G6PD

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Editing File

Objectives:

- Explain the biochemical basis of G6PD deficiency anemia
- Recognize the precipitating factors for G6PD deficiency anemia
- Classify various classes of G6PD deficiency anemia (variant enzymes)
- Describe the diagnostic methods for G6PD deficiency anemia

Overview:

- G6PD deficiency hemolytic anemia
- Biochemical basis of G6PD deficiency hemolytic anemia
- Different classes of G6PD deficiency hemolytic anemia
- Diagnosis of G6PD deficiency hemolytic anemia

Background

An alternative oxidative pathway for glucose

No ATP production

Hexose monophosphate pathway (HMP) or Pentose Phosphate Pathway (PPP)

Major pathway for NADPH production

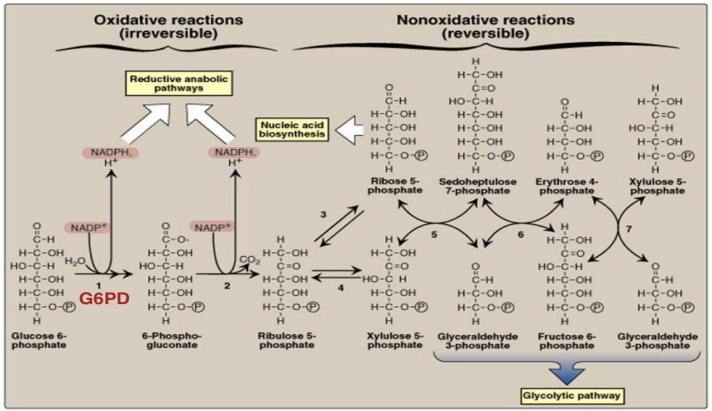
Produces ribose-5-phosphate for nucleotide synthesis

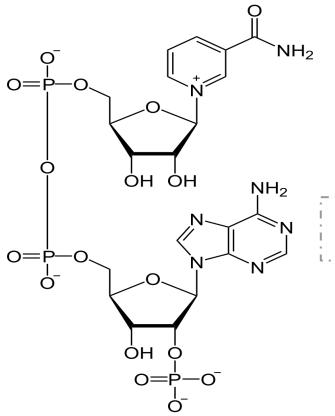
NADPH

Uses of NADPH

1. Reductive biosynthesis e.g , fatty acid biosynthesis
2. Antioxidant (part of glutathione system)
3. Oxygen-dependent phagocytosis by WBCs
4. Synthesis of nitric oxide (NO)

PPP
For illustration



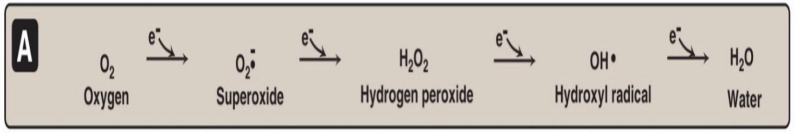


NADPH

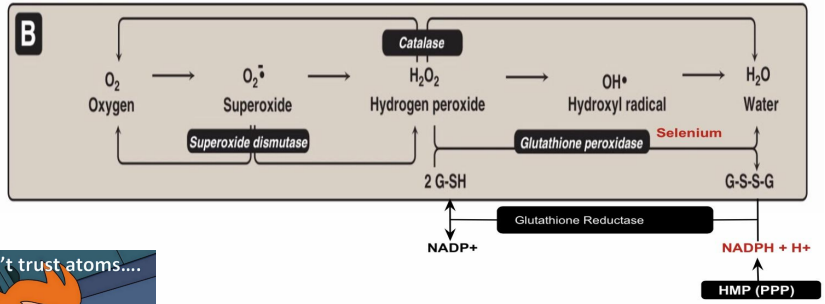
Background

Reactive Oxygen Species (ROS)

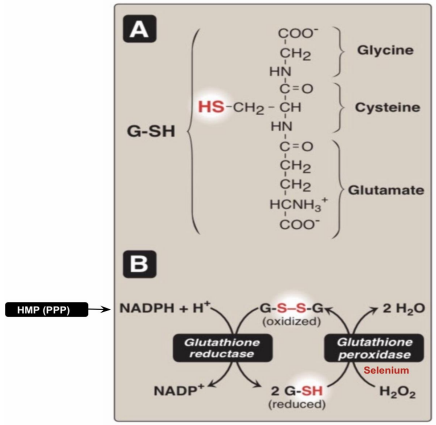
-Oxygen-derived Free radicals: e.g., Superoxide and hydroxyl
-radicals Non-free radical: Hydrogen peroxide



Antioxidant Mechanisms



Glutathione System



Oxidative Stress:
Imbalance between oxidant production and antioxidant mechanisms

