



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

CARBOHYDRATE METABOLISM – REOXIDATION OF GLYCOLYTIC NADH

Prof. Michele Di Foggia

Dipartimento di Scienze Biomediche e
Neuromotorie – DIBINEM – via Irnerio 48, Bologna

REOXIDATION OF GLYCOLYTIC NADH

Glycolysis is an oxidative pathway that reduces NAD^+ to NADH at the step of glyceraldehyde-P dehydrogenase.

Two NADH /glucose are produced.

How is NADH reoxidized in order to allow glycolysis to proceed?

Remember that glycolysis takes place in the cytosol, whereas NADH -linked oxidative phosphorylation occurs in mitochondria.



REOXIDATION OF GLYCOLYTIC NADH

Anaerobiosis: reduction of pyruvate to lactate in the cytosol.

Aerobiosis: reducing equivalents from NADH are transported to mitochondria.

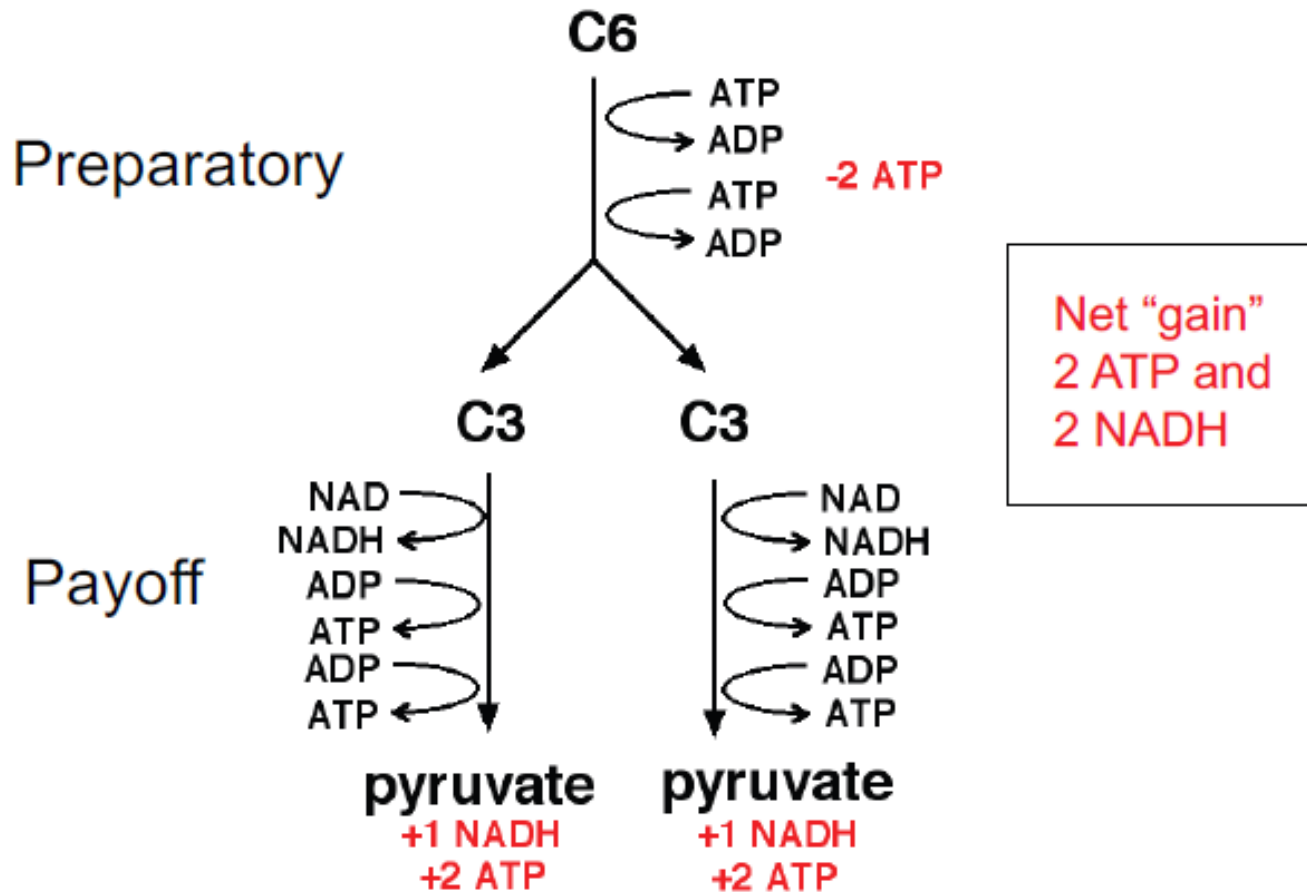
- *glycerol-3-P shuttle*
- *malate/aspartate shuttle*

Under conditions favouring biosynthesis (such as insulin), glycolytic NADH serves as a source of reducing power in the cytosol, supporting lipid synthesis.

