METABOLISM

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ARKAN ACADEMY

Pentose Phosphate Pathway (PPP)

- This pathway is important for:
  1. Production of NADPH, which is used in many biosynthetic pathways
  2. Metabolism of pentoses (five-carbon sugars)
     - ✓ Pentoses are used in the production of *nucleotides* and other anabolic intermediates

- PPP occurs at ***high glucose level***, as an alternative pathway
  - ➢ It is also called ***Hexose Monophosphate Shunt***

- PPP consists of 2 phases:

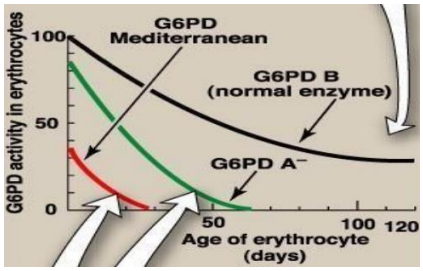
1) Oxidative irreversible phase (Irreversible)

- Hexokinase or Glucokinase phosphorylate glucose into *Glucose 6-Phosphate*
- Glucose-6-phosphate dehydrogenase (***G6PD***) oxidizes the first carbon of Glucose 6-phasphate into carboxyl forming *6-phosphogluconate* and reduce $NADP^+$ into NADPH
- 6-Phosphogluconate dehydrogenase (**6PGD**) oxidizes and decarboxylates 6-phosphogluconate into *Ribulose 5-phosohate*, with the release of CO_2 and NADPH

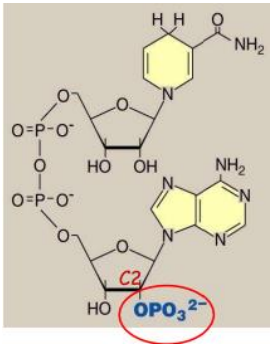
2) Non-oxidative reversible phase (Reversible)

- After producing **2** Ribulose 5-phosphate from the oxidative phase
  - ➢ The first ribulose 5-phosphate will be isomerized to *Ribose 5-Phosphate* by ***isomerase***
    - ✓ Ribose 5-phosphate can be used to ***produce nucleotide***
  - ➢ The other ribulose 5-phosphate is epimerized on C3 into *xylulose 5-phosphate* by ***epimerase***
- Ribose 5-phosphate + xylulose 5-phosphate, produce *sedoheptulose 7-phosphate* , *G3P* by ***transketolase***
- They are then converted into *fructose 6-phosphate* , *erythrose 4-phosphate* by ***transaldolase***
- A **third** glucose can be converted into ribulose 5-phosphate by the oxidative phase
  - ➢ Ribulose 5-phosphate is epimerized into *xylulose 5-phosphate*
  - ➢ Xylulose 5-phosphate + erythrose 4-phosphate produce *fructose 6-phosphate* , *G3P* by ***transketolase***
- Products of PPP:
  - ➢ Oxidative Phase Alone per glucose molecule: *2 NADPH, 1 Ribulose 5-Phosphate, 1* CO_2
  - ➢ Net process by consuming 3 glucose molecules: ***2*** *Fructose 6-Phosphate*, ***1*** *G3P*, ***3*** CO_2, ***6*** *NADPH*
    - ✓ They can complete glycolysis to release energy and produce ATP
  - ➢ Net process by consuming 6 glucose molecules: ***4*** *Fructose 6-Phosphate*, ***2*** *G3P*, ***6*** CO_2, ***12*** *NADPH*
    Or it could be: ***5*** *Fructose 6-Phosphate*, ***6*** CO_2, ***12*** *NADPH*
- ***Insulin*** is released during the well-feed state (high glucose level) which upregulates the gene expression of G6PD enzyme (activation of PPP)
- High levels of ***NADPH*** inhibit PPP

