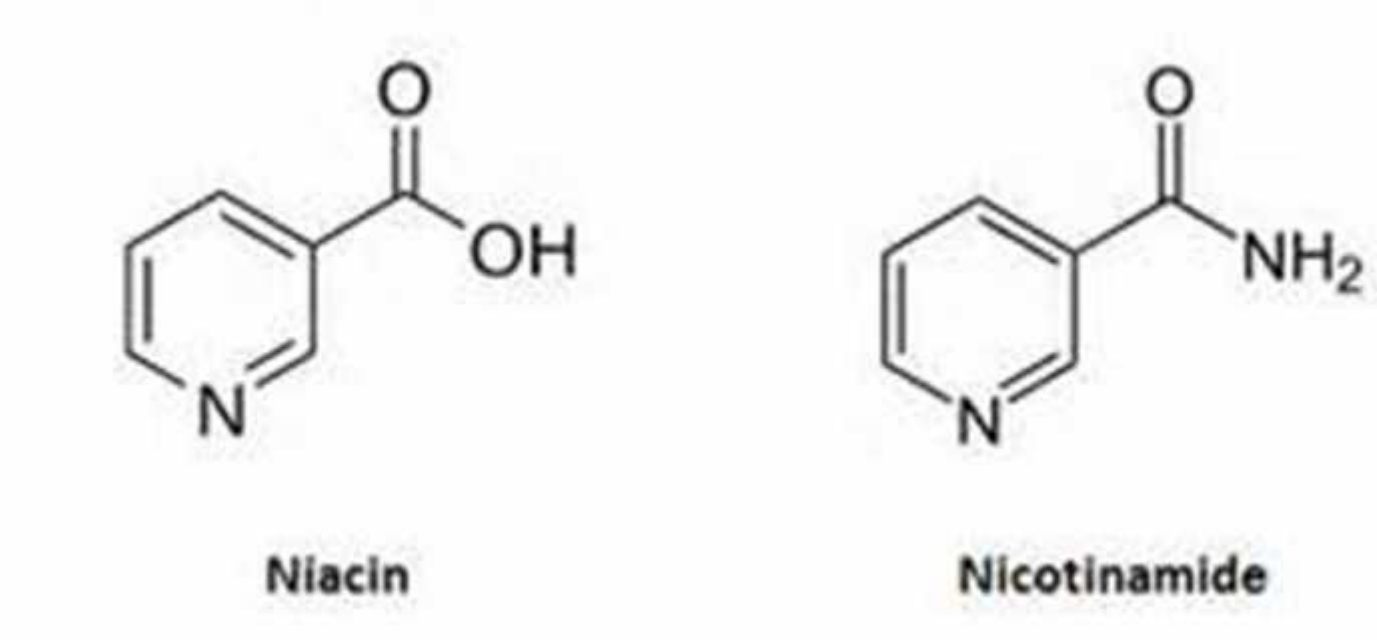
B-COMPLEX VITAMINS

NIACIN (Vitamin B_3)

Chemistry

- Nicotinic acid, P-factor (pellagra preventive factor)
- Pyridine-3-carboxylic acid
- Tissues-present as amide



Biosynthesis

- From Trp- 60 mg Trp give 1 mg niacin
- Intestinal bacteria can synthesize from Glu, Pro, Gly, ornithine

- HUMAN: 1.dietary source, 2. Trp, 3. Intestinal bacteria

- RDA: Adults 17-21 mg
  Children 6mg

- Synthesized from Trp amino acid

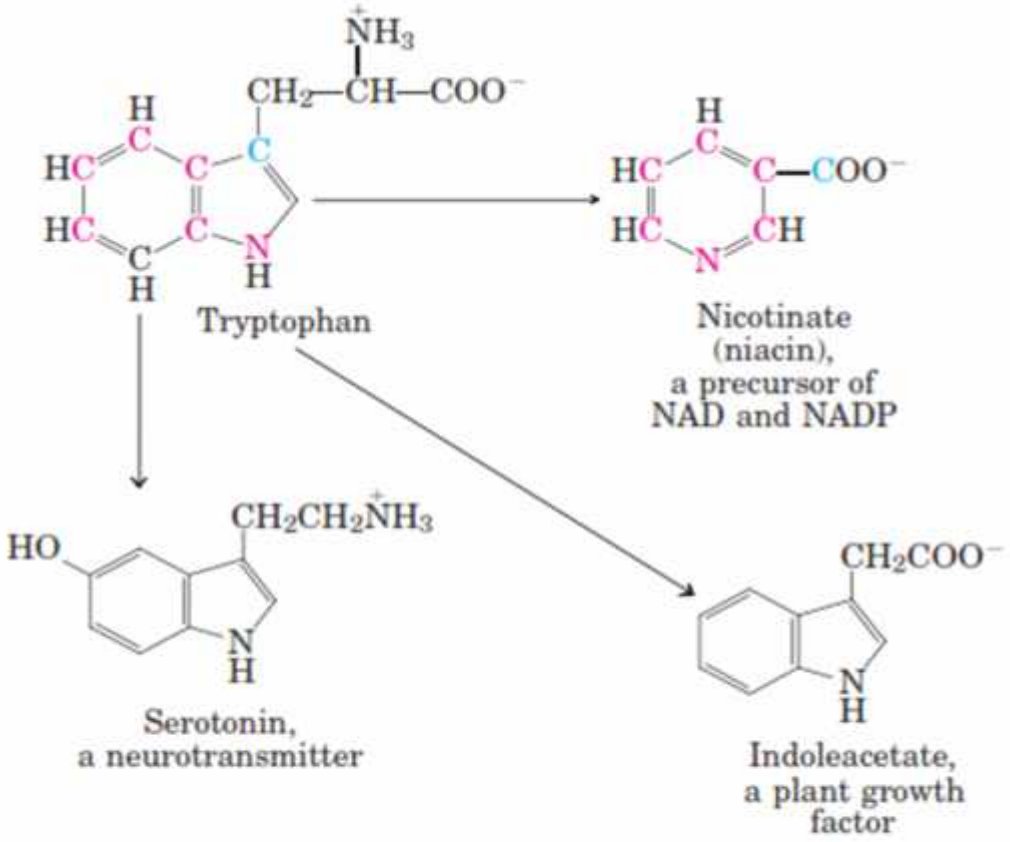


FIGURE 18–22 Tryptophan as precursor. The aromatic rings of tryptophan give rise to nicotinate, indoleacetate, and serotonin. Colored atoms trace the source of the ring atoms in nicotinate.