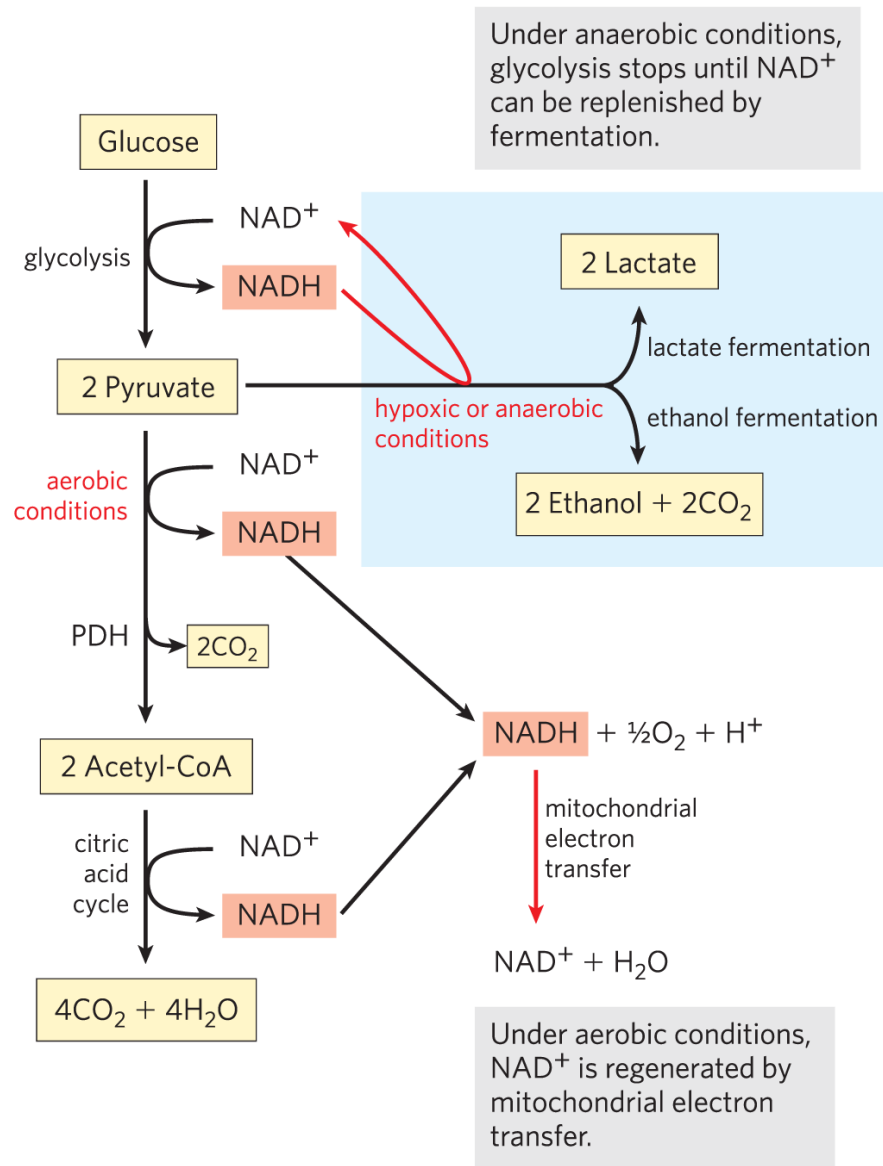


REOXIDATION OF GLYCOLYTIC NADH

Glycolysis overview



REOXIDATION OF GLYCOLYTIC NADH

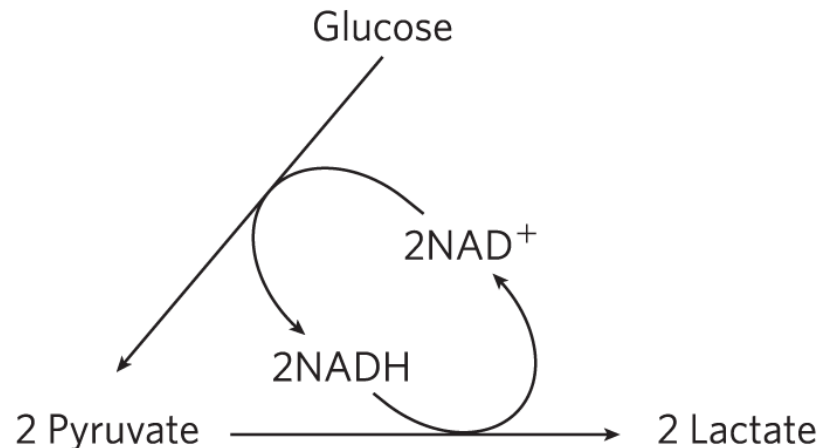
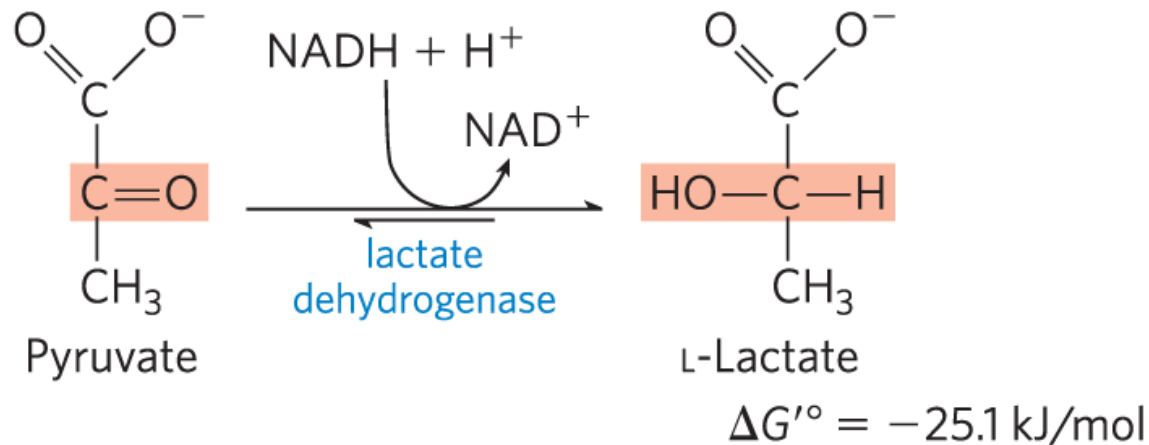


Nelson & Cox, *Lehninger Principles of Biochemistry*, 8e, © 2021 W. H. Freeman and Company

