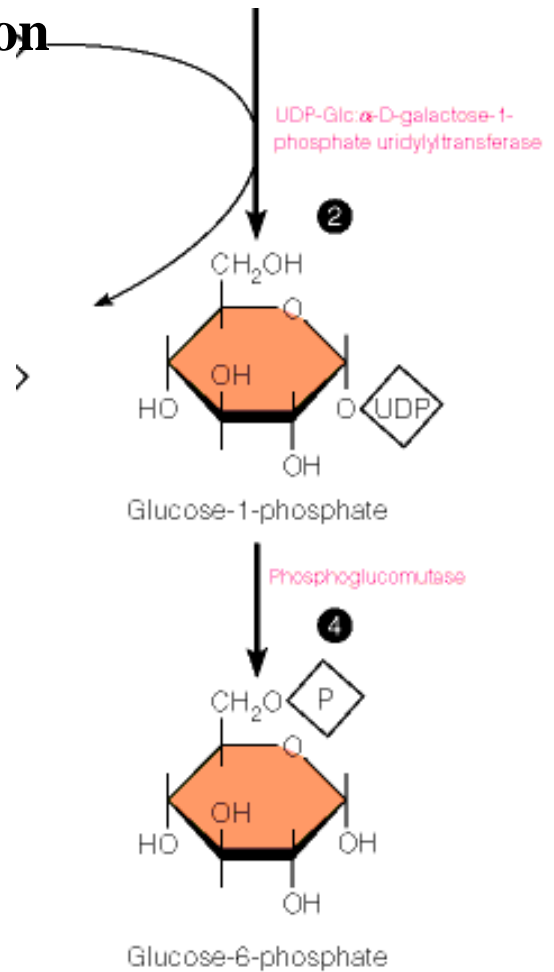
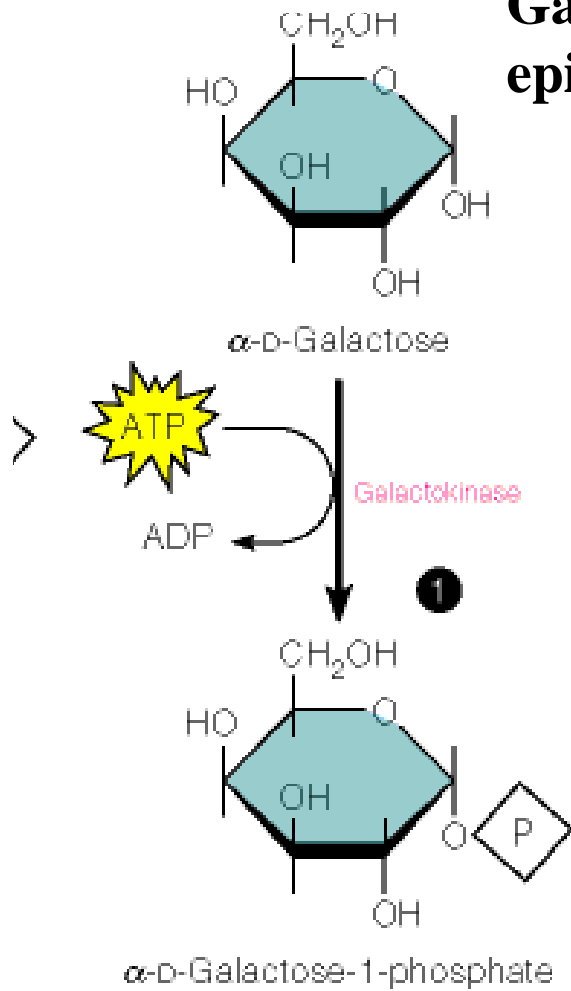
(fructose may escape PFK regulation and be converted to fat
Via G3P and triacylglycerols)