- *Glucose 6-phosphate dehydrogenase (G6PD) deficiency:* Very Common genetic
  - Characterized by *hemolytic anemia* (RBCs die earlier)
  - 200 – 400 million individuals worldwide mainly in *Middle East*, *S.E*. *Asia*, *Mediterranean countries*
  - *X-linked* inheritance (higher chance in males), caused by > 400 different mutations
    - ✓ Majority of these mutation are point mutations that cause missense in the gene expression
    - ✓ Large deletion or frame shift mutations are not observed
  - Deficiency provides *resistance to falciparum malaria* (which attacks RBCs)
- RBCs die and regenerated each 120 days
- Precipitating factors in G6PD deficiency:
  - *Oxidant drugs:* antibiotics (sulfamethoxazole), antimalaria (primaquine), antipyretics (acetanilid)
  - *Vicine* and *covicine* in fava beans causes favism for G6PD patients
  - *Infection*
  - *Neonatal Jaundice*

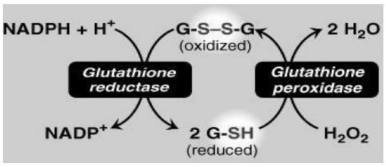


- G6PD Deficiency Variants:
  - *Wild type B* (G6PD Normal)
  - *Class IV:* no clinical symptoms (G6PD more than 60% activity)
  - *African Variant A⁻ (Class III):* moderate with 2 point-mutations (G6PD 10-50% active)
  - *Mediterranean Variant B⁻ (Class II):* severe (G6PD less than 10% active)
  - *Class I:* Very severe deficiency (G6PD less than 2% active)

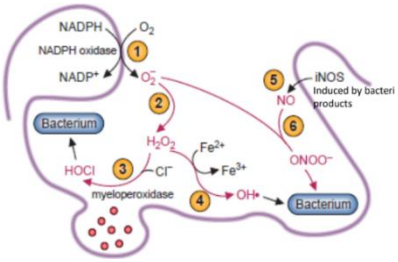


- NADH and NADPH are relatively similar in the structure
  - NADH has an OH on C2 but NADPH has a phosphate group on C2
- They have different roles, used in specific pathways with specific enzymes
  - NAD^+ is usually reduced in the degradative pathways
  - NADPH is usually oxidized in the biosynthetic pathways
- NADH exists mainly in the ***oxidized*** form (NAD^+)
- NADPH exists mainly in the ***reduced*** form (NADPH)
- In the cytosol of a hepatocyte:
  - $NADP^+$/NADPH = 1/10
  - NAD^+/NADH = 1000/1
- NADPH is used in:
  - **Reductive biosynthesis,** such as:
    - ✓ Biosynthesis of *fatty acids* (liver, lactating mammary glands, adipose tissue)
    - ✓ Biosynthesis of *steroid hormones* (Testes, ovaries, placenta, adrenal cortex)

- **Protection against ROS** including hydrogen peroxide (H_2O_2), superoxide, hydroxy radical
  - ✓ ROS are formed continuously as by-products of aerobic metabolism and interaction with drugs and toxins and they can produce damage to cell components causing death
  - ✓ *Glutathione peroxidase:* which reduces H_2O_2 by the *reducing agent glutathione* (GSH)
    - When GSH is oxidized it becomes GSSG (2 glutathione linked by disulfide bond)
    - GSH is a tripeptide (GSH reduced, GSSG oxidized)
    - GSH peroxidase requires ***Selenium***
    - GSH is regenerated by ***GSH reductase*** (requires NADPH)