REOXIDATION OF GLYCOLYTIC NADH

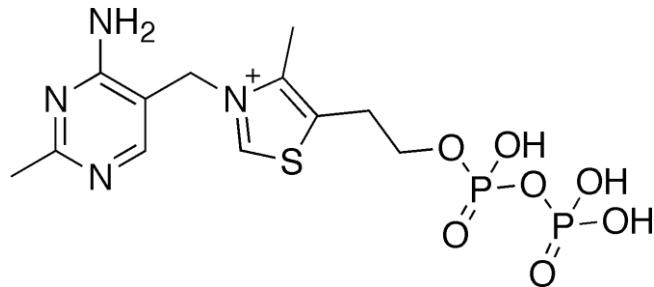
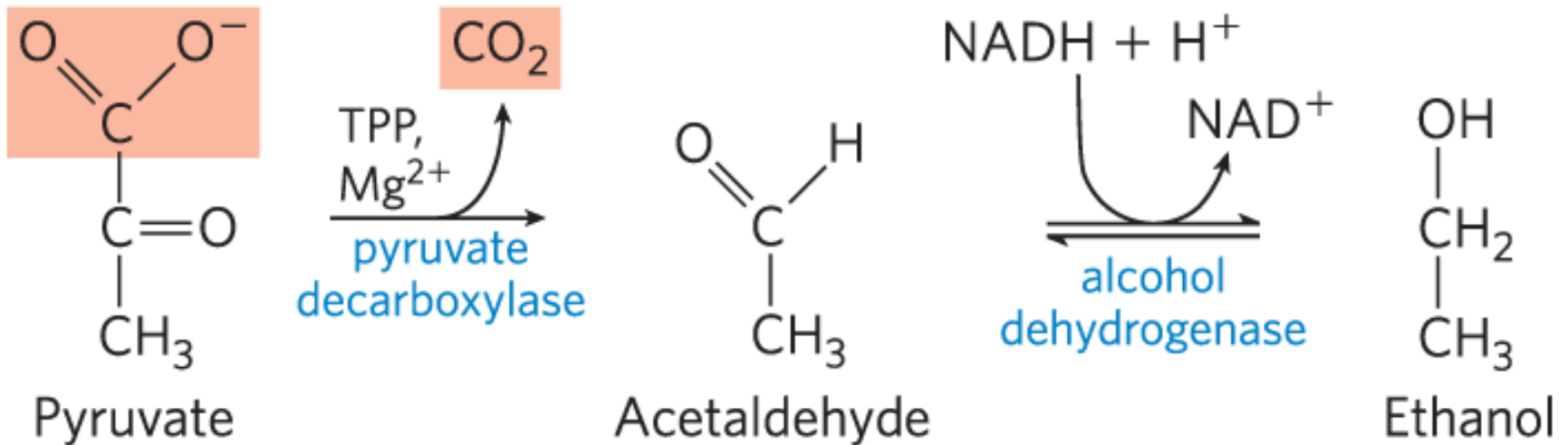
Fermentations: ways to anaerobically regenerate NAD^+ from NADH to maintain a high rate of glycolysis.

1) **Pyruvate to lactate** (athletes; bacteria making yoghurt; tumor cells)



REOXIDATION OF GLYCOLYTIC NADH

2) Pyruvate to ethanol (in yeast)



Thiamine pyrophosphate (Vitamin B1)

REOXIDATION OF GLYCOLYTIC NADH

“Pasteur effect”: the rate and total amount of glucose consumption under anaerobic conditions is many times greater than under aerobic conditions.

This occurs because the ATP yield from glycolysis alone is much smaller (2 ATP per glucose) than complete oxidation to CO_2 (30 or 32 ATP per glucose).



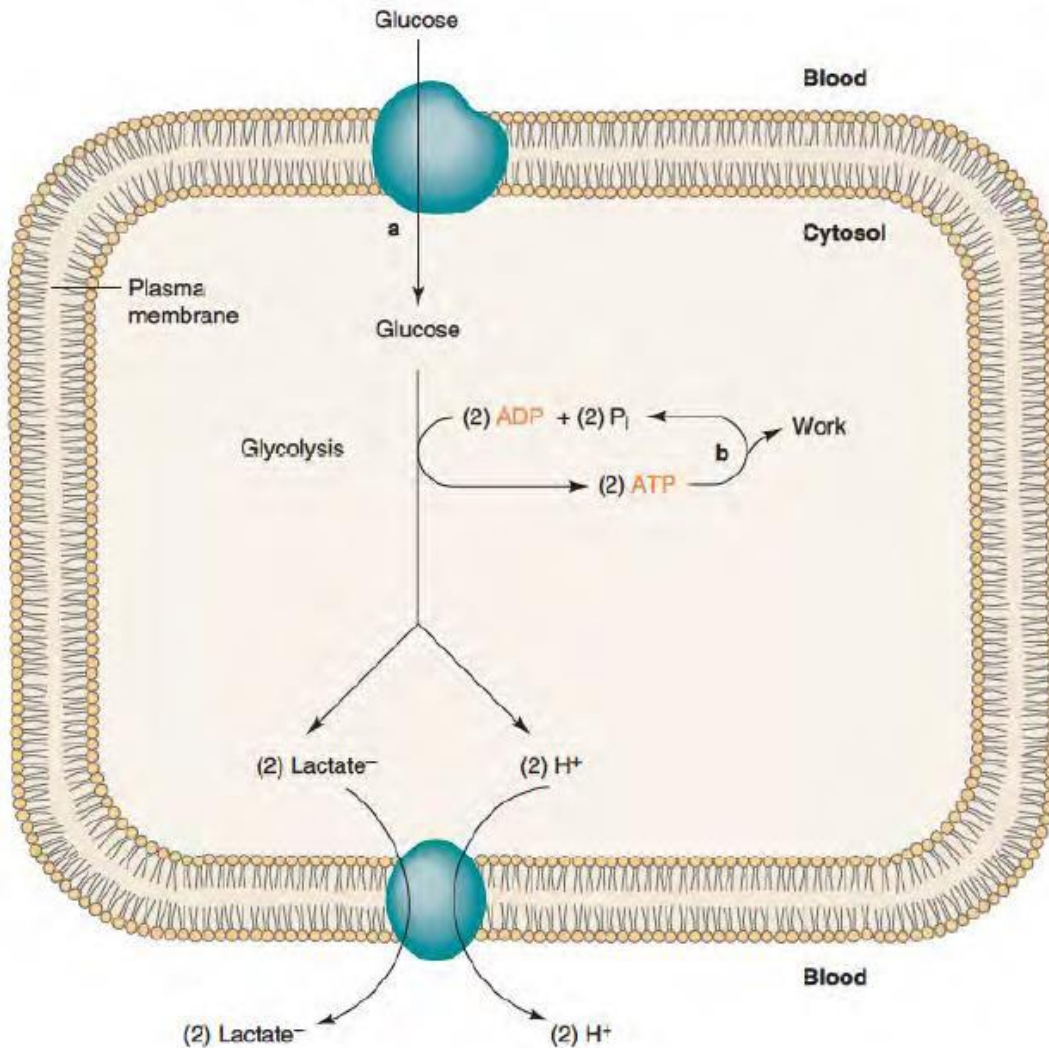
LACTATE OXIDATION



- For **energetic purposes** with further oxidation of pyruvate to acetyl-CoA and TCA cycle (e. g., in heart muscle, red fibres of the skeletal muscle, etc.): acidification resulting from ionisation of lactic acid in muscle and blood limits the period of vigorous activity.
- For **gluconeogenesis** in the liver (Cori cycle).