Occurrence & Sources

- Both nicotinamide & coenzymes widely distributed in animals & plants
- Animal sources: liver, kidney, meat, fish
- Plants sources: Legumes, peas, beans, nuts, coffee, tea, cereal grains, yeast

Metabolism

- Absorption: Niacin & its amide absorbed in small intestine
- RBCs: 1.3 mg (most of niacin in blood is here)
- Excretion: as nicotinic acid, as amide & as methylnicotin amide

Toxicity

Nicotinic acid has been used to treat hyperlipidemia when of the order of 1–6 g/d are required

Caused

Dilation of blood vessels

skin irritation

Intakes of both nicotinic acid and nicotinamide in excess

of 500 mg/d can cause liver damage

- Active forms: NAD^+, $NADP^+$

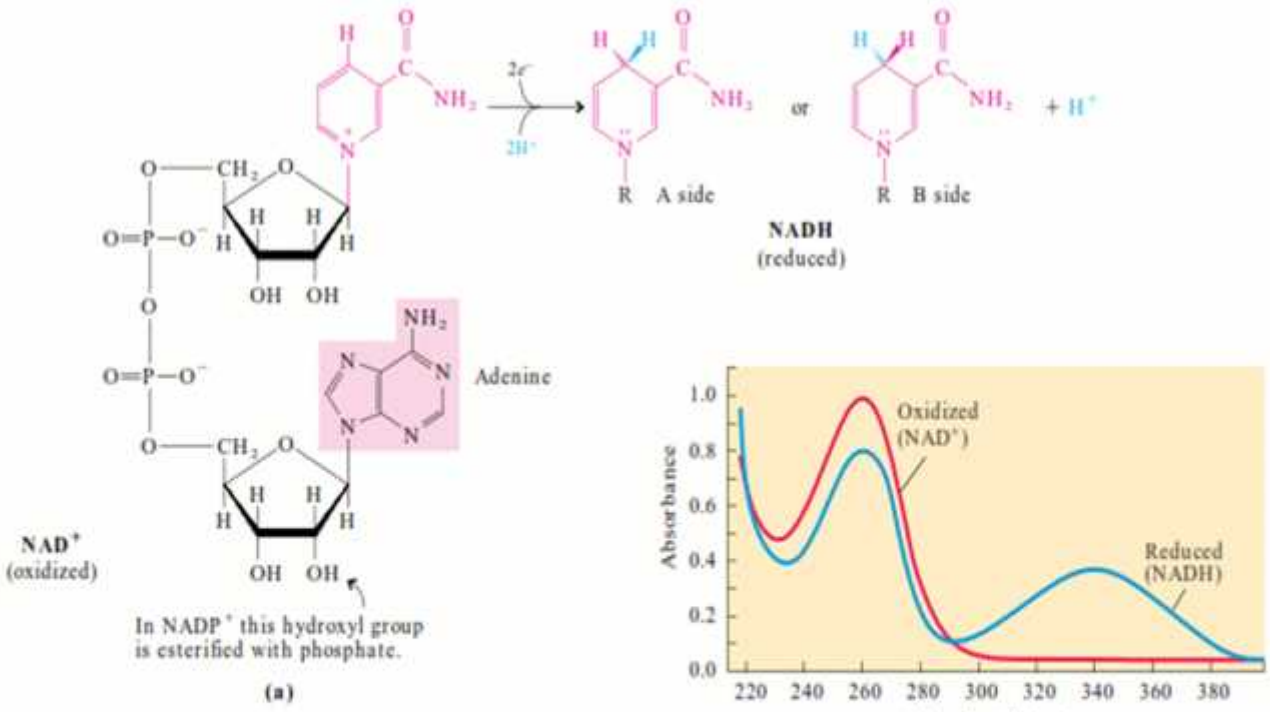


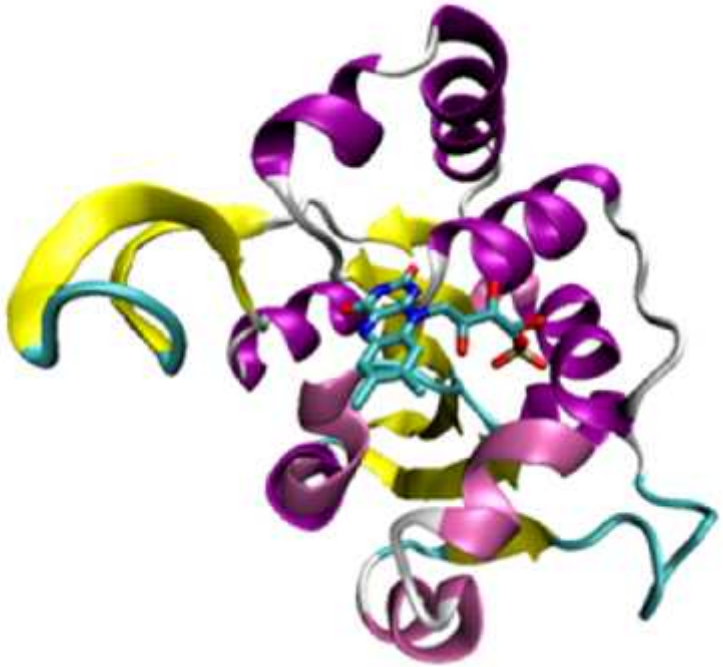
FIGURE 13-15 **NAD and NADP.** **(a)** Nicotinamide adenine dinucleotide, NAD^+, and its phosphorylated analog $NADP^+$ undergo reduction to NADH and NADPH, accepting a hydride ion (two electrons and one proton) from an oxidizable substrate. The hydride ion is added to either the front (the A side) or the back (the B side) of the planar nicotinamide ring (see Table 13–8). **(b)** The UV absorption spectra of NAD^+ and NADH. Reduction of the nicotinamide ring produces a new, broad absorption band with a maximum at 340 nm. The production of NADH during an enzyme-catalyzed reaction can be conveniently followed by observing the appearance of the absorbance at 340 nm (the molar extinction coefficient $\varepsilon_{340} = 6{,}200\ M^{-1}cm^{-1}$).