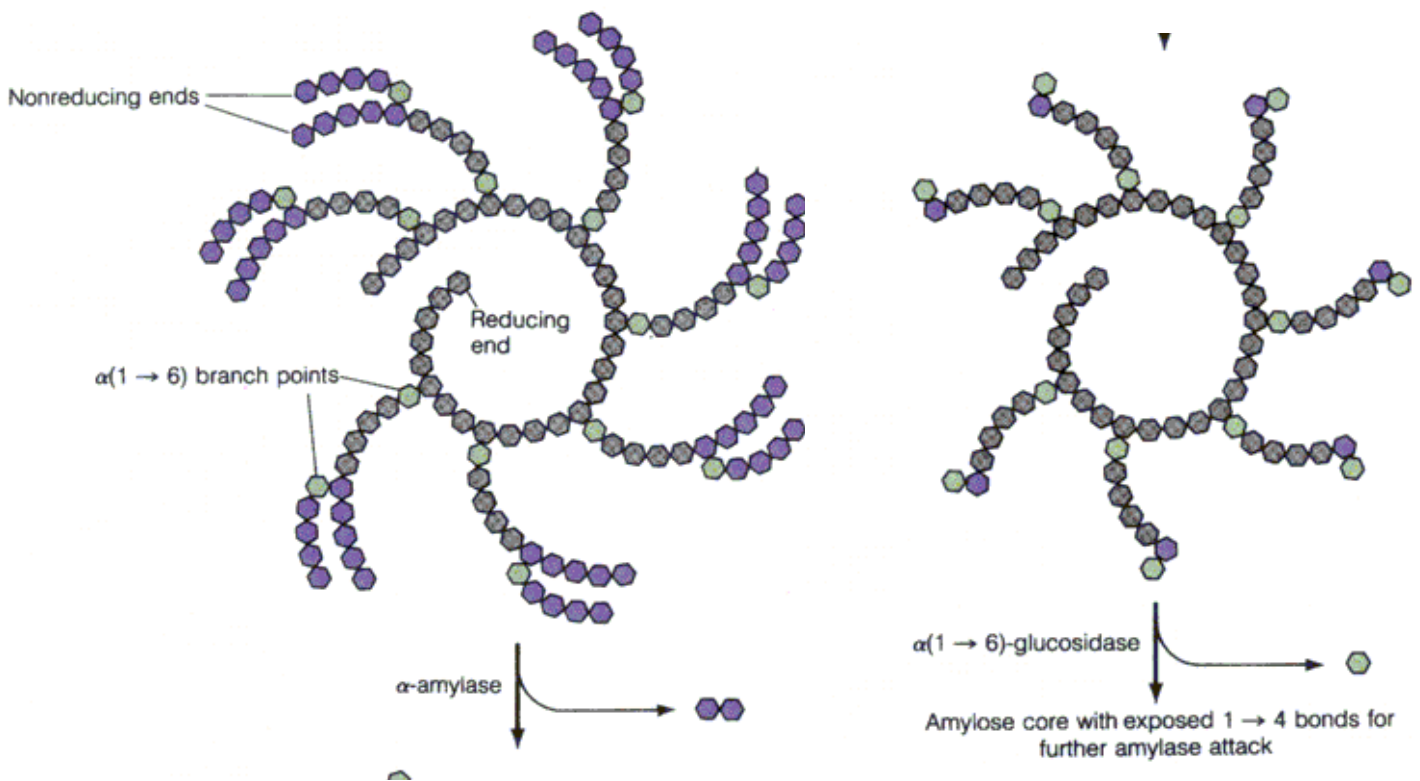
Converting galactose to glucose requires converting 1 stereocenter (C4)

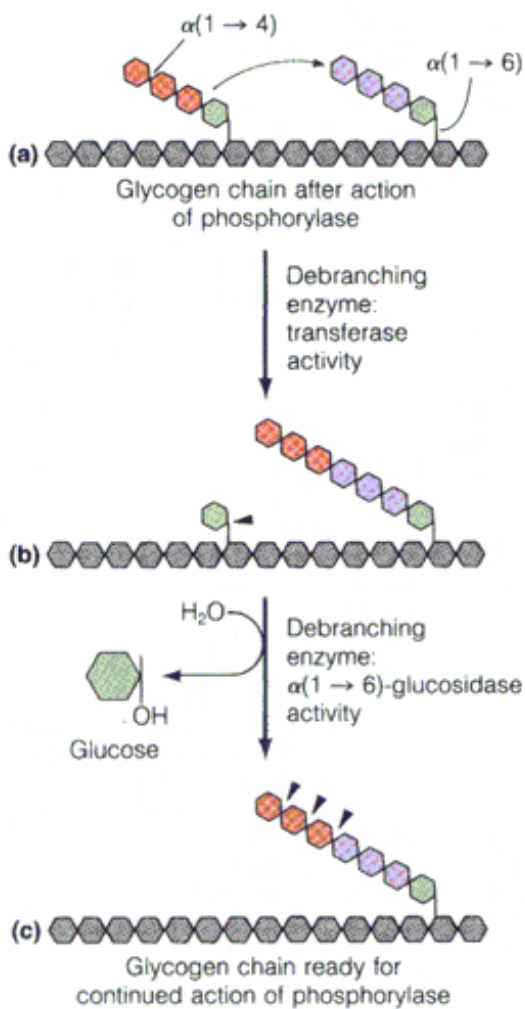
Oxidation then reduction requires NAD^+

Galactose must be modified before epimerization



Amylase removes non-reducing ends but only 1,4 linkages
Alpha 1, 6 glucosidase removes branches.

