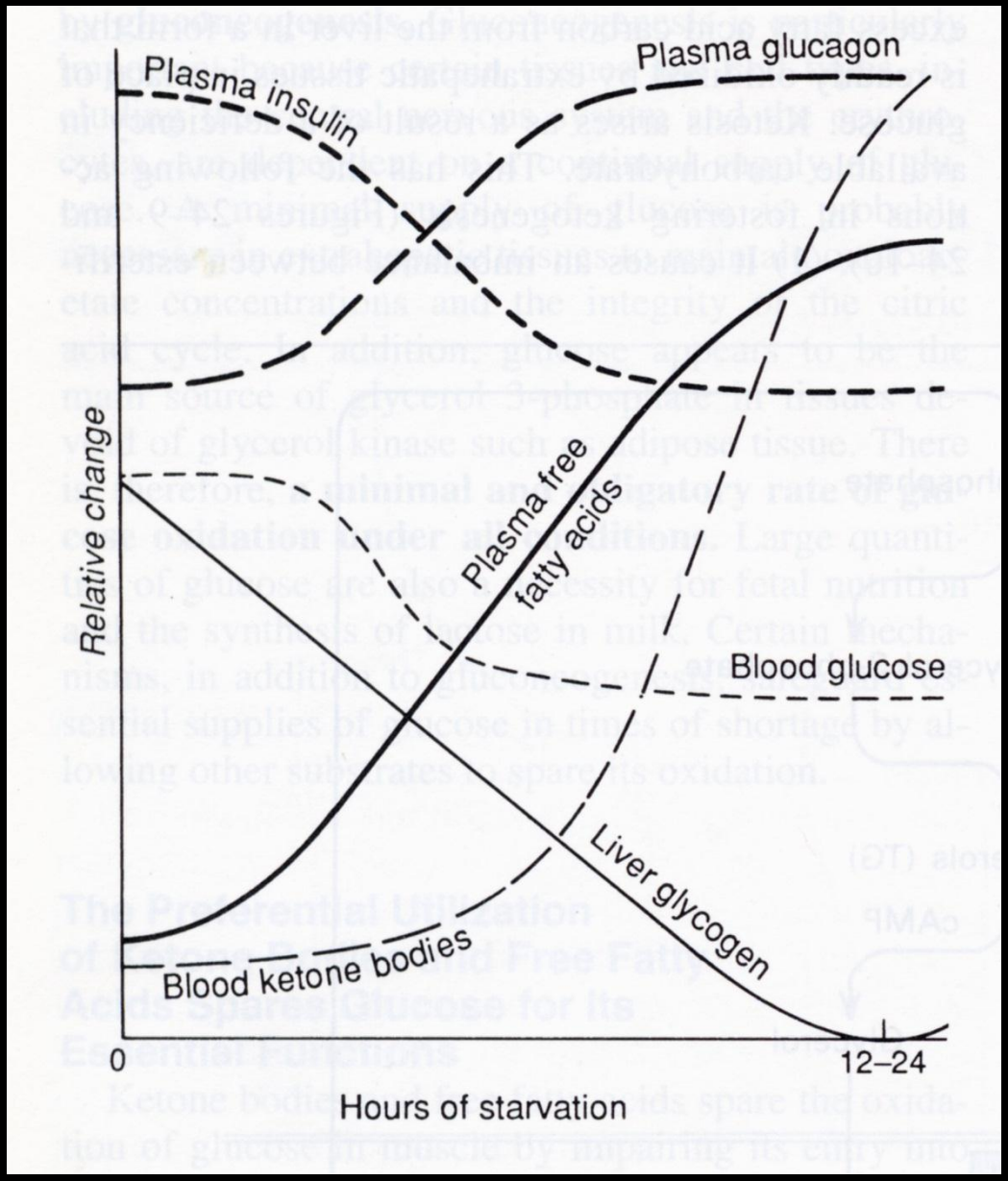
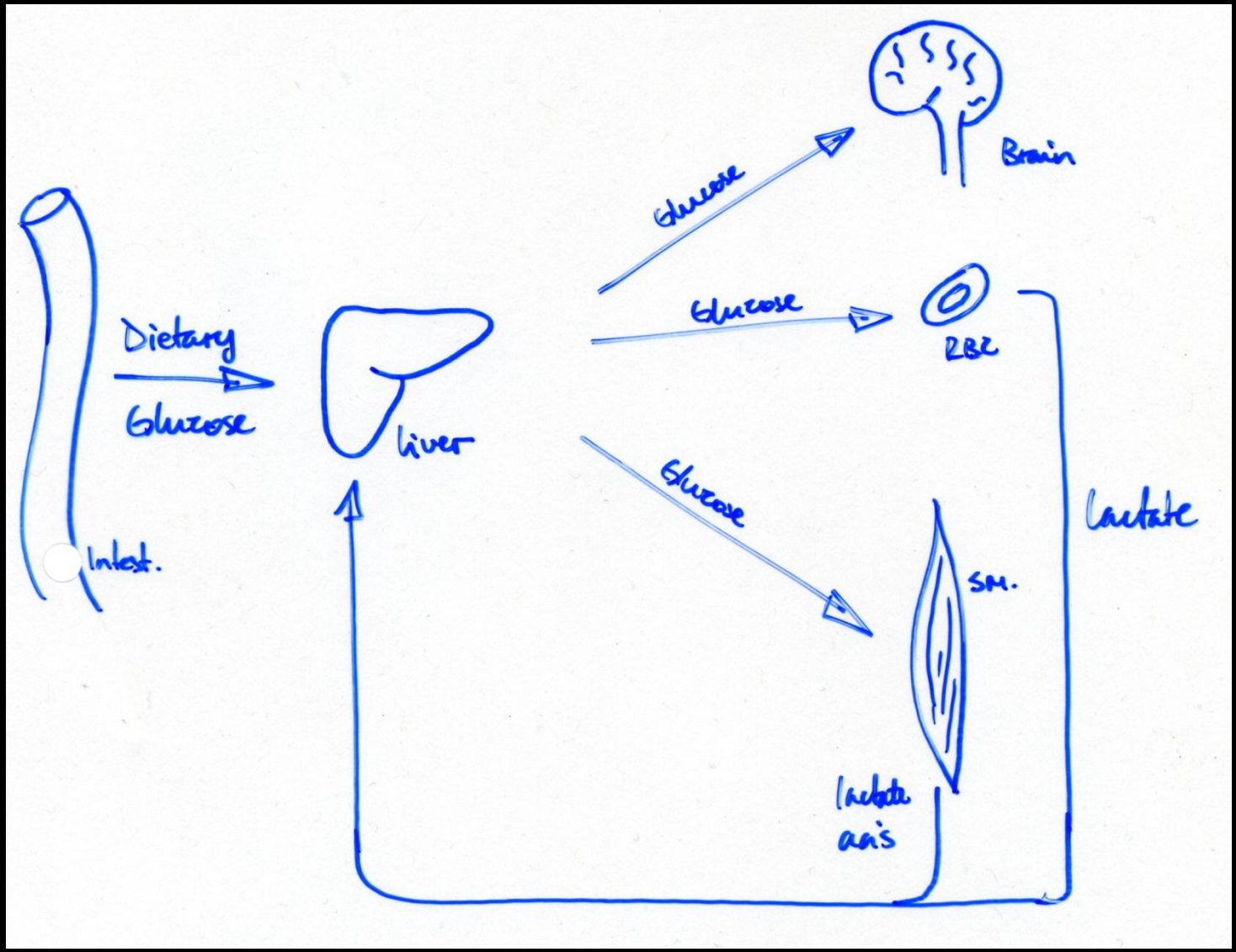
# Gluconeogenesis