TABLE 13-8 Stereospecificity of Dehydrogenases That Employ NAD^+ or $NADP^+$ as Coenzymes

Enzyme	Coenzyme	Stereochemical specificity for nicotinamide ring (A or B)	Text page(s)
Isocitrate dehydrogenase	NAD^+	A	XXX-XXX
α-Ketoglutarate dehydrogenase	NAD^+	B	XXX
Glucose 6-phosphate dehydrogenase	$NADP^+$	B	XXX
Malate dehydrogenase	NAD^+	A	XXX
Glutamate dehydrogenase	NAD^+ or $NADP^+$	B	XXX
Glyceraldehyde 3-phosphate dehydrogenase	NAD^+	B	XXX
Lactate dehydrogenase	NAD^+	A	XXX
Alcohol dehydrogenase	NAD^+	A	XXX

- NAD & NADP - freely diffusible coenzymes of many dehydrogenases
- Both NAD & NADP accept 2 electrons & 1 proton
- NAD & NADP bound to dehydrogenases in a widely conserved structural motif called the Rossmann fold

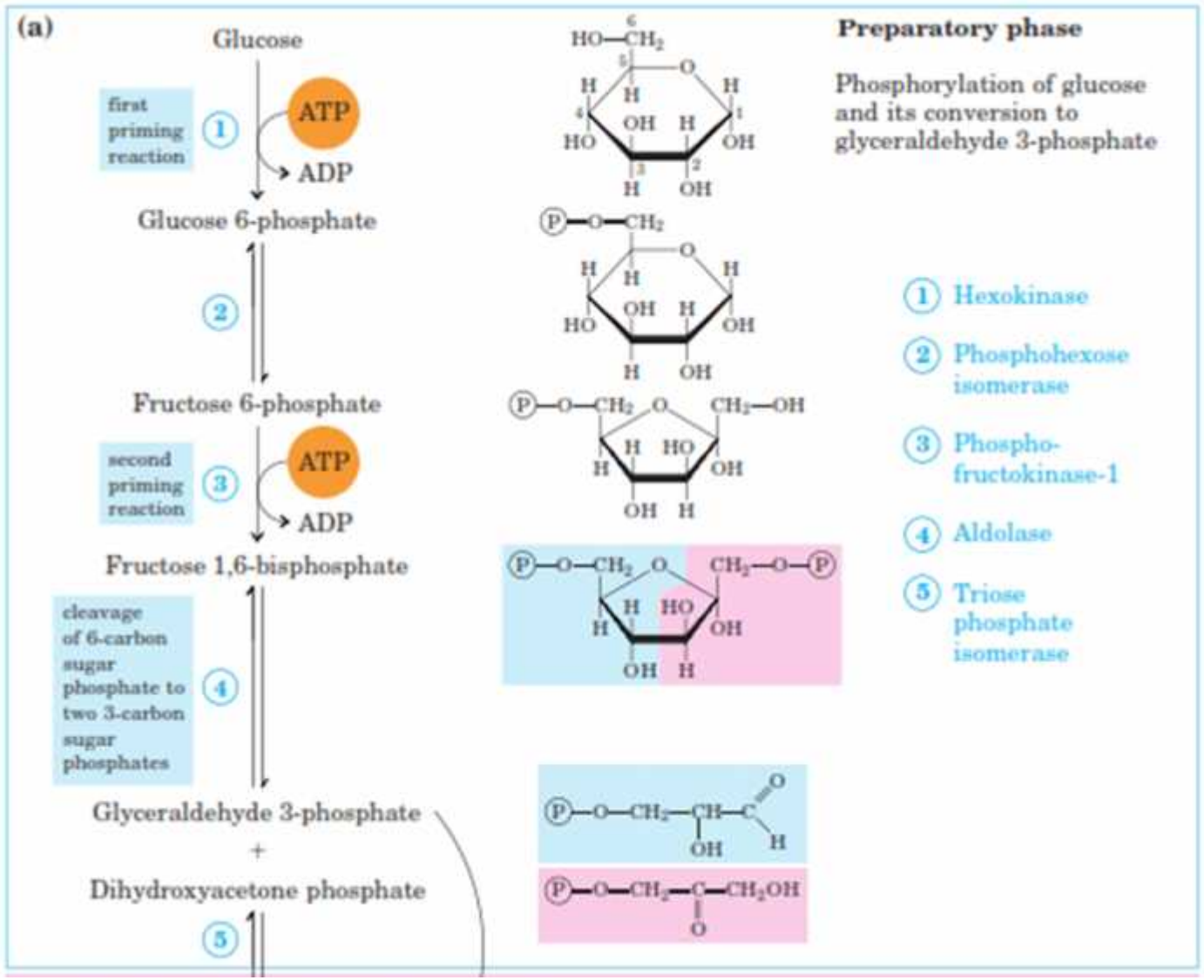
- **Rossmann fold** - a protein structural motif
- Found in proteins that bind nucleotides, especially the cofactor NAD
- Structure composed of 6 parallel beta strands linked to 2 pairs of alpha helices