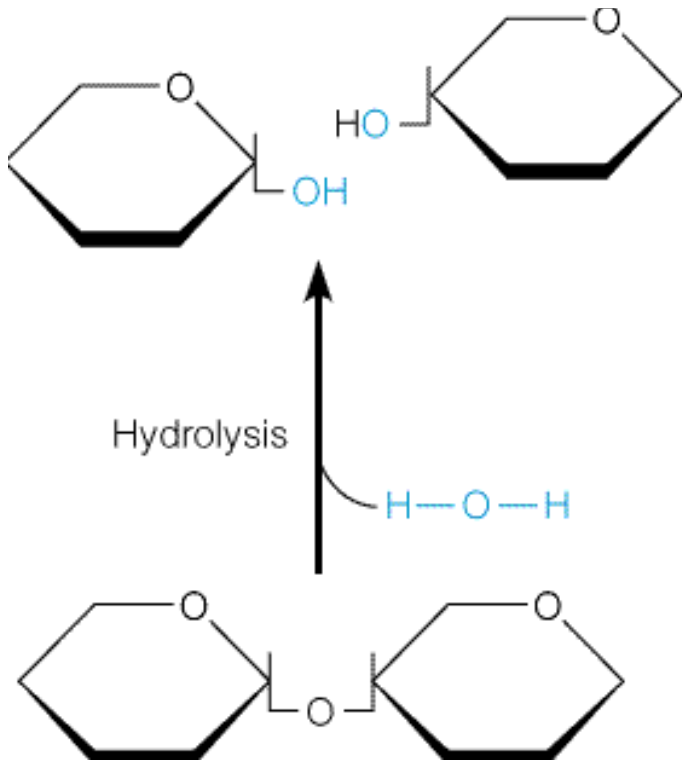




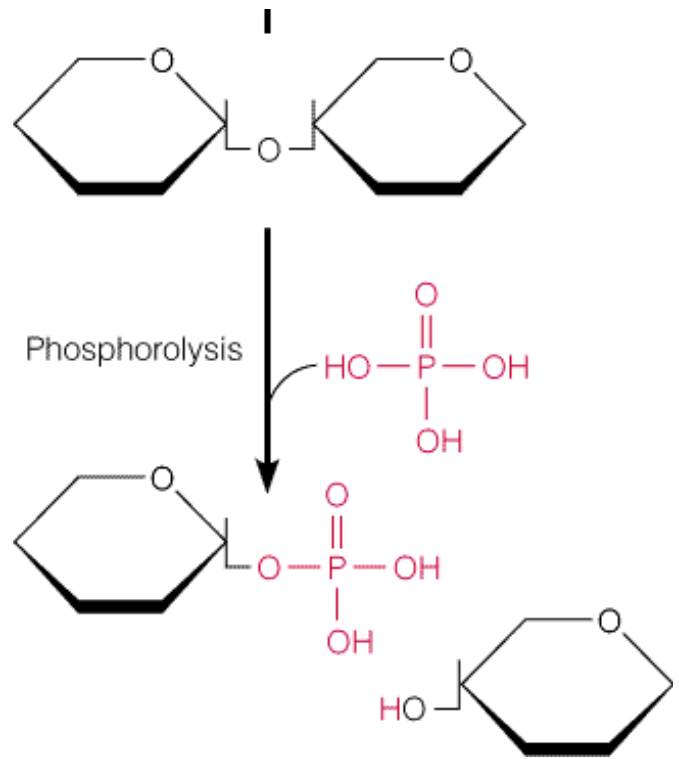
Glycogen mobilization Requires 2 enzymes