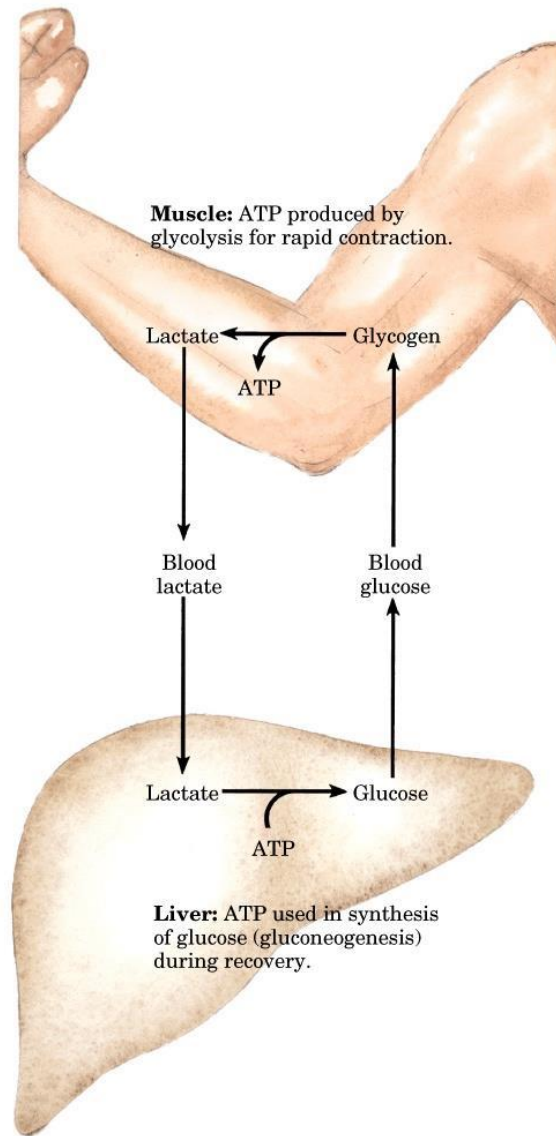


LACTATE OXIDATION

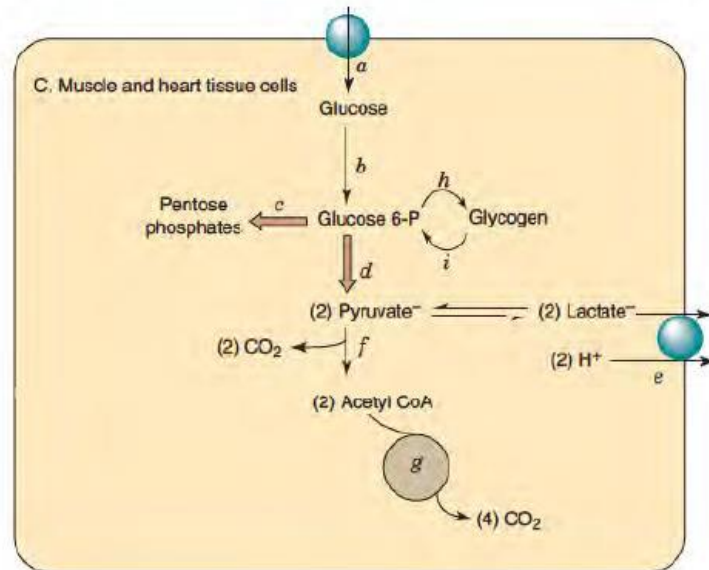
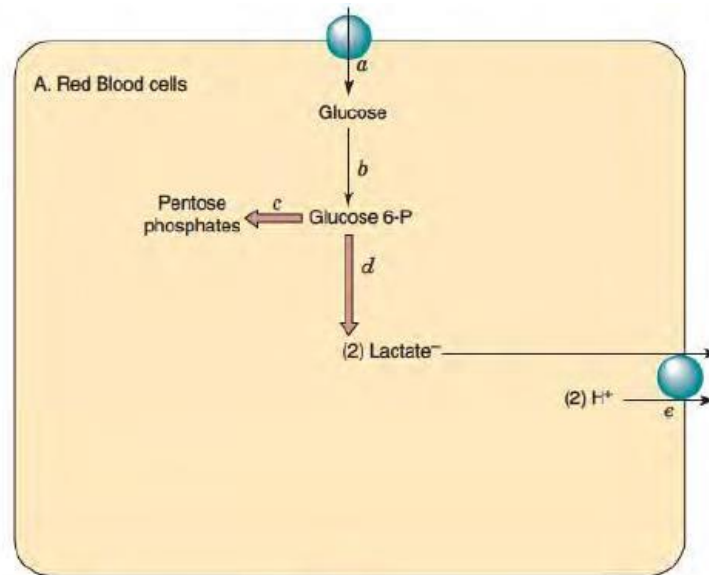


Unless lactate formed by glycolysis is transported out of the cell, the intracellular pH will decrease due to the accumulation of intracellular lactic acid. The low pH decreases PFK-1 activity, thereby inhibiting further lactic acid production by glycolysis.

LACTATE OXIDATION



LACTATE OXIDATION



LACTATE DEHYDROGENASE

LDH is a tetramer with two types of subunits (M [muscle], and H [heart]).

5 combinations:

H₄ (LDH₁); H₃M (LDH₂); H₂M₂ (LDH₃); HM₃ (LDH₄); M₄ (LDH₅).