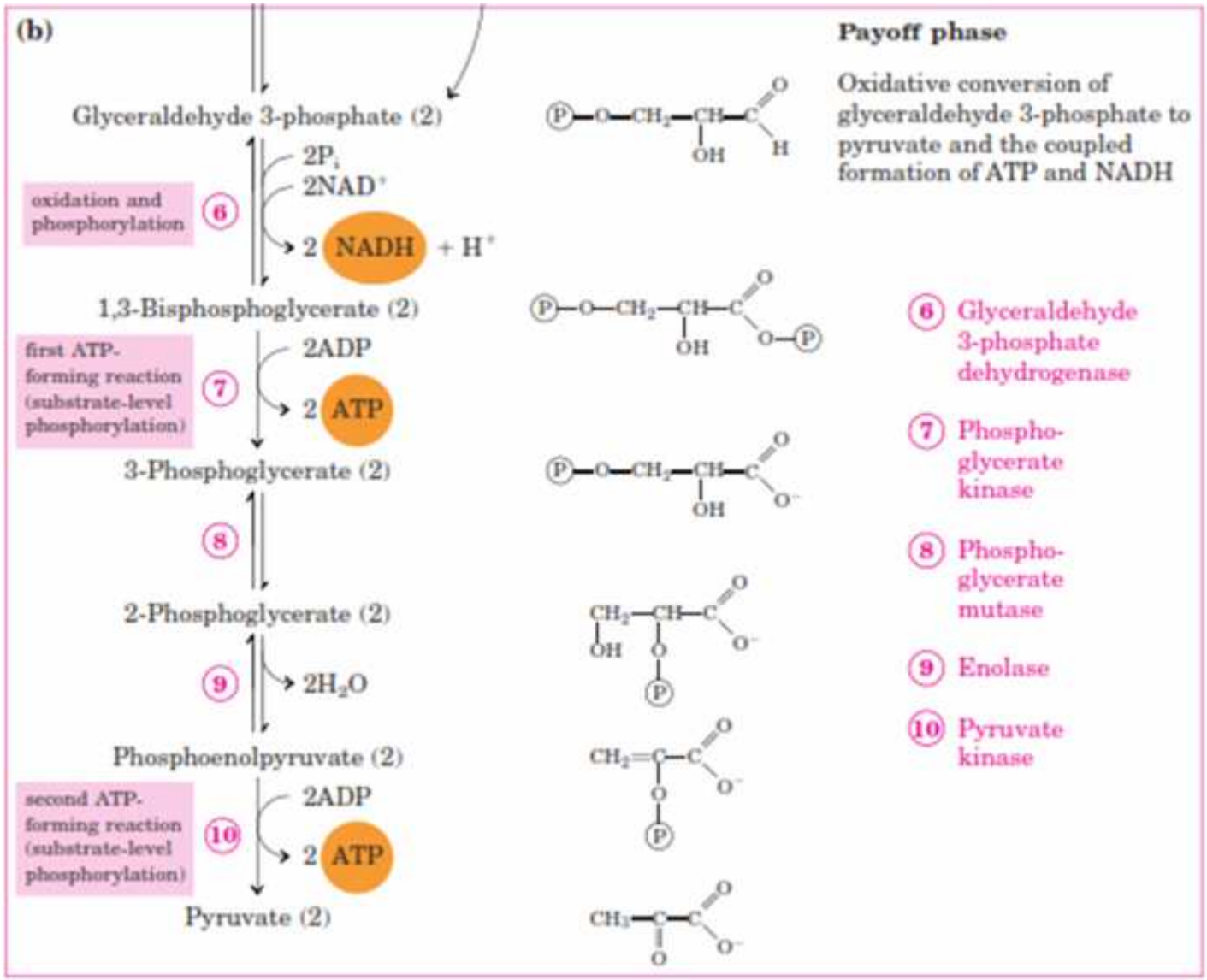


- Motif is named for Michael Rossmann, who first pointed out that this is a frequently occurring motif in nucleotide binding proteins, such as dehydrogenases

- In 1989, Israel Hanukoglu discovered that the NADP binding site in some enzymes that utilize NADP differs from the NAD binding motif
- This discovery was used to re-engineer coenzyme specificities of enzymes

Glycolysis


(a)
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to two 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
1 Hexokinase
2 Phosphohexose isomerase
3 Phospho-fructokinase-1
4 Aldolase
5 Triose phosphate isomerase


(b)
Payoff phase
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH
Glyceraldehyde 3-phosphate (2)
2P$_i$
2NAD$^+$
oxidation and phosphorylation
6
2 NADH + H$^+$
1,3-Bisphosphoglycerate (2)
first ATP-forming reaction (substrate-level phosphorylation)
7
2ADP
2 ATP
3-Phosphoglycerate (2)
8
2-Phosphoglycerate (2)
9
2H$_2$O
Phosphoenolpyruvate (2)
second ATP-forming reaction (substrate-level phosphorylation)
10
2ADP
2 ATP
Pyruvate (2)
6 Glyceraldehyde 3-phosphate dehydrogenase
7 Phospho-glycerate kinase
8 Phospho-glycerate mutase
9 Enolase
10 Pyruvate kinase