Plasma glucagon
Plasma insulin
Relative change
Plasma free fatty acids
Blood glucose
Liver glycogen
Blood ketone bodies
0
12–24
Hours of starvation

# Gluconeogenesis

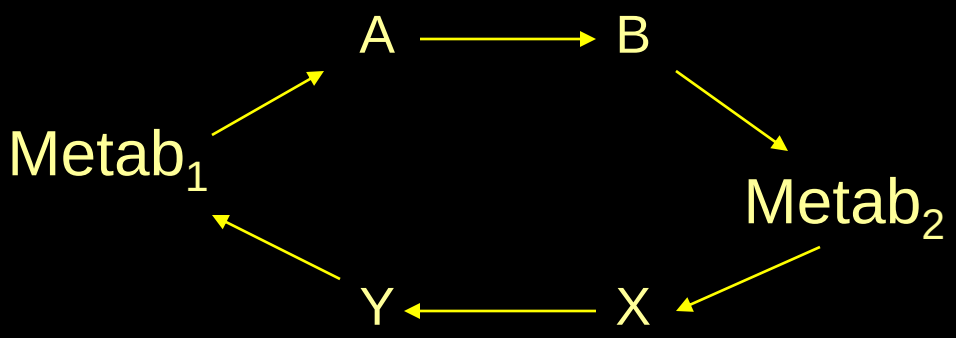


# Gluconeogenesis

-Metabolic Pathways are Irreversible

$\Delta G$ between the 1st & last metabolite is large (huge) & neg.

- If metabolite 1 and 2 are interconvertible (metab 1 $\rightleftharpoons$ metab 2), the path from Metab 1 → Metab 2 must be different from that of Metab 2 → Metab 1



For example:

Glucose → 2 Pyruvate $\quad \Delta G = -42.3$ kcal/mol

$2ADP + 2P_i \rightarrow 2ATP \quad \Delta G = 24$ kcal/mol

$\Delta G = -18.3$ kcal/mol

$\Delta G$ for glucose $\longrightarrow$ pyruvate $\approx$ -20 kcal/mol!

Gluconeogenesis is not the reverse reaction of glycolysis, rather it must use a different pathway that is coupled to the input of energy