Oxidative damage to

1- DNA
2- Proteins
3- Lipids (unsaturated fatty acids)

Oxidative stress and diseases

1- Inflammatory conditions e.g., Rheumatoid arthritis Atherosclerosis and coronary heart diseases
2- Obesity
3- Cancers
4- G6PD deficiency hemolytic anemia

G6PD Deficiency Hemolytic Anemia

Inherited X-linked recessive disease

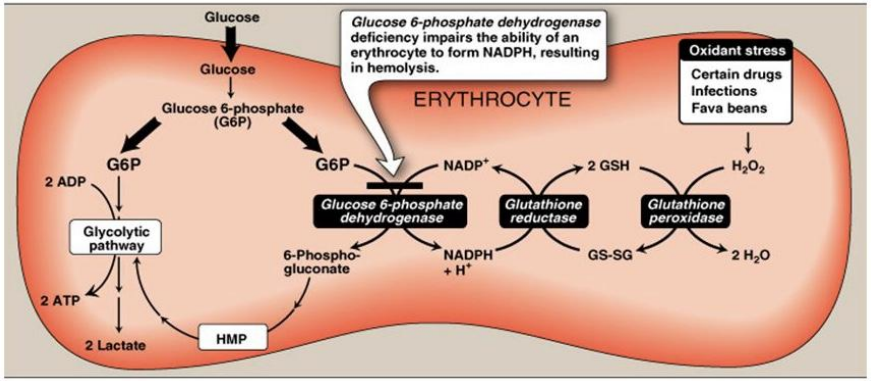
Most common enzyme-related hemolytic anemia

Highest prevalence: Middle East, Tropical Africa Asia and Mediterranean

~400 different mutations affect G6PD gene, but only some can cause clinical hemolytic anemia

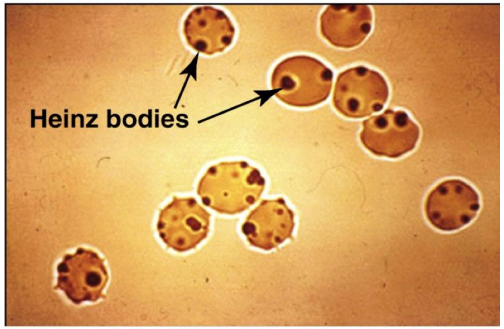
G6PD deficient patients have increased resistance to infestation by falciparum malaria

Biochemical Basis of G6PD Deficiency Hemolytic Anemia



-G6PD convert G6P to 6-phosphogluconate and make NADPH So if I don't have this enzyme "G6PD" I will not have NADPH and I will not have reduced glutathione thus I can not convert hydrogen peroxide"H2O2" to H2O

-Accumulation of H2O2 will cause oxidative stress that will damage the proteins and this include the cell membrane of the RBCs which is protein leading to hemolysis



Oxidation of sulfhydryl (SH) groups of proteins inside RBCs causes protein denaturation and formation of insoluble masses (Heinz bodies) that attach to RBCs membranes

Al though G6PD deficiency affects all cells, it is most severe in RBCs ..... Why?

Other cells have other sources for NADPH production: e.g., Malic enzyme that converts malate into pyruvate

Precipitating factors for G6PD deficiency hemolytic anemia

G6PD deficient patient will develop hemolytic attack upon:

1 Intake of oxidant drugs (AAA):
Antibiotics e.g : sulfa preparation
Antimalarial e.g : Primaquine
Antipyretics

2 Exposure to infection

3 Ingestion of fava beans (favism , mediterranean variant)

Chronic nonspherocytic anemia:
Hemolytic attack in absence of precipitating factors .
(severe form due to class I mutation)

Different classes of G6PD Deficiency Hemolytic Anemia

I (very severe)

II (Severe: mediterranean)

III (Moderate: G6PD A-)

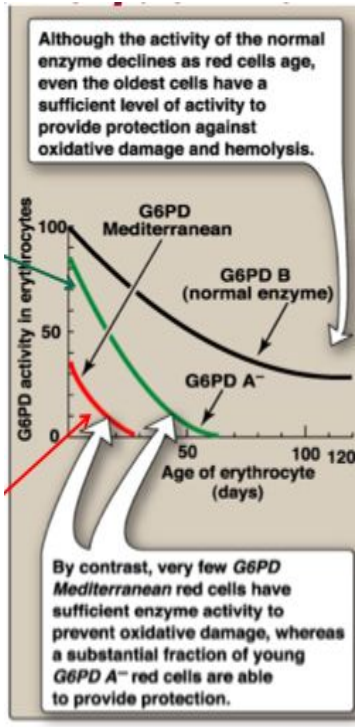
IV (Normal)

This classification is based on the residual enzyme activity
(Least in class I, and Highest in class IV)