Krebs cycle

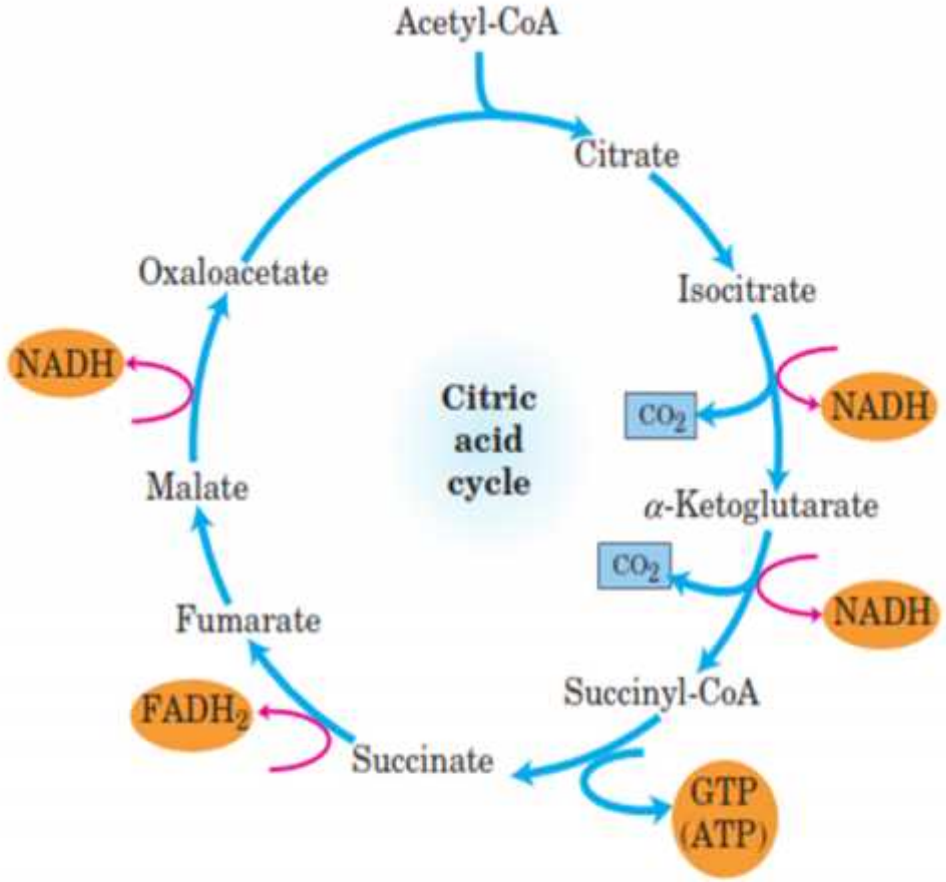
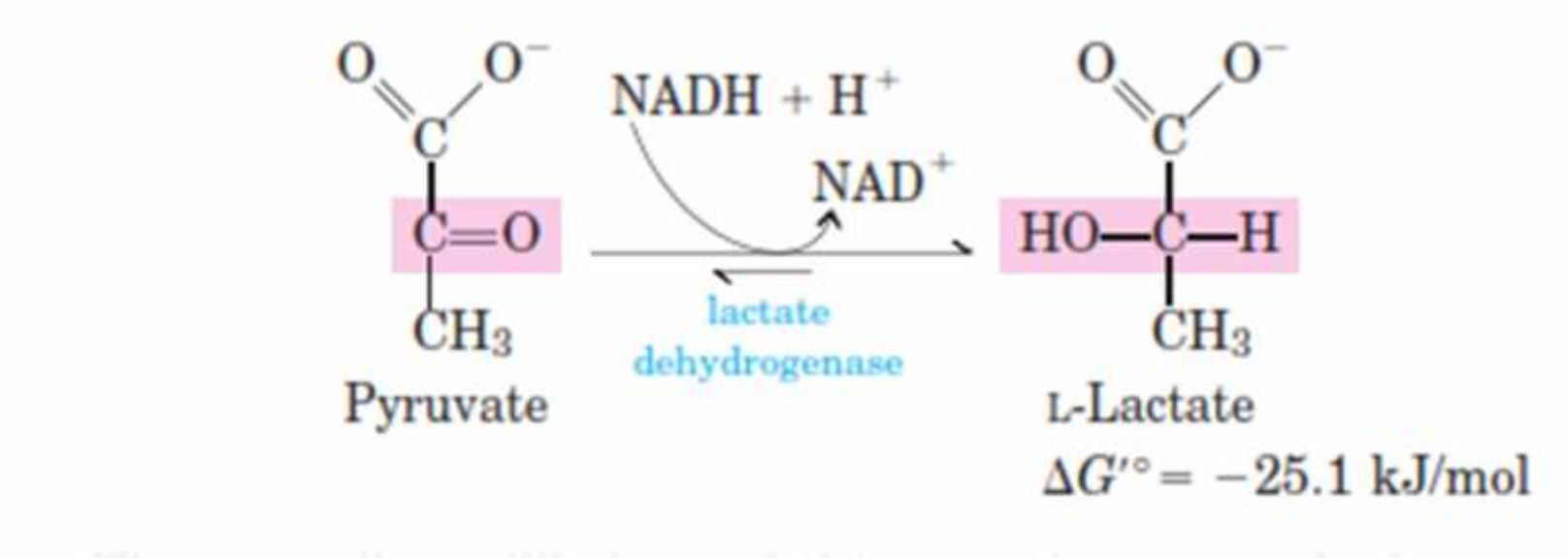


FIGURE 16–13 Products of one turn of the citric acid cycle. At each turn of the cycle, three NADH, one $FADH_2$, one GTP (or ATP), and two CO_2 are released in oxidative decarboxylation reactions. Here and in several following figures, all cycle reactions are shown as proceeding in one direction only, but keep in mind that most of the reactions are reversible (see Fig. 16–7).