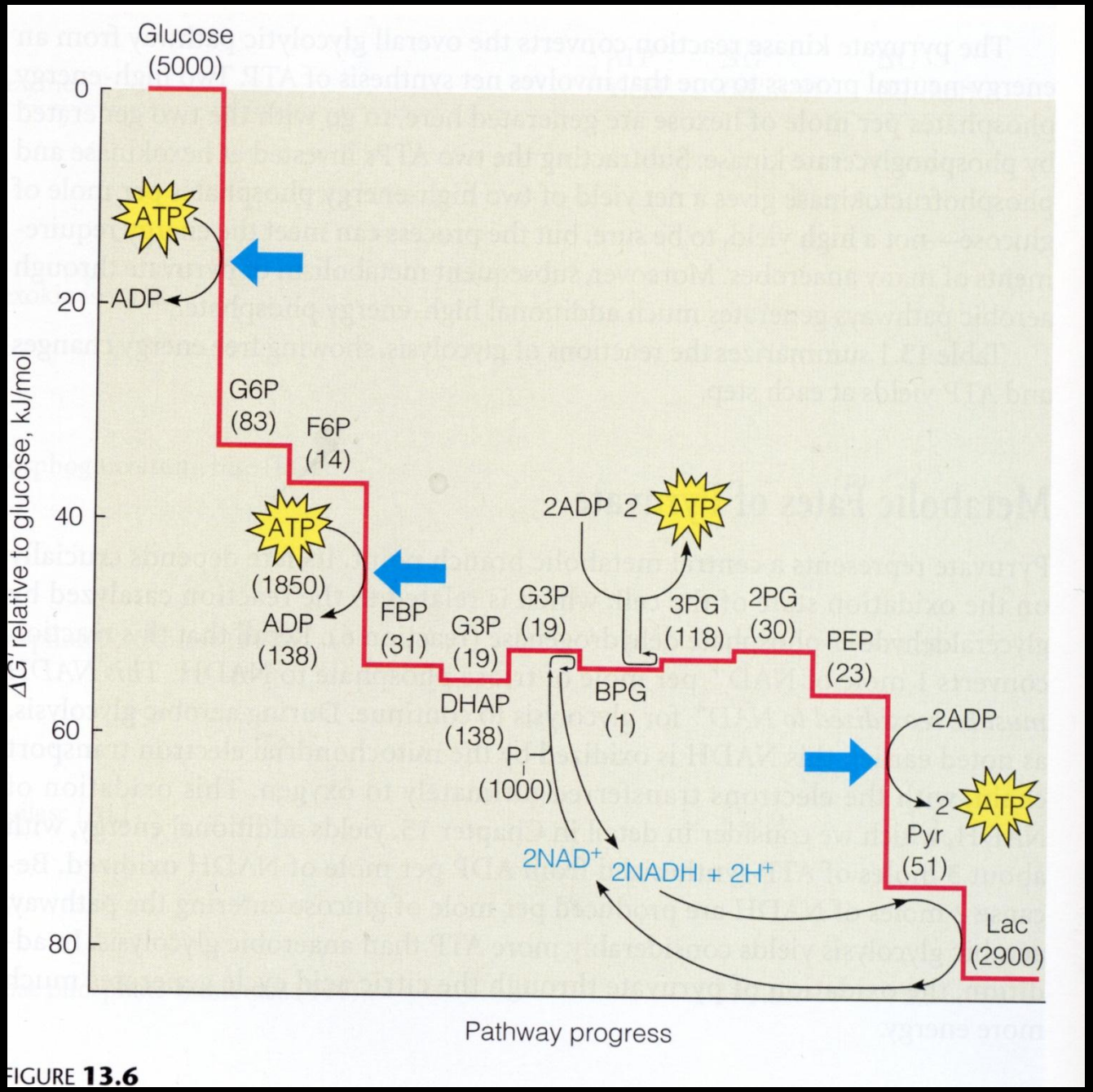
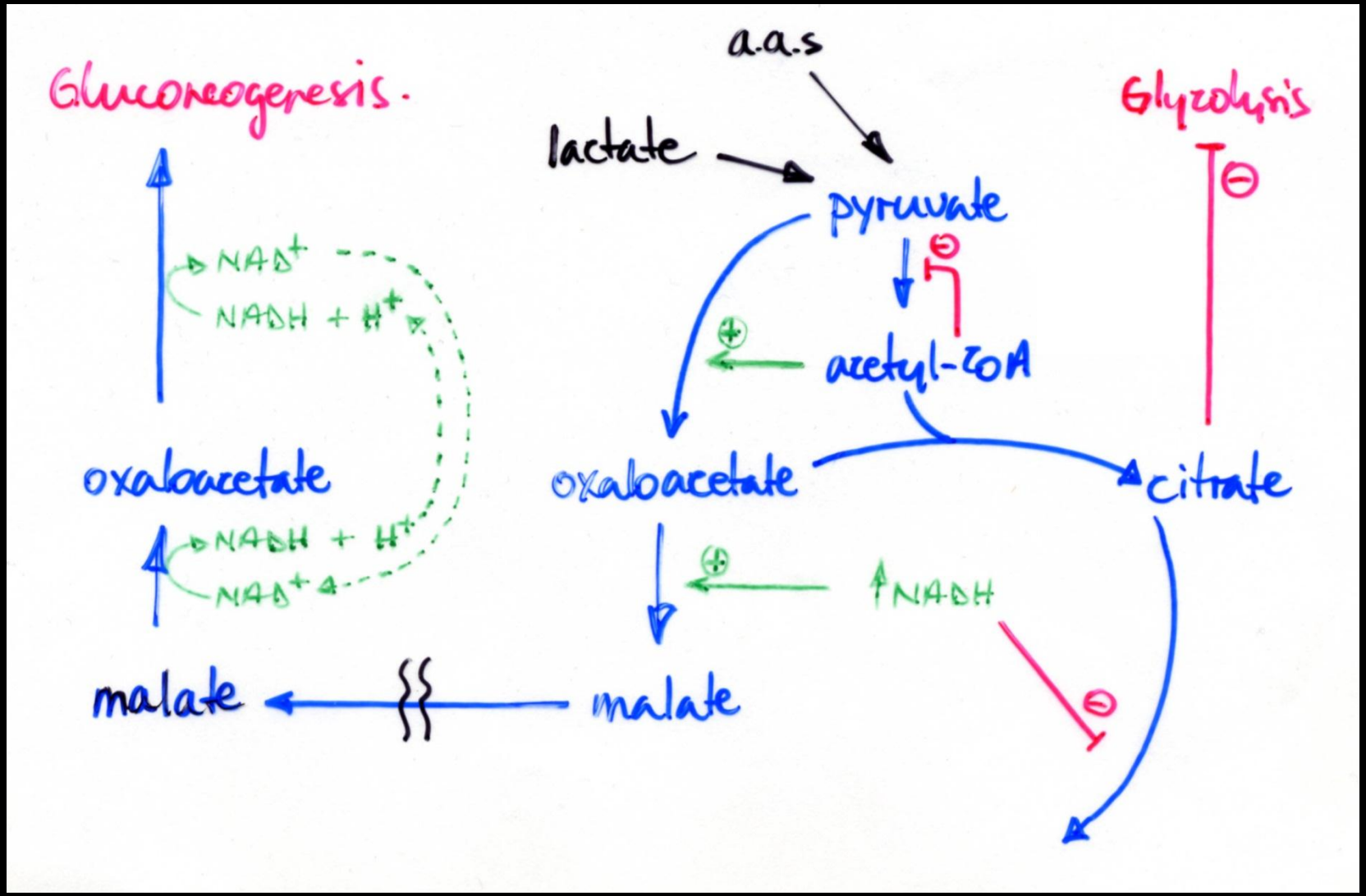

Glucose
(5000)
0
20
40
60
80
ΔG' relative to glucose, kJ/mol
ATP
ADP
G6P
(83)
F6P
(14)
ATP
(1850)
ADP
(138)
FBP
(31)
G3P
(19)
DHAP
(138)
G3P
(19)
2ADP
2
ATP
3PG
(118)
2PG
(30)
PEP
(23)
BPG
(1)
Pi
(1000)
2NAD+
2NADH + 2H+
2ADP
2
ATP
Pyr
(51)
Lac
(2900)
Pathway progress

FIGURE **13.6**

- Gluconeogenesis can use most of the enzymes of glycolysis in reverse, except for 3:
    - A. Pyruvate kinase
    - B. PFK
    - C. Hexokinase

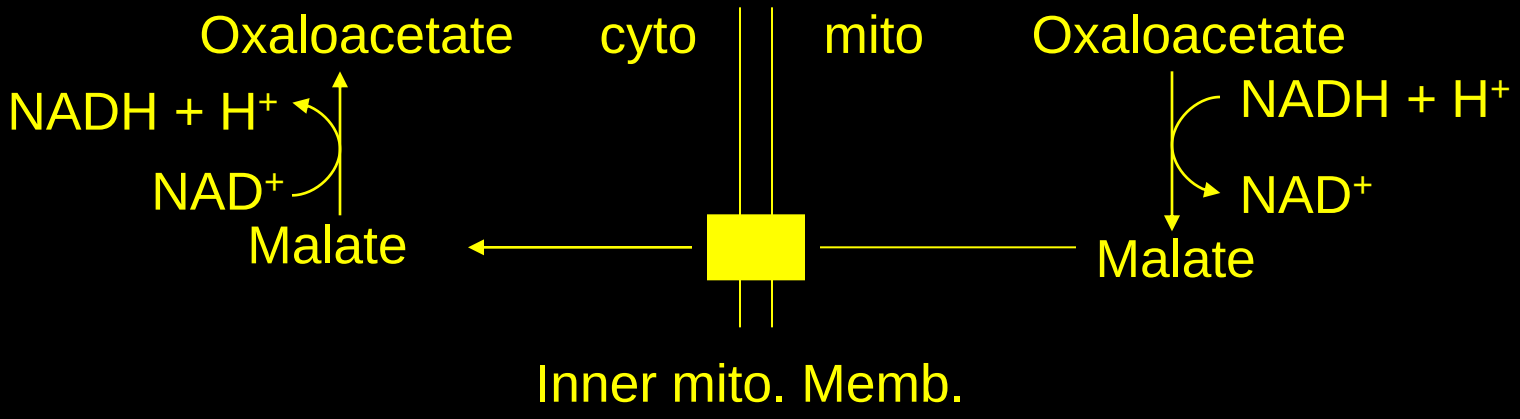
- The starting point for gluconeogenesis is pyruvate.