H₄, H₃M prevail in heart; M₃H, M₄ in muscle and in liver.

M forms are kinetically favorable to pyruvate reduction (anaerobic muscle).

H forms are kinetically favorable to lactate oxidation (heart).

LDH isozymes as diagnostic tools (heart attack).

TABLE 10.2 • Lactate Dehydrogenase Isozymes

<i>Type</i>	<i>Composition</i>	<i>Location</i>
LDH ₁	HHHH	Myocardium and RBC
LDH ₂	HHHM	Myocardium and RBC
LDH ₃	HHMM	Brain and kidney
LDH ₄	HMMM	
LDH ₅	MMMM	Liver and skeletal muscle



LACTATE THRESHOLD

The point at which blood lactic acid suddenly rises during incremental exercise

Anaerobic threshold

Mechanisms for lactate threshold

Low muscle oxygen

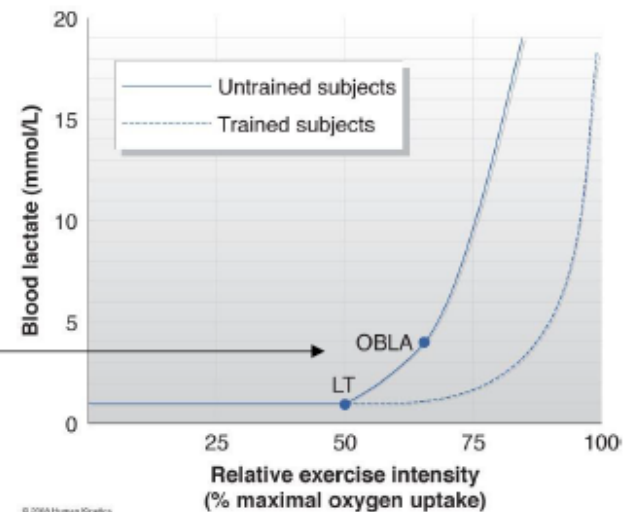
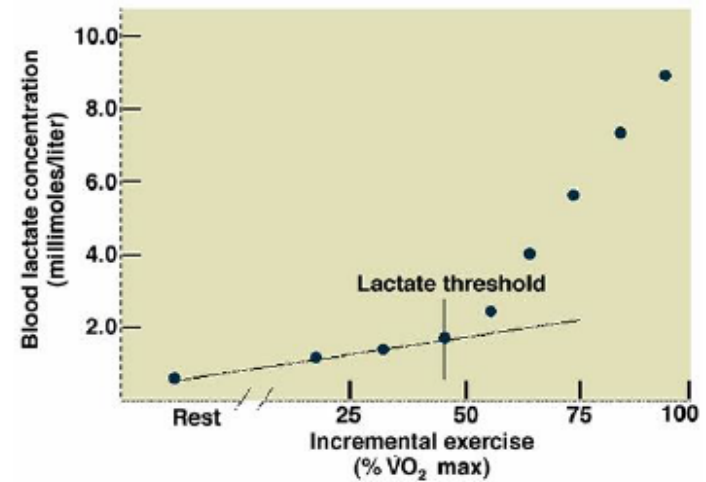
Accelerated glycolysis-role for epinephrine

Recruitment of fast-twitch muscle fibers with different isozymes

Reduced rate of lactate removal from the blood

Practical uses in prediction of performance and as a marker of exercise intensity

Onset of Blood Lactate Accumulation (OBLA)



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SHUTTLES

Malate/Aspartate Shuttle

Glycerol-3-P Shuttle

IMM impermeable to NAD^+/NADH .

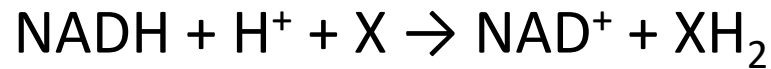
Two pools of NAD: cytosolic and mitochondrial.

Redox-active metabolite permeable through IMM.

Two sets of isoenzymes: cytosolic and mitochondrial.