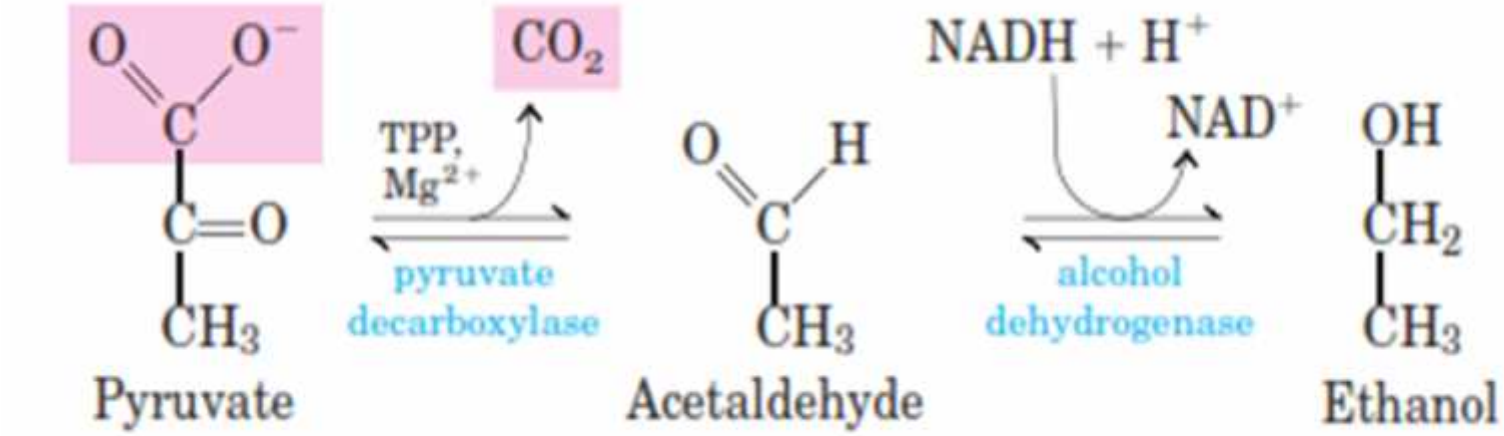
NAD^+

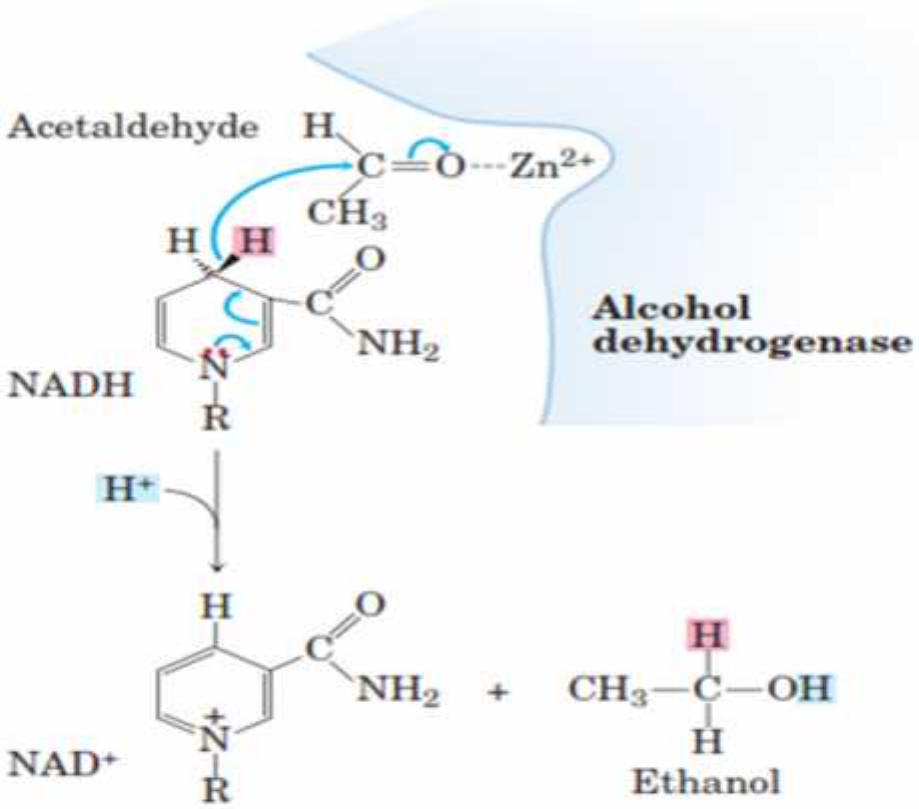
NIACIN

Lactic acid Fermentation



Ethanol Fermentation





MECHANISM FIGURE 14–12 The alcohol dehydrogenase reaction. A Zn^{2+} at the active site polarizes the carbonyl oxygen of acetaldehyde, allowing transfer of a hydride ion (red) from the reduced cofactor NADH. The reduced intermediate acquires a proton from the medium (blue) to form ethanol. Alcohol Dehydrogenase Mechanism

- $NADP^+$ - Pentose phosphate pathway

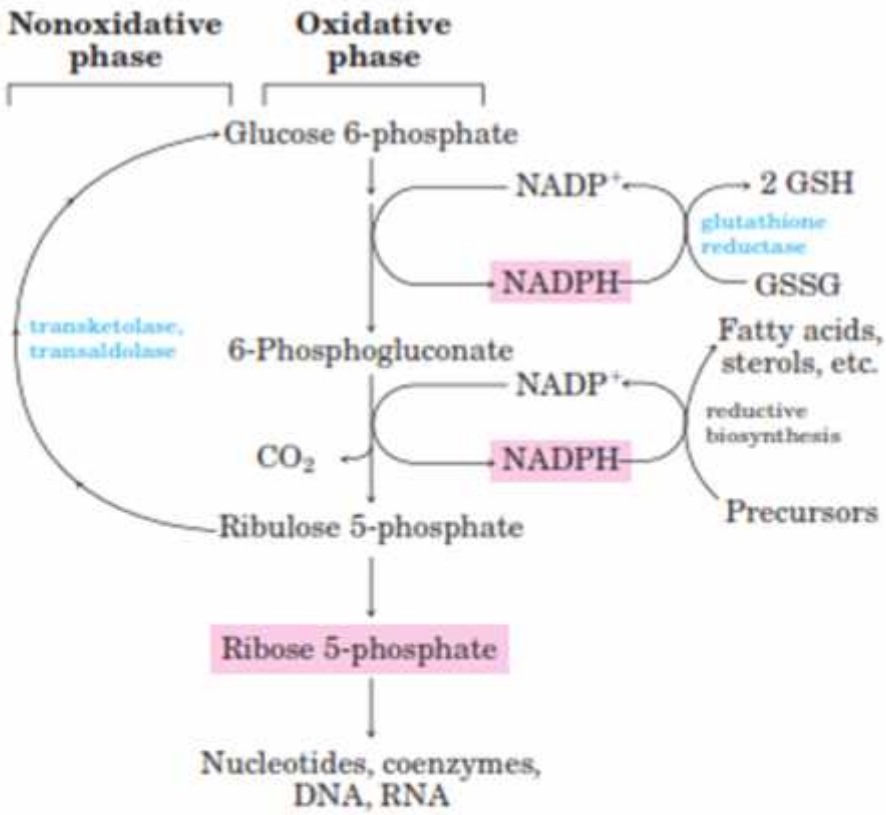


FIGURE 14–20 General scheme of the pentose phosphate pathway. NADPH formed in the oxidative phase is used to reduce glutathione, GSSG (see Box 14–3) and to support reductive biosynthesis. The other product of the oxidative phase is ribose 5-phosphate, which serves as precursor for nucleotides, coenzymes, and nucleic acids. In cells that are not using ribose 5-phosphate for biosynthesis, the nonoxidative phase recycles six molecules of the pentose into five molecules of the hexose glucose 6-phosphate, allowing continued production of NADPH and converting glucose 6-phosphate (in six cycles) to CO_2.