# Pyruvate enters the mitochondria to initiate Gluconeogenesis

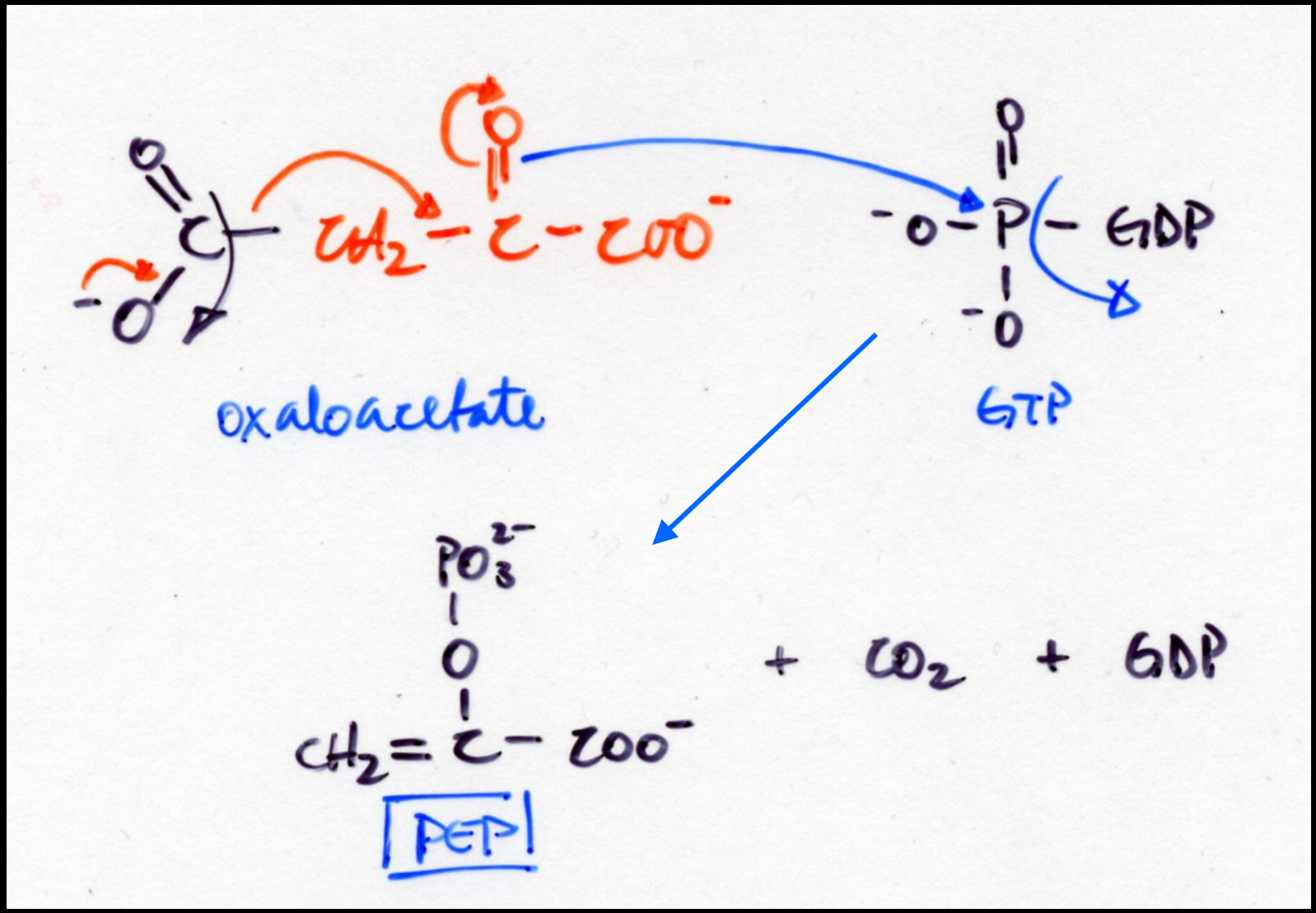


# A. Circumventing Pyruvate Kinase - Conversion of Pyruvate to Phosphoenolpyruvate

1. Carboxylation of pyruvate to oxaloacetate √
2. Transport of oxaloacetate out of mitochondria



# 3. Decarboxylation of Oxaloacetate followed by phosphorylation yields PEP



# 4. Overall Reaction

- Pyruvate + $P_i$ $\rightleftharpoons$ PEP $\quad \Delta G° = 14.8$ kcal/mol
- ATP $\rightleftharpoons$ ADP + $P_i$ $\quad \Delta G° = -7.3$
- GTP $\rightleftharpoons$ GDP + $P_i$ $\quad \Delta G° = -7.3$