SHUTTLES

- In cytosol, glycolytic NADH reduces X



- XH_2 crosses IMM \rightarrow matrix

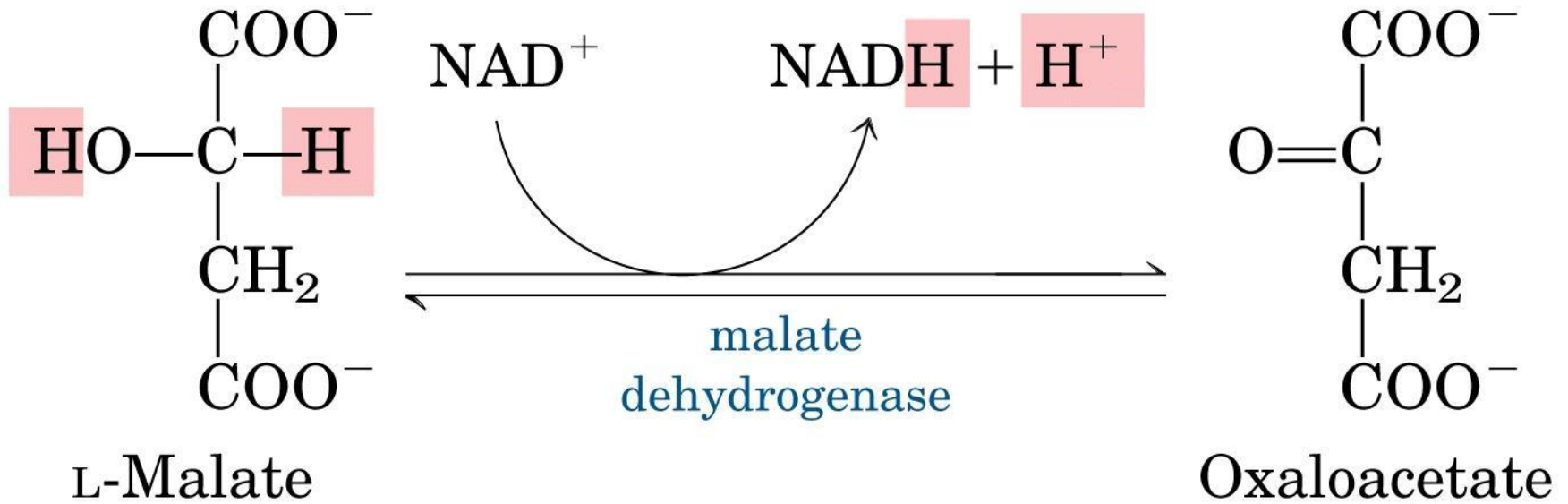
- In matrix XH_2 is oxidized by NAD^+



- NADH is oxidized by respiratory chain
- X goes back to cytosol through IMM

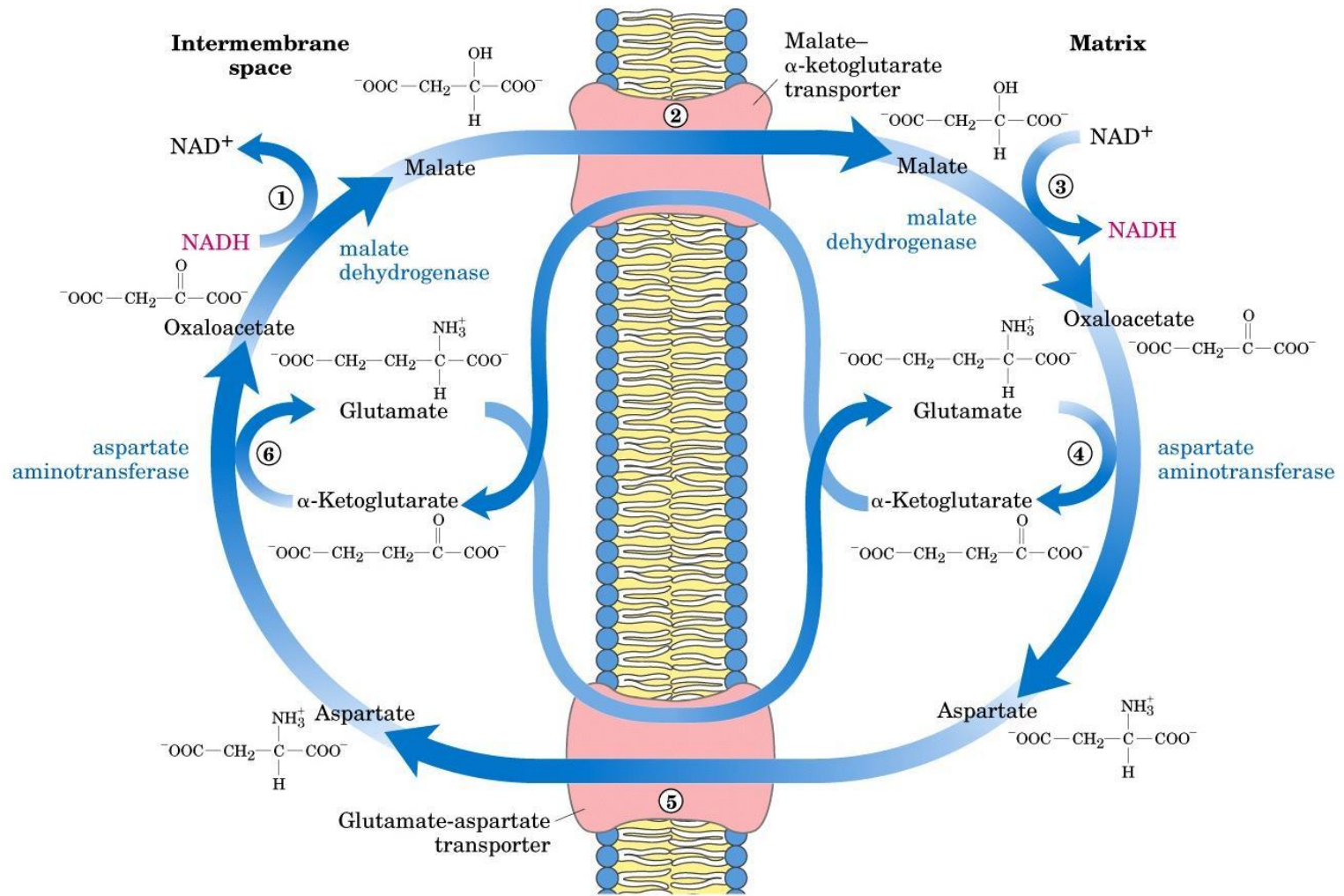


SHUTTLES



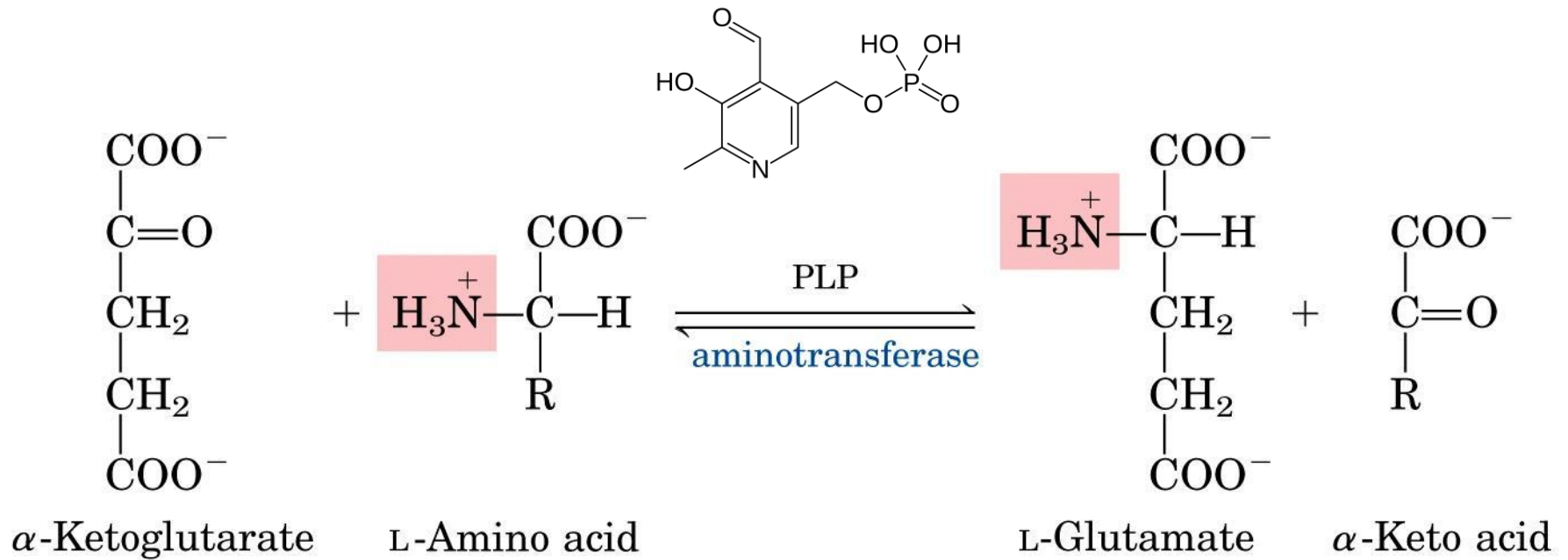
$$\Delta G'^{\circ} = 29.7 \text{ kJ/mol}$$