$NADP^+$

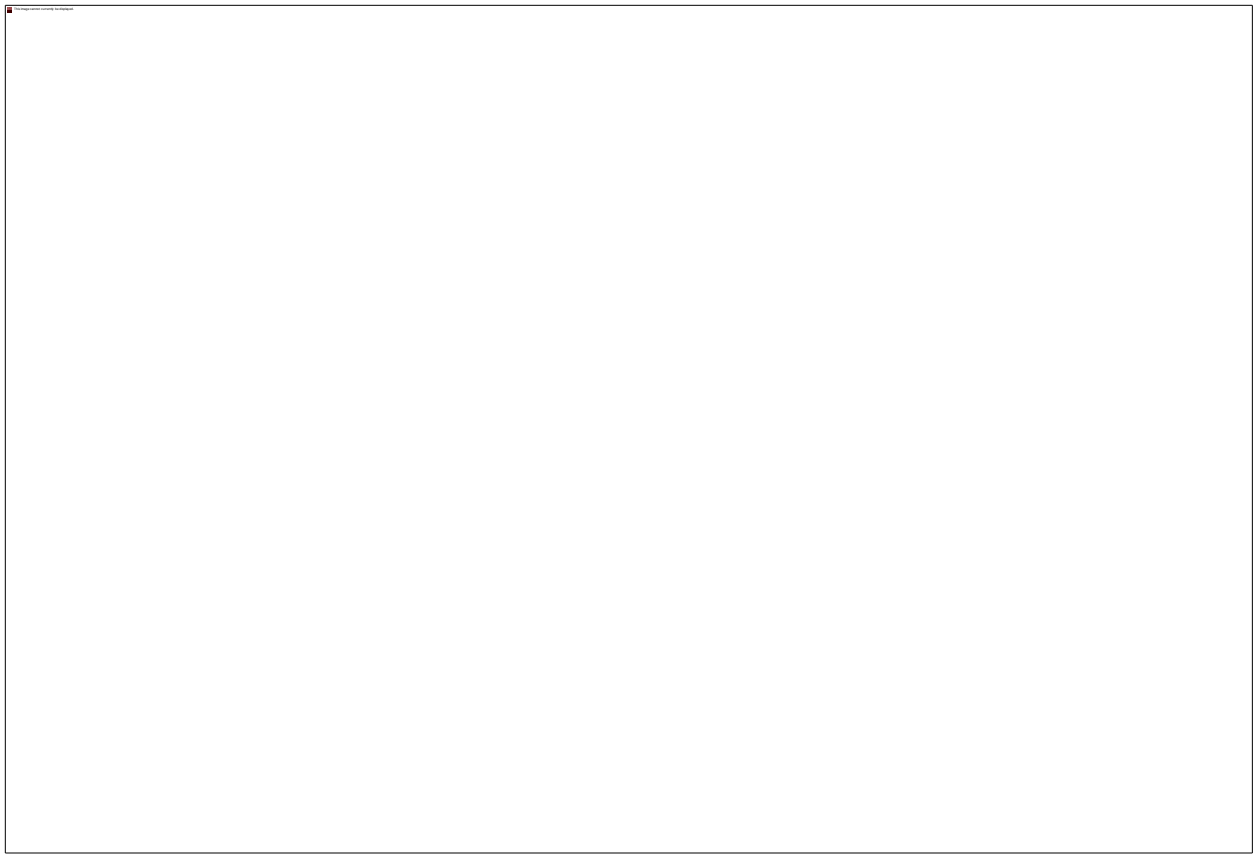
- Pentose phosphate pathway OR Phosphogluconate pathway OR hexose monophosphate pathway
- Brings about oxidation and decarboxylation at C-1 of glucose 6-phosphate, reducing NADP to NADPH and producing pentose phosphates
- NADPH provides reducing power for biosynthetic reactions

Anaplerotic Reactions

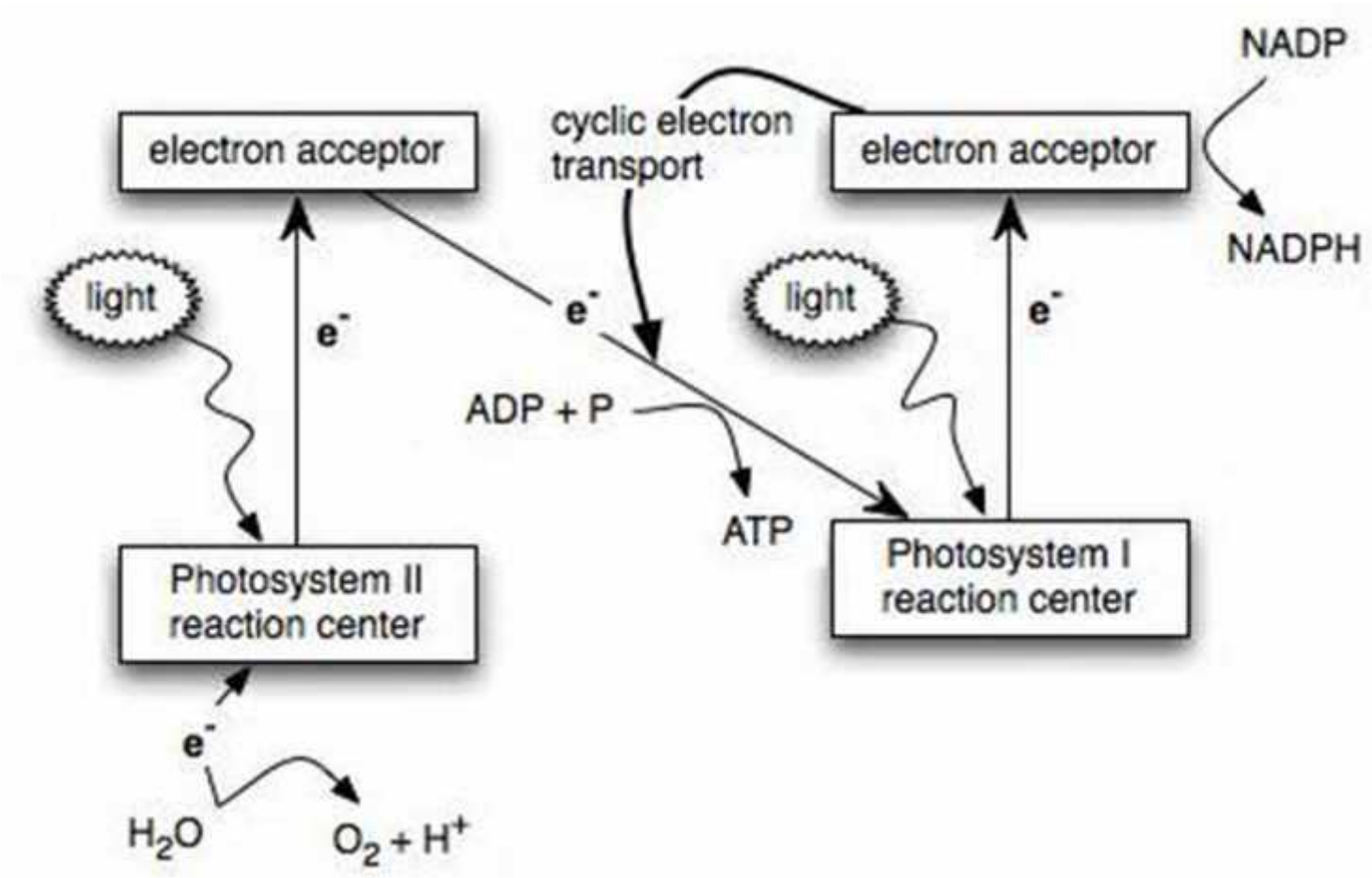
TABLE 16-2 Anaplerotic Reactions

Reaction	*Tissue(s)/organism(s)*
$\text{Pyruvate} + HCO_3^- + \text{ATP} \xrightleftharpoons{\text{pyruvate carboxylase}} \text{oxaloacetate} + \text{ADP} + P_i$	Liver, kidney
$\text{Phosphoenolpyruvate} + CO_2 + \text{GDP} \xrightleftharpoons{\text{PEP carboxykinase}} \text{oxaloacetate} + \text{GTP}$	Heart, skeletal muscle
$\text{Phosphoenolpyruvate} + HCO_3^- \xrightleftharpoons{\text{PEP carboxylase}} \text{oxaloacetate} + P_i$	Higher plants, yeast, bacteria
$\text{Pyruvate} + HCO_3^- + \text{NAD(P)H} \xrightleftharpoons{\text{malic enzyme}} \text{malate} + \text{NAD(P)}^+$	Widely distributed in eukaryotes and prokaryotes