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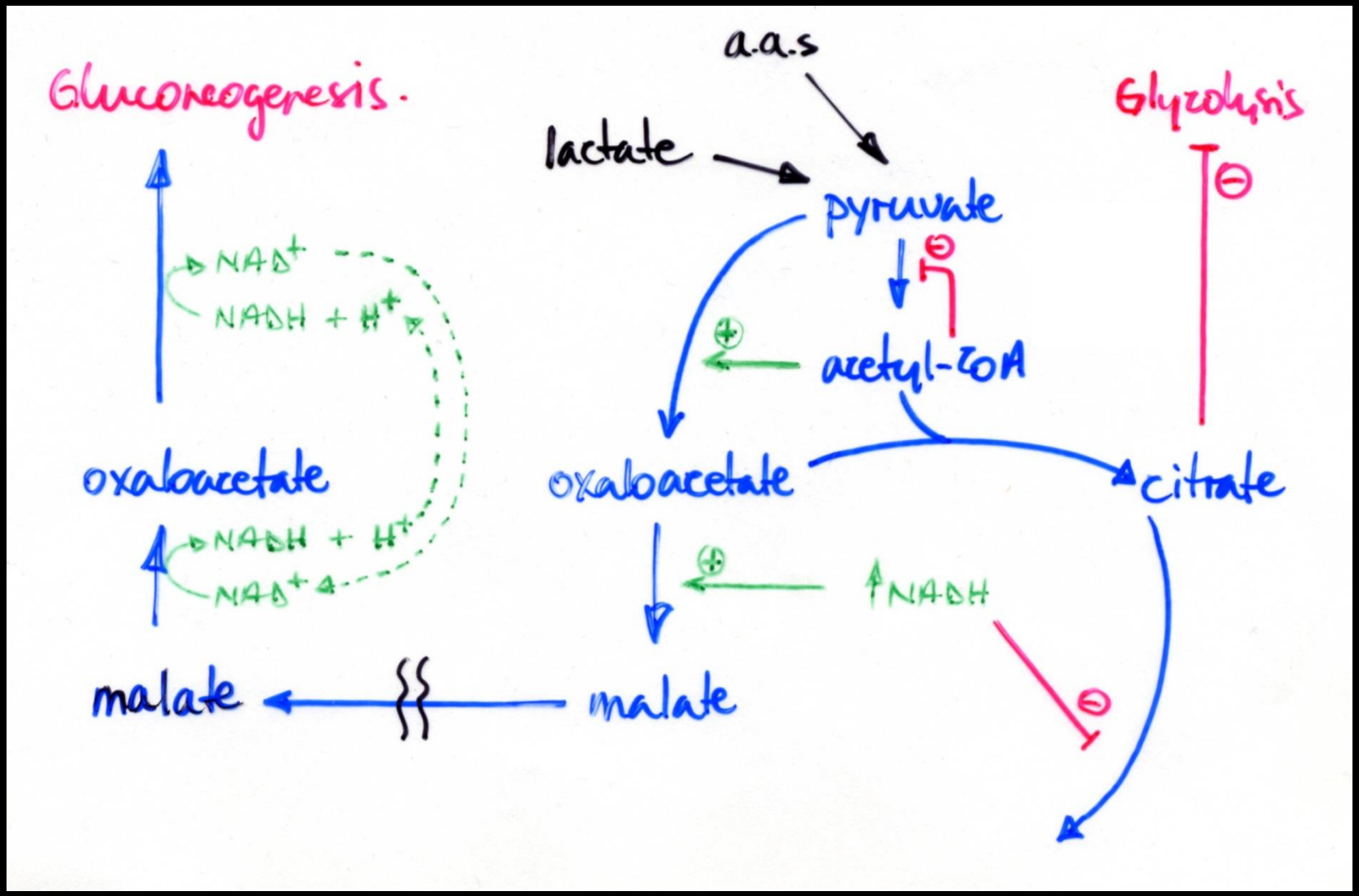
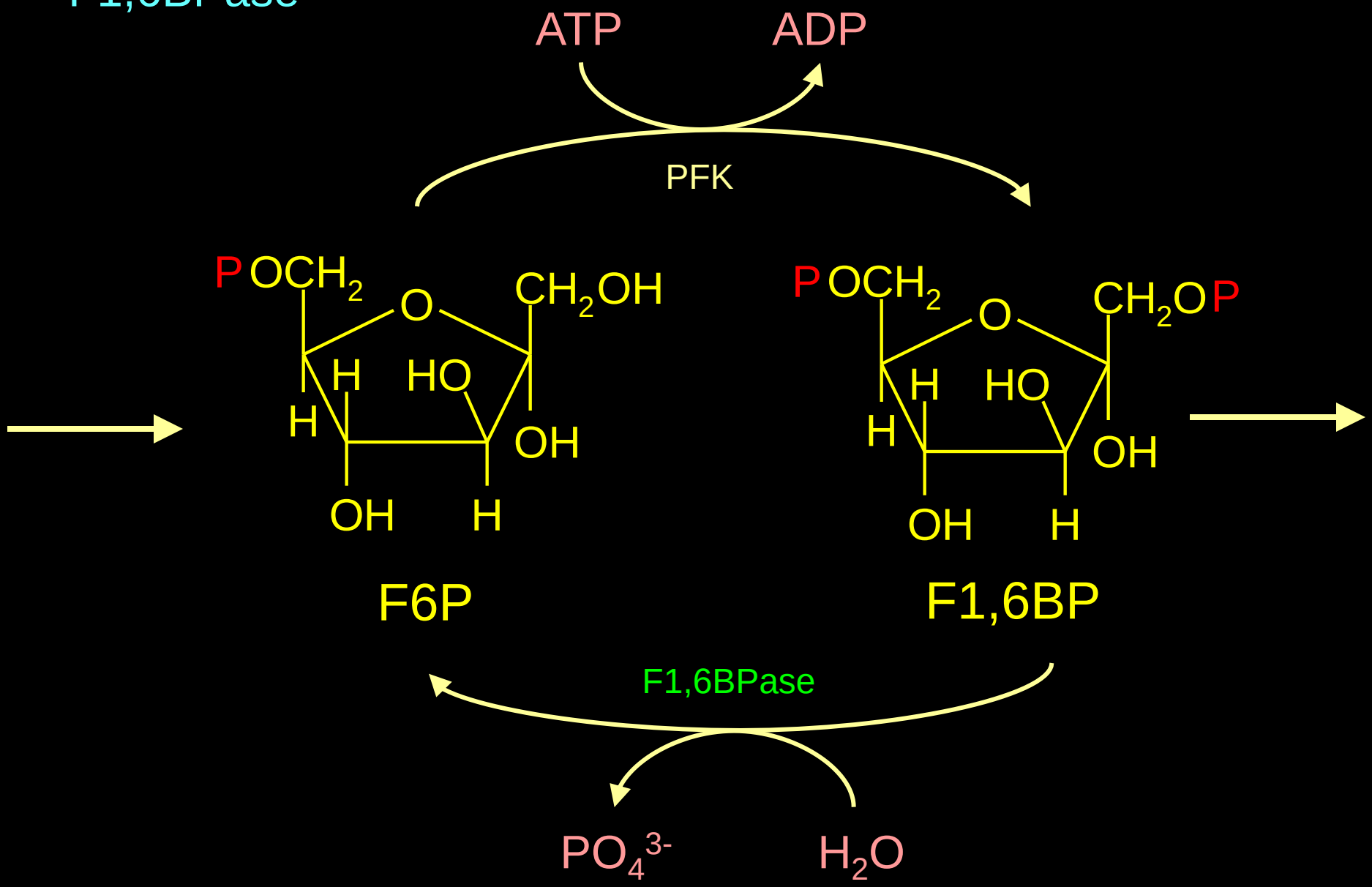
+0.2 kcal/mol

# High NADH favors Gluconeogenesis



# B. Circumventing PFK – dephosphorylation of F1,6BP by F1,6BPase



PFK reverse reaction:

F1,6 BP + ADP $\rightleftharpoons$ F6P + ATP $\quad \Delta G° = +3.4$ kcal/mol

Phosphoryl grp is transferred to ADP (to form ATP)

Dephosphorylation:

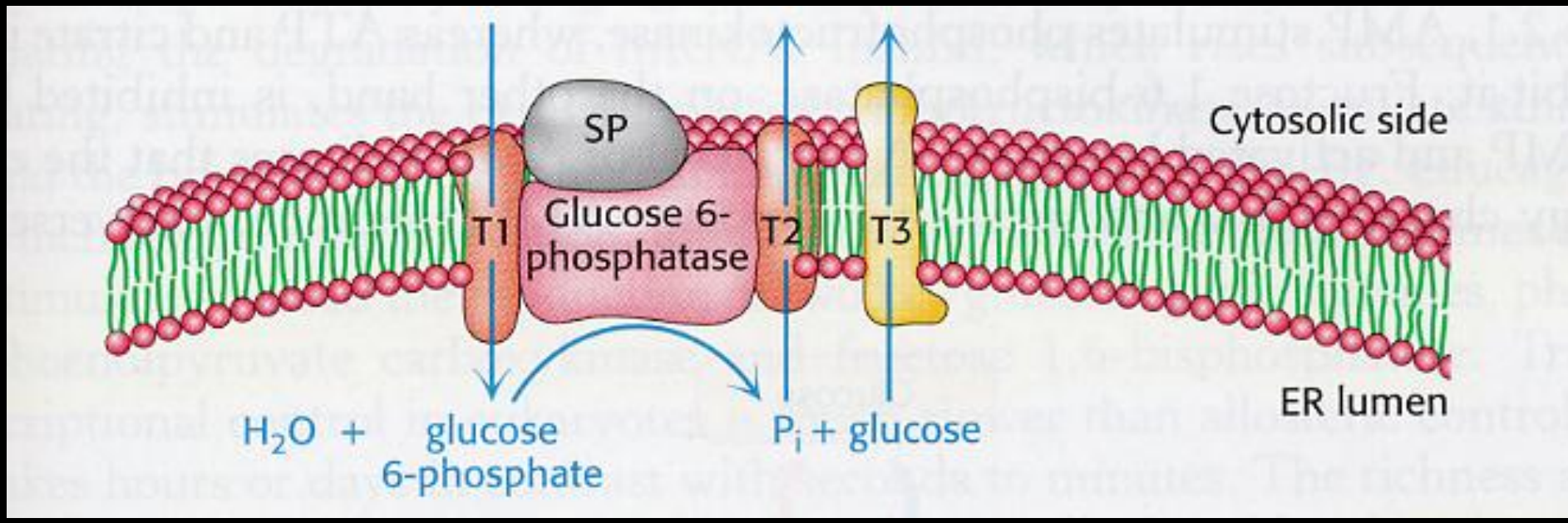
F1,6 BP + $H_2O$ $\rightleftharpoons$ F6P + $PO_4$ $\quad \Delta G° = -3.9$ kcal/mol

Phosphoryl grp is transferred to $H_2O$ (to form $PO_4^{3-}$ )

## C. Circumventing Hexokinase – dephosphorylation of G6P

- Mediated by G6Pase
- G6Pase is present only in liver and kidney
- Hence, these are the only tissues that can synthesize and secrete glucose into the blood

# Glucose-6-phosphatase activity relies on multiple components.



# A Defect in G6Pase Activity can be due to:

1. Defect in G6Pase itself
2. Defect in T1 transporter

Can Be distinguished by biochemical analysis:

Liver extracts treated by freeze-thawing results in release of ER proteins.

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| G6Pase Activity | | | |
|---|---|---|---|
| Before F/T | After F/T | | |
| – | – | → | Defect in G6Pase |
| – | + | → | Defect in T1 |

# Stoichiometry of Gluconeogenesis

- 2 Pyruvate
- 2 ATP – Carboxylation of Pyruvate
- 2 GTP – Synth. of PEP from oxaloacetate
- 2 ATP – P'n of 3-PG to form 1,3 BPG
- 2 NADH – reduction 1,3 BPG to Gly-3P
- 2 $PO_4^{3-}$ - are generated