SHUTTLES



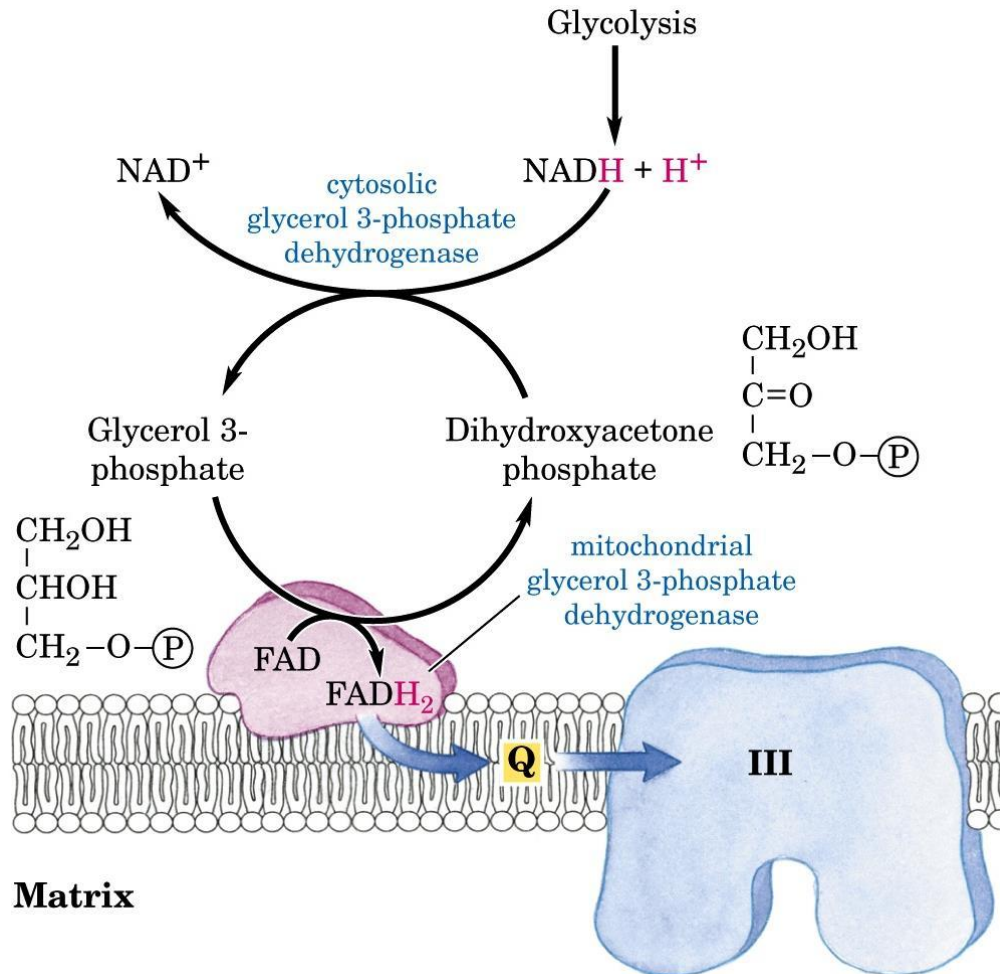
SHUTTLES

Transamination (PLP, vitamin B6)



SHUTTLES

During glycerol-P shuttle, dihydroxyacetone-P (DHOP) is not removed from glycolysis, because it is continuously regenerated.