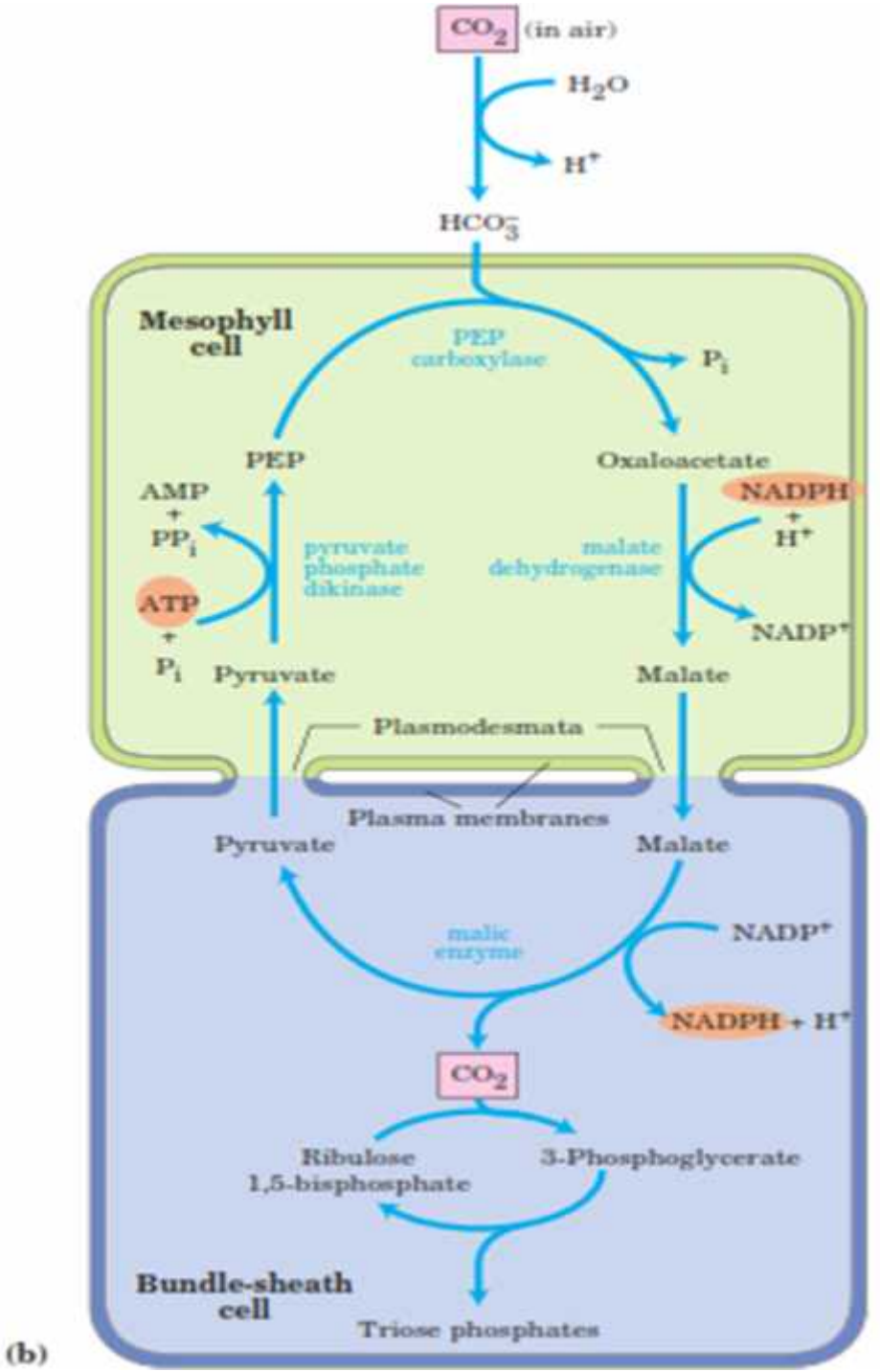
- Light reactions - photosynthesis



Z - Scheme


NADP
electron acceptor
cyclic electron transport
electron acceptor
NADPH
light
e-
e-
light
e-
ADP + P
ATP
Photosystem II reaction center
Photosystem I reaction center
e-
H2O
O2 + H+

Hatch Slack Pathway-C4 plants



Pellagra

- Pyridine-like rings of NAD & NADP – derived from the vitamin **niacin**
- Niacin - synthesized from tryptophan
- Humans generally cannot synthesize niacin in sufficient quantities, & this is especially so for those with diets low in tryptophan (maize, for example, has a low tryptophan content)
- Niacin deficiency affects all the NAD(P)-dependent dehydrogenases, causes the serious human disease pellagra (Italian for "rough skin")
- Characterized by the "three Ds": dermatitis, diarrhea, and
- dementia, followed in many cases by death (4^{th} D?)

- Dermatitis: skin lesions etc (face, neck, wrist, forearms, elbows). Skin is reddened, later brown, thickened & scaly
- Diarrhoea: GI manifestations etc (anorexia, nausea, vomiting, alternating constipation/diarrhoea)
- Dementia: Psychosis etc (insomnia, depression, mild psychoneurosis, severe psychosis)

- Pellagra can develop according to several mechanisms, all of which ultimately revolve around niacin deficiency

- 1ST- simple dietary lack of niacin
- 2ND - it may result from deficiency of Trp (an essential amino acid)
- 3rd -it may be caused by excess leucine though the relationship is unclear

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- Murray, R.K., D.A. Bender, K. M. Botham , P.J. Kennelly,V.W. Rodwell and P.A.Weil. 2009. Harper's Illustrated Biochemistry. 28th ed. McGraw Hill. New York.