- Glycolysis generates 2 ATP
- Gluconeogenesis uses 6 ATP/GTP

Diff. of 4 ATP's

$4\ ATP \rightarrow ADP + P_i$ $\quad \Delta G = -48$ kcal/mol

2 Pyruvate → 1 Glucose $\quad \Delta G = +42$

$-6$ kcal/mol

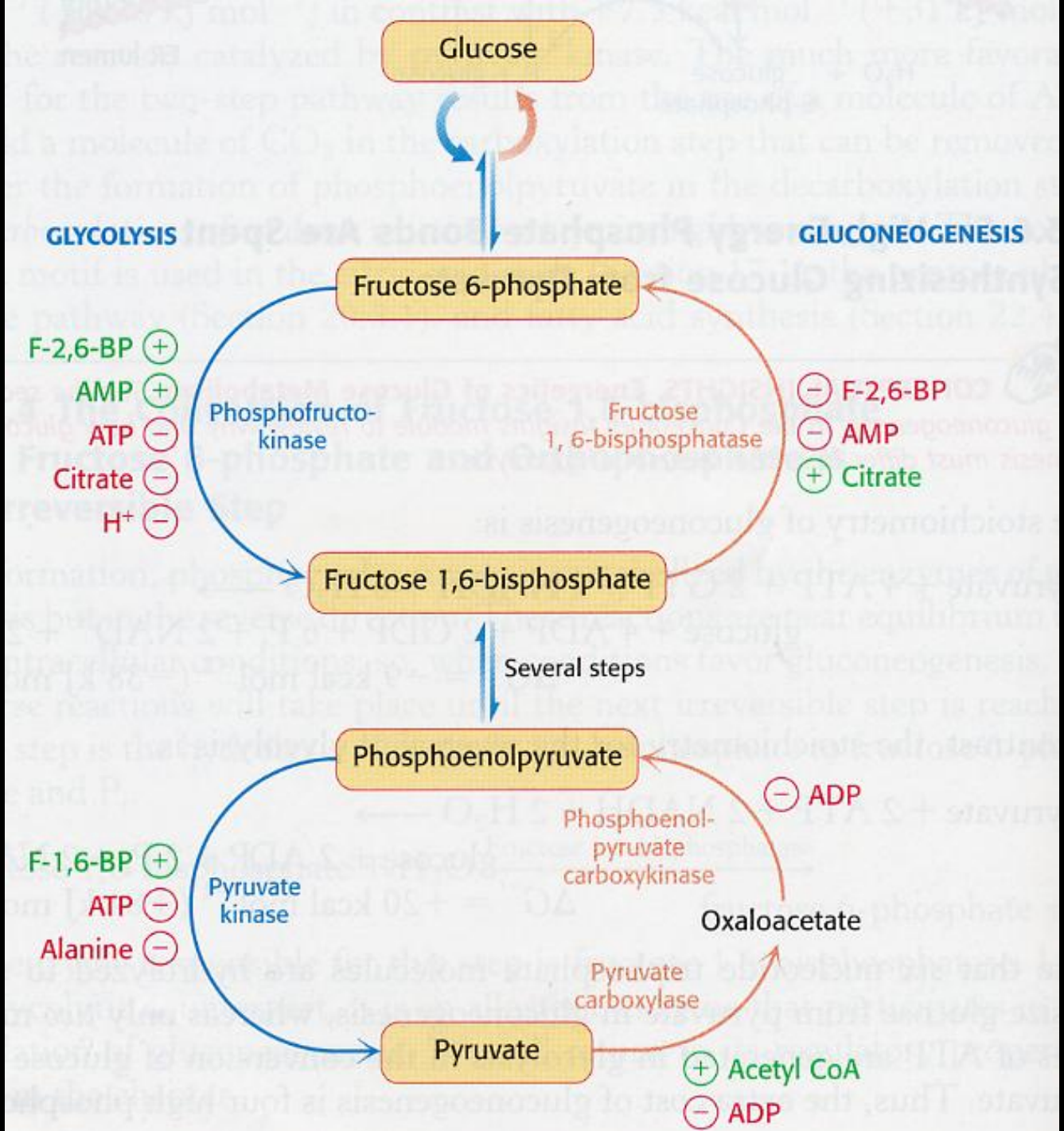
# Regulation of Gluconeogenesis

- Energy charge
- Levels of biosynthetic precursors
- Hormonal Control

1. Allosteric Regulation

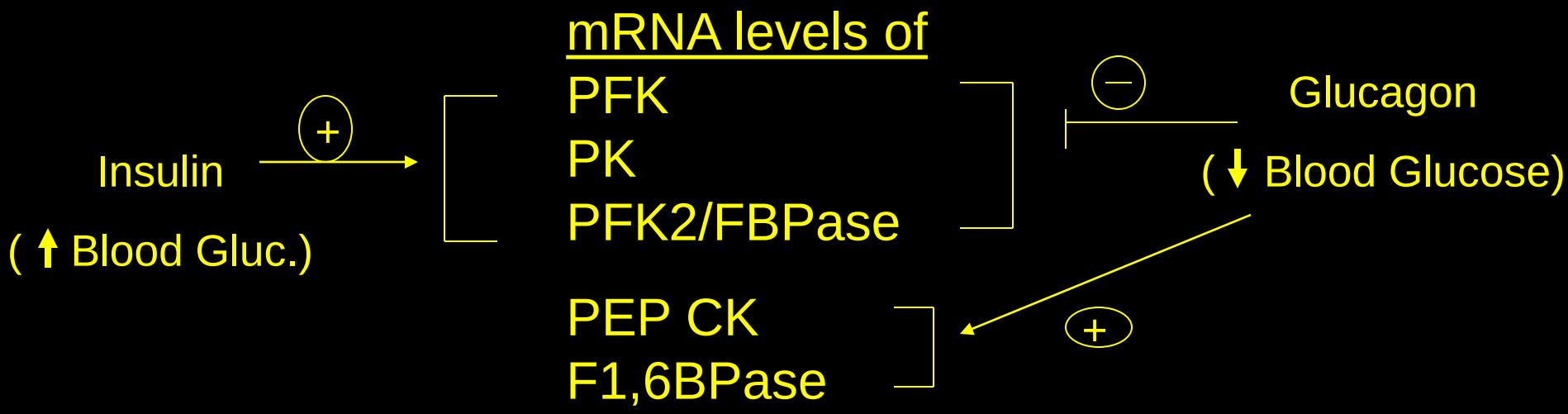

SO: ↓ Blood Glucose → ↑ glucagon → (-) Glycolysis

(+) Gluconeogenesis


Glucose
GLYCOLYSIS
GLUCONEOGENESIS
Fructose 6-phosphate
F-2,6-BP +
AMP +
ATP −
Citrate −
H+ −
Phosphofructo-kinase
Fructose 1, 6-bisphosphatase
− F-2,6-BP
− AMP
+ Citrate
Fructose 1,6-bisphosphate
Several steps
Phosphoenolpyruvate
− ADP
Phosphoenol-pyruvate carboxykinase
F-1,6-BP +
ATP −
Alanine −
Pyruvate kinase
Oxaloacetate
Pyruvate carboxylase
Pyruvate
+ Acetyl CoA
− ADP

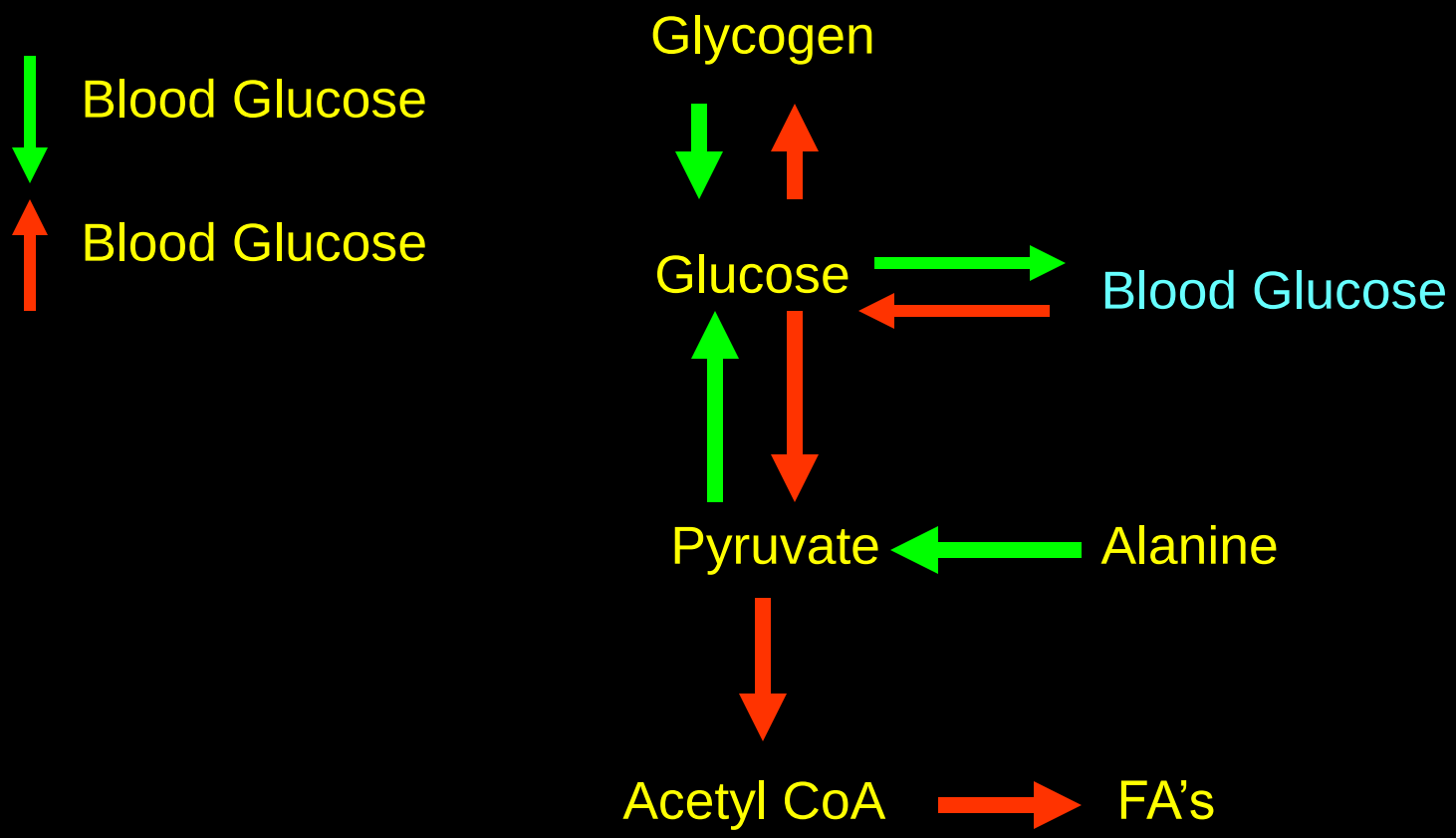
## 2. Transcriptional Regulation

- Allosteric Control – achieved in seconds to minutes.
- Transcriptional Control – hours to days.