One for 1,4 linkages &
One for branches

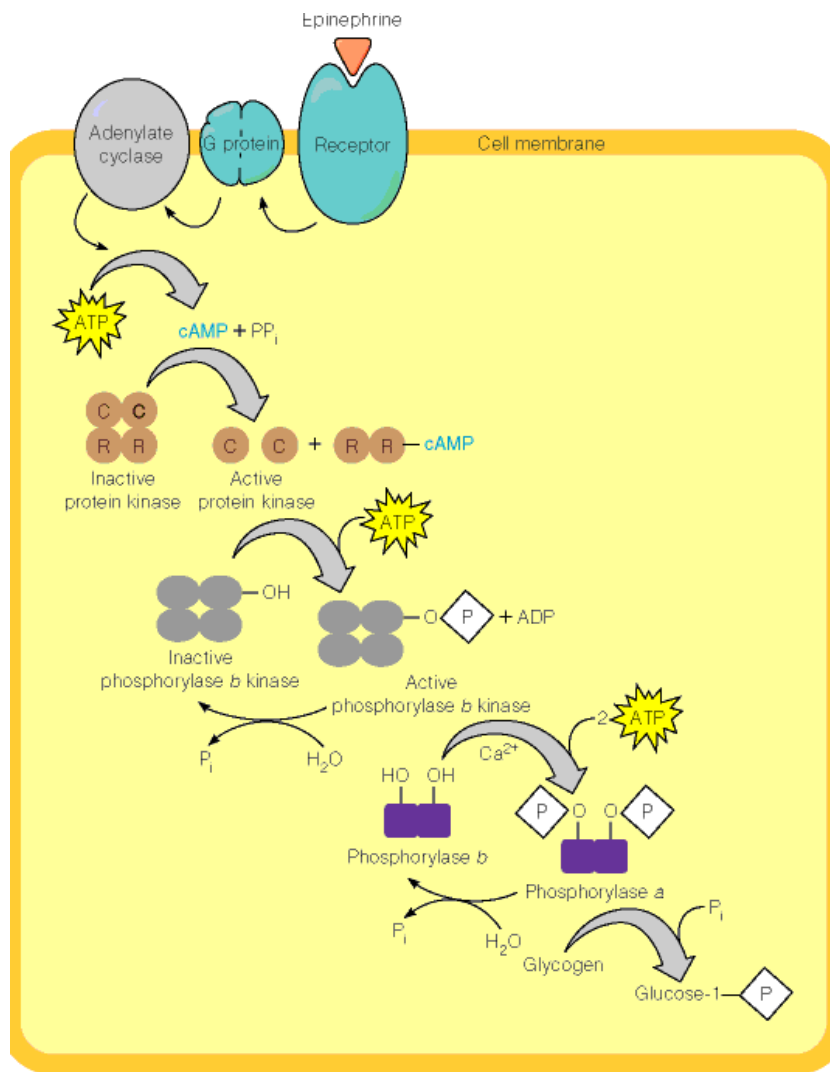
but within 4 sugars of a
branch, the debranching enzyme
transfers 3 sugars to branch
and removes remaining 1, 6 linked
sugar.



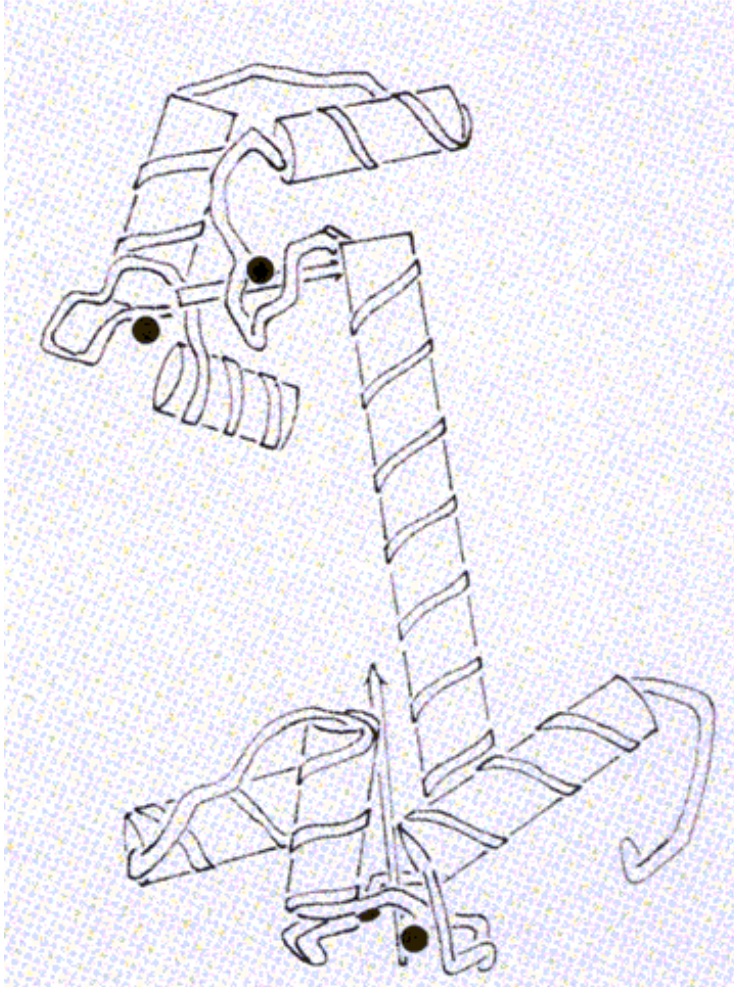
**Product is exportable, but
ATP required to make G6P**



**Product will not traverse
Membrane, but G6P synthesis
Does not require ATP**



Glycogen mobilization is under hormonal control (adrenaline) or non-hormonal where AMP can activate phosphorylase.



**Calmodulin
binds calcium
allosterically and
modulates the calcium
levels.**

**This is an important
link to muscles and
nerves.**