Variant Enzymes of G6PD Deficiency Hemolytic Anemia

G6PD A-(class III)
Moderate, young RBCs contain enzymatic activity. Unstable enzyme, but kinetically normal

G6PD Mediterranean(II)
Enzyme with decreased stability Resulting in decreased activity (severe). Affect all RBCs (both young and old)



Diagnosis of G6PD deficiency hemolytic anemia

Diagnosis of hemolytic anemia

Complete Blood Count (CBC) & reticulocytic count

Screening

Qualitative assessment of G6PD enzymatic activity (UV-based test)

Confirmatory test:

Quantitative measurement of G6PD enzymatic activity

Molecular test:

Detection of G6PD gene mutation

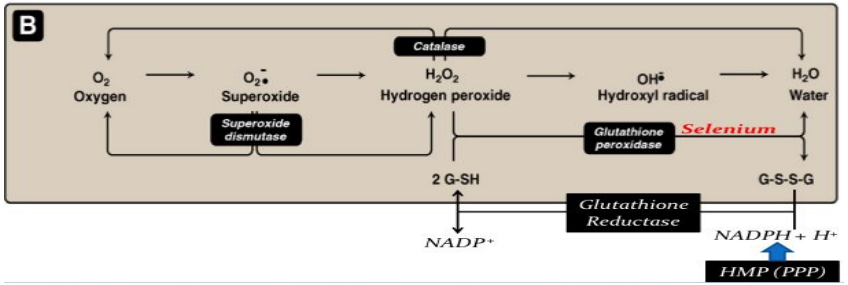
Take Home Messages

- G6PD deficiency impairs the ability of cells to form NADPH.
- RBCs are particularly affected because they do not have other sources of NADPH.
- NADPH is essential for the antioxidant activity of Glutathione peroxidase/reductase system
- G6PD deficiency is an X-linked disease characterized by hemolytic anemia.
- The precipitating factors of hemolysis includes administration of oxidant drugs, ingestion of fava beans or severe infections.
- G6PD deficiency is classified according to the residual activity of the G6PD
- Class I variant (the most severe) class is associated with chronic nonspherocytic hemolytic anemia.

Summary

Hexose monophosphate pathway (HMP) or Pentose Phosphate Pathway (PPP)

Major pathway for NADPH production
Uses of NADPH:
1)Reductive biosynthesis e.g., fatty acid biosynthesis
2)Oxygen-dependent phagocytosis by WBCs
3)Antioxidant (part of glutathione system)
4)Synthesis of nitric oxide (NO)



G6PD converts G6P to 6-phosphogluconate and makes NADPH

When G6PD is deficient their will be no production of NADPH

So I will have no reduced glutathione

Thus I cannot convert H_2O_2 to H_2O

Accumulation of H_2O_2 causes oxidative stress and damage to proteins

Screening

Molecular test

Diagnosis of G6PD deficiency hemolytic anemia

Complete blood count

Confirmatory test

Quiz

MCQs:

Q1: which one is not one of the uses of NADPH

a) part of glutathione system
b) synthesis of NO
c) Biosynthesis of fatty acid
d) non-oxygen dependent phagocytosis

Q2: while glutathione reductase converts GSSG to 2GSH —— will also be converted to ——.

a) NADP+,NADPH+H+
b) NADPH+H+,NADP+
c) NADPH+,H+
d) NADPH+H+,NADPH+

Q3: which one of the following is true about G6PD deficiency hemolytic anemia?

a) Inherited x link dominant disease
b) Almost all mutations of the gene for G6PD cause hemolytic anemia
c) Increase resistant infestation to falciparum malaria

Q4: The moderate state of G6PD deficiency is classified as class:

a) 2 **b)** 3 **c)** 1 **d)** 4

Q5: For the diagnosis of G6PD deficiency,the confirmatory test is by

a) Qualitative assessment of G6PD enzymatic activity
b) CBC
c) Detection of G6PD gene mutation
d) Quantitative measurement of G6PD enzymatic activity

SAQs :

Q1: List 3 uses of NADPH

Q2: Give 2 examples of ROS free radicals and non free radicals

Q3: Which class of G6PD deficiency effects all RBC

Q4: Oxidation of SH groups of proteins inside RBC causes denaturation and formation of insoluble masses known as:

★ **MCQs Answer key:**

1) D 2)B 3) C 4) B 5) D

★ **SAQs Answer key:**

1) Antioxidants,reductive biosynthesis,synthesis of NO
2) Free radical:superoxide ,hydroxyl. Non free radicals hydrogen peroxide
3) Second class
4) Hienz bodies

Team members

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اللهم لا سهلا الا ماجعلته سهلا
وأنت تجعل الحزن اذا شئت سهلا

438 BIOCHEMISTRY TEAM

We hear you