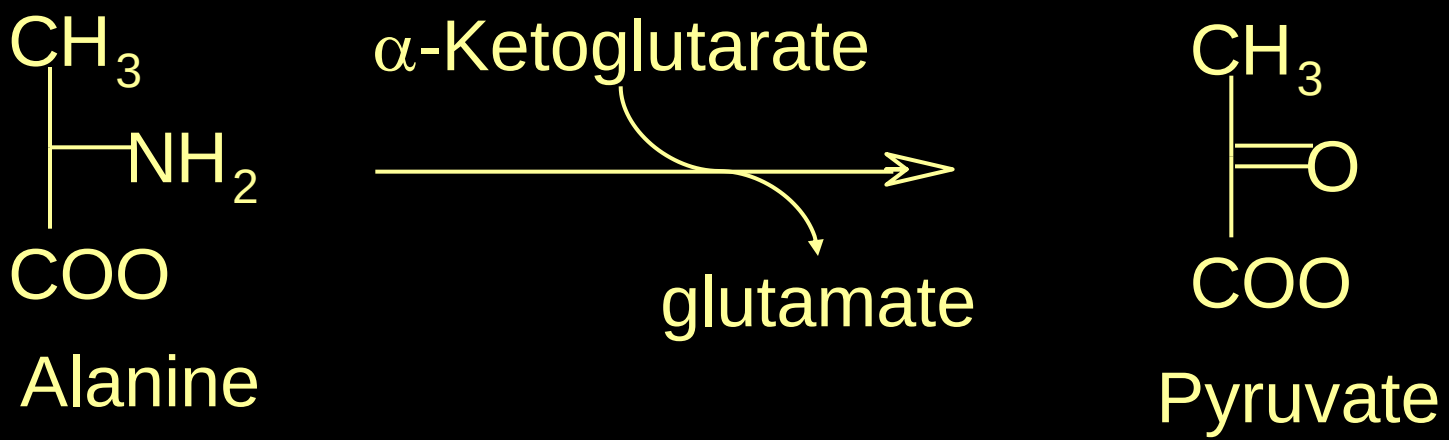



- Thus Insulin promotes synthesis of glycolytic enzymes
- Glucagon inhibits synthesis of glycolytic enzymes, and promotes snythesis of gluconeogenic enzymes.

# The Gluconeogenic Response is Activated Largely by the State of Feeding/Fasting

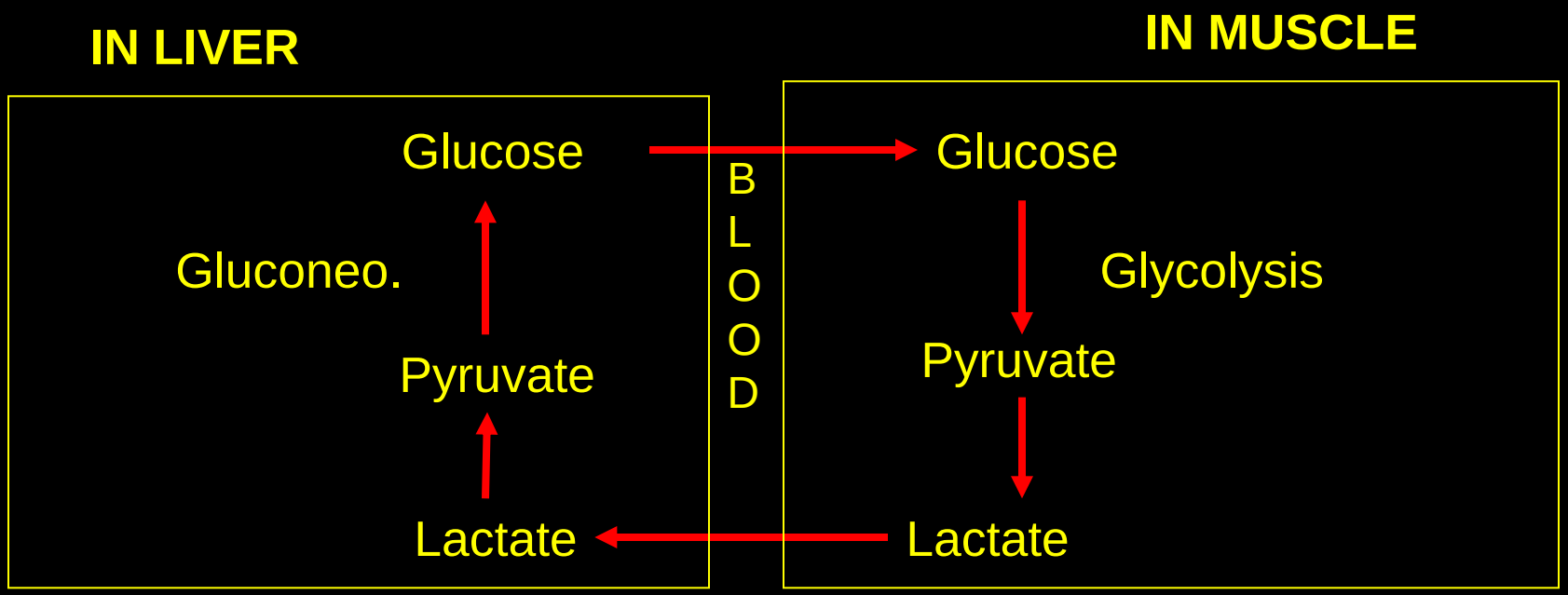


"Transamination"




*** The main substrate for gluconeogenesis in the fasting/starvation state is ALANINE***

# Gluconeogenesis & Glycolysis can Occur at the Same Time in Different Organs




*** The main substrate during exercise is LACTATE***

Main producers of lactate:

- Fast twitch muscle
- Red blood cells

Main consumers of lactate:

- Liver: gluconeogenesis
- Heart: oxidation as fuel
- Slow twitch muscle: oxidation as fuel