- Other enzymes that catalyze antioxidant reactions
  - *Superoxide dismutase* that converts superoxide ($O2^{\bullet -}$) into hydrogen peroxide
  - *Catalase* (heme containing) converts hydrogen peroxide into water and O_2
- Antioxidant chemicals: *Vitamin E*, *Vitamin C*, *Carotenoids* (vitamin A)
- Sources of ROS in the cell:
  - ***Oxidases:*** they mostly produce H_2O_2 (peroxidase)
    - ✓ Oxidases are confined to sites equipped with protective enzymes
  - ***Oxygenase***
    - ✓ *Monooxygenases (hydroxylases)* such as *Cytochrome P450 (CYP)*
      - CYP is a super family of structurally related enzymes of mixed function
      - They are found in the *mitochondria* (synthesis by hydroxylation of ***steroids***, ***bile acids***, active form of ***Vitamin D***) and *microsomes* (***detoxification*** of foreign compounds, activation or inactivation of ***drugs*** and solubilization to facilitate excretion in urine or feces)
      - It contains heme which contains *iron in the ferrous* state
      - Cytochrome P450 can accidentally release free radical intermediates
    - ✓ *Dioxygenases* in the synthesis of ***prostaglandins***, ***thromboxane***, ***leukotrienes***
  - ***Coenzyme Q in Respiratory chain***
    - ✓ It is the *major source* of free radicals by *accidental non-specific interaction*
    - ✓ The mitochondria is an O_2-rich environment, this O_2 may be converted into ($O_2\bullet^-$) by CoQ
    - ✓ O_2 is converted into water by complex IV in the respiratory chain (***binuclear center***) which prevents the release of free radicals
  - **Respiratory Burst (during phagocytosis)**
    - ✓ Large amounts of ROS and RNOS are required for the destruction of the microbe
    - ✓ O_2 is converted into *superoxide* ($O_2\bullet^-$) by NADPH oxidase
    - ✓ $O_2\bullet^-$ is converted spontaneously into *hydrogen peroxide* (H_2O_2)
    - ✓ Myeloperoxidase (Heme containing) converts H_2O_2 into hypochlorous acid (OCl^-) or hydroxyl free radical ($OH\bullet$)



- **Ionizing radiation** $OH\bullet$ by X-ray and UV light

- NO and Reactive Nitrogen Oxygen Species (RNOS)
- NO is a neurotransmitter that diffuse readily (gaseous), and it is essential for life but also toxic
  - It causes *muscle relaxation*, *prevent platelet aggregation*, neurotransmitter and *vasodilator*, mediate *tumoricidal and bactericidal* effect in macrophages
  - At high concentration NO can combine with O_2 or $O_2\bullet^-$ producing RNOS which are involved in neurodegenerative diseases and inflammatory diseases
- NO synthase converts ***arginine*** amino acid into citrulline with the production of NO
  - It involves the *oxidation of NADPH* into $NADP^+$
  - It uses many coenzymes including *FMN*, *FAD*, *heme*, *tetrahydrobiopterin*
- NO synthase has 3 isoforms:
  - nNOS: in the neural tissue
  - eNOS: in the endothelial tissue
    - ✓ NO in the endothelium causes vasodilation by activating ***guanylyl cyclase***, producing cGMP which activates PKG, which phosphorylates Ca^{+2} channels which decreases Ca^{+2} in the smooth muscles cause their relaxation and vasodilation which lowers the blood pressure
  - iNOS: inducible form of NOS which requires a stimulus to be transcribed, synthesized and activated
    - ✓ It is used in many immune cells, induced by *TNF alpha* and *interferons*
    - ✓ It is Ca^{+2} independent

Past Papers

1. About PPP, which is true?
   - A. First phase is oxidative & reversible while the second is non-oxidative & irreversible
   - B. PPP produces pentoses and NADH
   - C. Transketolases and transaldolases are used to transfer 2 & 3 carbons
   - D. There is production of ATP

2. Which one is a correct pair of amino acid precursor & its hormone?
   - A. Tyrosine – Melatonin.
   - B. NO – Arginine
   - C. Tryptophan – GABA

3. What enzyme catalyzes the synthesis of reactive nitrogen in phagocytes?

   A. eNOS
   B. nNOS
   C. iNOS
   D. P450

4. (Xylulose 5 Phosphate + Ribose 5 Phosphate → A + B). Considering this reaction, choose the TRUE answer:

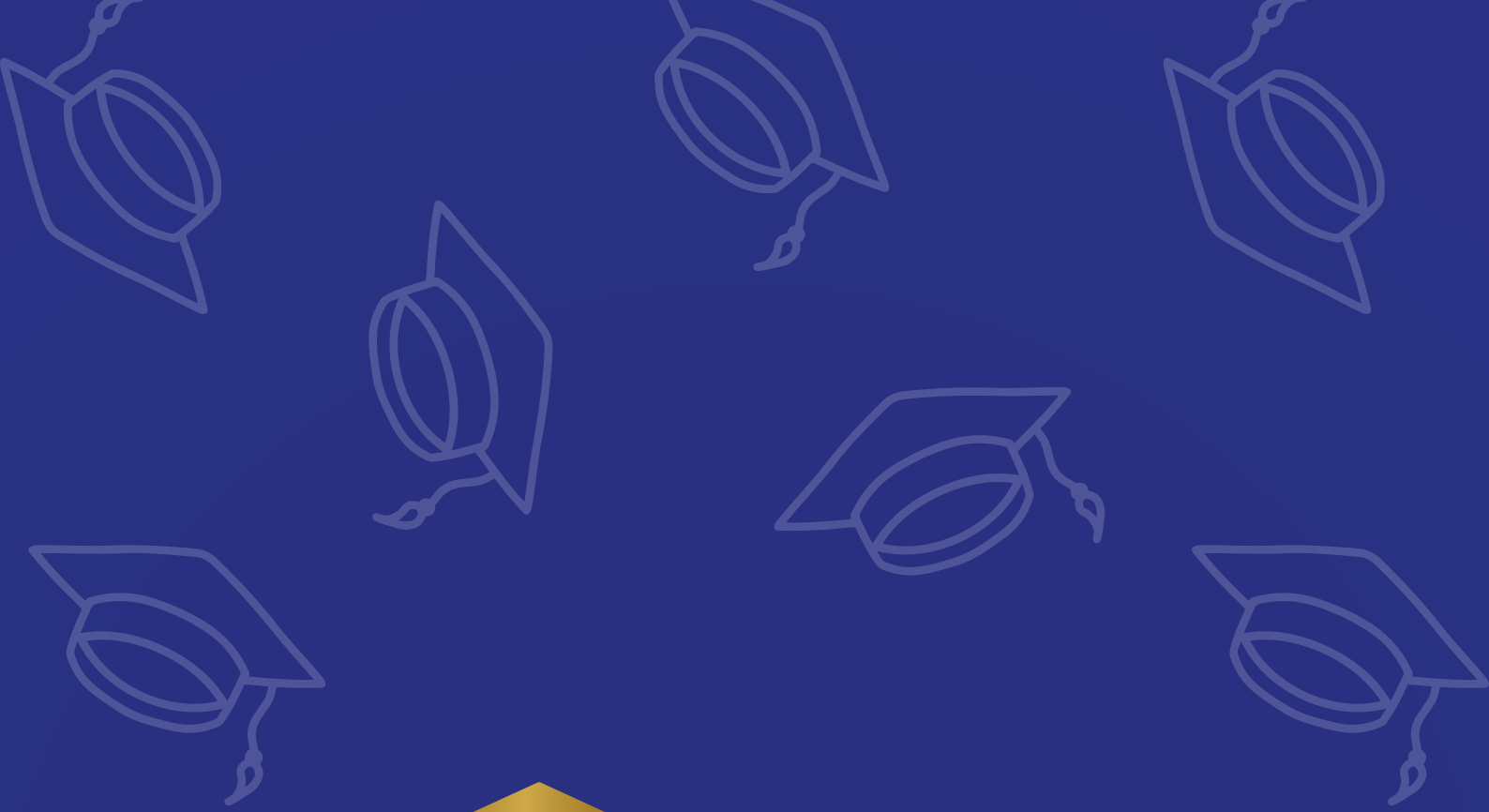
   A. The products are Erythrose 4-phosphate and fructose 6 phosphate.
   B. The products are aldose and ketose.
   C. It involves the transfer of one carbon group.
   D. It is catalyzed by transaldolase
   E. It is an irreversible reaction

5. (6-phosphogluonate + A → B + C), What are substance B and C in this reaction?

   A. NADPH + CO2
   B. FADH2 + CO2
   C. NADP+ + CO2
   D. NAD+ + H2O
   E. ADP + Pi

6. All of the following regarding the oxidized form of glutathione are correct EXCEPT:

   A. It is the substrate of glutathione peroxidase.
   B. One molecule of the oxidized form contains two sulfur atoms
   C. It is converted to the reduced form in an NADPH requiring reaction
   D. Its level in the RBC is increased in patients with G6PD deficiency.
   E. H_2O_2 leads to increase in oxidized/reduced ratio



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