Alternative pathways of CHO metabolism

Pentose Phosphate Pathway (PPP): (Hexose monophosphate shunt; HMS or HMP)

**Function:** provides a source of NADPH for reductive biosynthesis and ribose 5-phosphate for nucleic acid synthesis, and provides a route for the use of pentose and their conversion to fructose 6-phosphate (Frc 6-P) and Glyceraldehyde-3-phosphate (Glycer. 3-P).

**Location:**

a) In tissues, the pathway is most active in the liver, mammary glands, adipose tissue and adrenal cortex.

b) Within the cell, the enzymes of this pathway are located in the cytoplasm.

**Reactions:**

1) \[ \text{Glc-6-P} \xrightarrow{\text{Glc-6-P dehydrogenase (G6PD)}} \text{6-phosphogluconolactone} \]

RBCs need NADPH production to keep glutathione in the reduced state

\( \text{glutathione} \rightarrow \text{(tripeptide: Gly-Cys-Glu)} \) (Glycine-Cysteine-Glutamate)

Reduced Glutathione is needed to maintain the integrity of the RBCs (Erythrocytes) membrane.

Glc 6PD or G6PD deficiency \( \rightarrow \) RBCs hemolysis and hemolytic anemia.
(Due to genetic deficiency)

\( \text{In people with low G6PD, certain drugs, like Aspirin, and the antimalarial primaquine that act as oxidizing substances of reduced glutathione (to form} \)
oxidized glutathione), can cause hemolytic Anemia.

Favabean cans can cause Favism, hemolytic effects of ingesting this type of beans in some people with G6PD deficiency in the Mediterranean region.

2) 6-phosphogluconolactone $\xrightarrow{\text{Hydrolase}}$ 6-phosphogluconate

$\star$ Hemolytic anemia may lead to a type of Jaundice known as Hemolytic Jaundice.

3) $\xrightarrow{\text{dehydrogenase}}$ Ribulose-5-Phosphate (Ribulose-5-P)

4) Ribulose-5-P $\xrightarrow{\text{isomerase}}$ Ribose-5-P $\xrightarrow{\text{nucleic acid synth.}}$

epimerase $\xrightarrow{\text{Xylulose-5-P}}$

5) Ribose-5-P + Xylulose-5-P $\xrightarrow{\text{Sedoheptulose-7-P (7-C) + Glycer. 3-P (3-C)}}$

$^{*}$ the enzyme is transketolase, coenzyme is Thiamine Pyrophosphate (TPP)

Chronic thiamine deficiency $\xrightarrow{\text{defective Transketolase and leads to Wernicke-Korsakoff syndrome.}}$

Symptoms are:
- Weakness or paralysis
- Impaired mental function

6) Sedo. 7-P + Glycer. 3-P $\xrightarrow{\text{transaldolase}}$ Erythrose 4-P (4-C) + Fructose 6-P (6-C)

7) xylulose-5-P + Erythrose-4-P $\xrightarrow{\text{transketolase}}$ Fructose 6-P + Glycer. 3-P
Summary of reactions:
\[
3\text{Glc-6-P} + 6\text{NADP}^+ \rightarrow 2\text{Frc-6-P} + 3\text{CO}_2 + 6\text{NADPH} + 6\text{H}^+
\]

Regulation of the pathway:
1) NADP\(^+\) concentration is the major factor in regulating Glc-6-P reactions (G6PD) reactions.
2) NADPH is a competitive inhibitor.
3) Key enzyme is G6PD.
4) G6PD is activated in starvation and DM and inhibited by carbohydrate feeding. \(\star\) induced by insulin.
5) Activated in the presence of TTP.

Notes:
1) The first three reactions are Oxidative + irreversible
2) The rest are non-oxidative + reversible.
3) Glyceraldehyde-3-P and Frc-6-P are intermediates of Glycolysis.
4) The pathway needs one ATP and provides no ATP unlike glycolysis and CAC.
5) The pathway provides Ribose.
6) It’s a route for conversion of hexose into pentose and pentose interconversion
7) Provides NADPH, which is used for synthesis of FAs, Steroids, glutathione...etc.
Uronic acid pathway (Glucuronic acid cycle)

1- The Glc-6-P is converted into Glc-1-P that takes high energy UTP and becomes UDP-Glc by the enzyme UDP-Glc dehydrogenase (NAD⁺ is required).

2- UDP glucuronic acid is produced and conjugated with Glucosamine and Galactosamine to form mucopolysaccharides. Utilized in detoxification by conjugation with Benzene (phenol), Bilirubin and other steroids.

3- UDP-glucuronic acid loses UMP and becomes D-glucuronic acid 1-P less, then loses Pi (phosphate) to become D-glucuronic acid, which may also come from diet (like meat) and this convert to L-glucuronic acid by reductase.

4- L-glucuronic acid is either converted into:
   a- L-gulonolactone which is converted into 2 keto L-gulonolactone that results in ascorbic acid (vit. C)
      ✿ this step is absent in human, primates (Monkeys) and guinea pigs, because of enzyme absence, So no vit. C is formed. But in other animals the enzyme’s present and thus vit. C can be synthesized.
   b- L-Xylulose is formed by decarboxylation and then reduced by NADPH to L-xylitol (alcohol) which loses H⁺ to NAD to become NADH and D-Xylulose results by a reductase enzyme, so if this enzyme is deficient then L-Xylulose accumulates in the blood, causing “Essential Pentoseuria”.
      D-Xylulose converts to Xylulose 5-P by kinase and by HMP shunt Ribose-5-P is produced then Frc-6-P and Glyceraldehyde-3-P are formed and so pyruvic acid that’s oxidized to CO₂, H₂O and energy is produced.