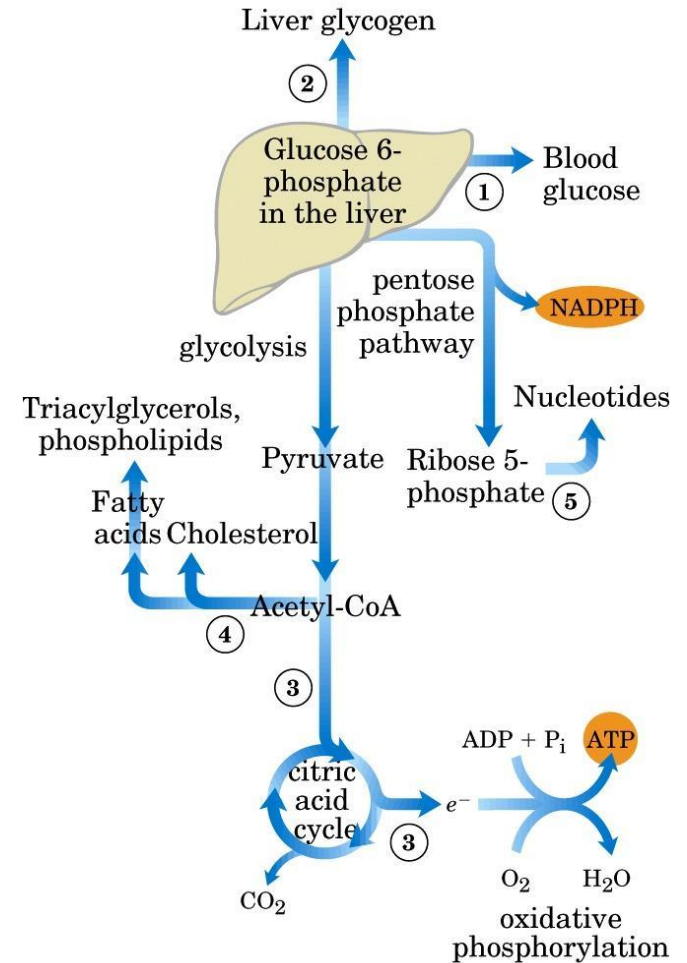


AFTER GLYCOLYSIS

Glycolysis provides the carbon atoms for lipid biosynthesis.

It also provides the required reducing power (NADH; NADPH).

After a carbohydrate meal, insulin promotes glycolysis and lipid biosynthesis.



AFTER GLYCOLYSIS

Anaerobiosis: glucose \rightarrow 2 pyruvate;

2 NADH oxidized to make 2 lactate

2 ATP/glucose (substrate level)

TOTAL 2 ATP

Aerobiosis: glucose \rightarrow 2 pyruvate \rightarrow further oxidation

2 NADH oxidized by malate/aspartate shuttle \rightarrow 2 NADH to the respiratory chain

2 ATP (substrate level) + (2.5 x 2) = 5 ATP (OXPHOS) **TOTAL 7 ATP**

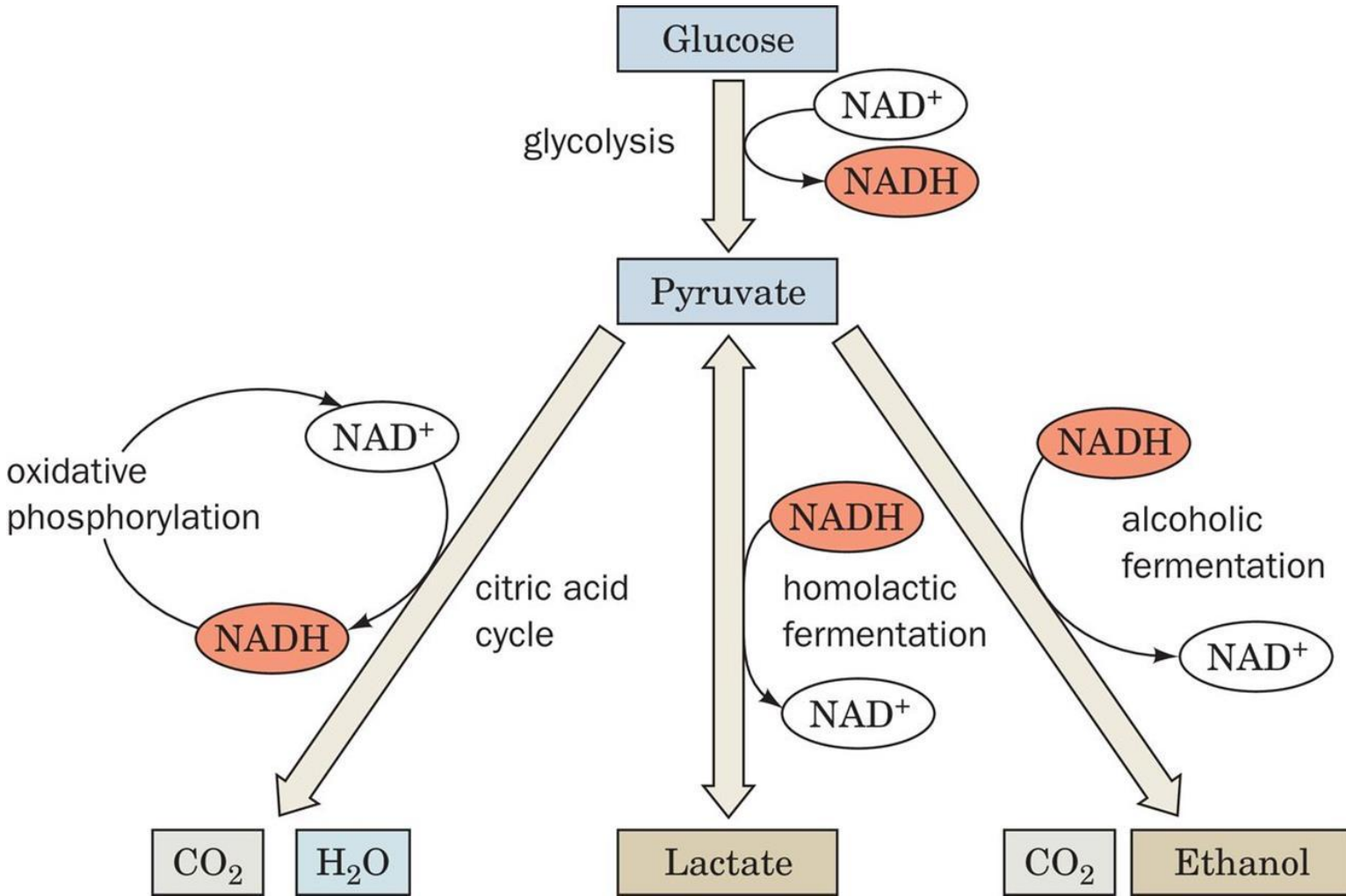
2 NADH oxidized by glycerol-P shuttle \rightarrow 2 glycerol-P to the respiratory chain

2 ATP (substrate level) + (1.5 x 2) = 3 ATP (OXPHOS) **TOTAL 5 ATP**

N.B: More ATP in further oxidation of pyruvate!



AFTER GLYCOLYSIS



Credits:

Prof. Michele Di Foggia

Dipartimento di Scienze Biomediche e Neuromotorie – Sezione di Biochimica

via Irnerio 48

Telephone: +39 051 2094281

michele.difoggia2@unibo.it

