CARBOHYDRATE METABOLISM

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Digestion of carbohydrate

The principle sites of carbohydrate digestion are the mouth and small intestine. The dietary carbohydrate consist of:

- **polysaccharides**: Starch, glycogen and cellulose
- **Disaccharides**: Sucrose and Lactose
- **Monosaccharides**: Mainly glucose and fructose

Monosaccharides need no digestion prior to absorption, whereas disaccharides and polysaccharides must be hydrolysed to simple sugars before their absorption.
**DIGESTION OF CARBOHYDRATE**

- **Salivary amylase** partially digests starch and glycogen to dextrin and few maltoses. It acts on cooked starch.
- **Pancreatic amylase** completely digests starch, glycogen, and dextrin with help of 1:6 splitting enzyme into maltose and few glucose. It acts on cooked and uncooked starch. Amylase enzyme is hydrolytic enzyme responsible for splitting α 1:4 glycosidic link.
- Cellulose is not digested due to absence of β-glucosidase
- **Maltase, lactase and sucrase** are enzymes secreted from intestinal mucosa, which hydrolyses the corresponding disaccharides to produce glucose, fructose, and galactose.
- **HCl** secreted from the stomach can hydrolyse the disaccharides and polysaccharides.
**ABSORPTION OF MONOSACCHARIDES**

- **Simple absorption (passive diffusion):** The absorption depends upon the concentration gradient of sugar between intestinal lumen and intestinal mucosa. This is true for all monosaccharides especially fructose & pentoses.

- **Facilitative diffusion by Na\(^+\)-independent glucose transporter system (GLUT\(_5\)).** There are mobile carrier proteins responsible for transport of fructose, glucose, and galactose with their conc. gradient.

- **Active transport by sodium-dependent glucose transporter system (SGLUT\(_1\)).** In the intestinal cell membrane there is a mobile carrier protein coupled with Na\(^+\)- K\(^+\) pump. The carrier protein has 2 separate sites one for Na\(^+\), the other for glucose. It transports Na\(^+\) ions (with conc. Gradient) and glucose (against its conc. Gradient) to the cytoplasm of the cell. Na\(^+\) ions is expelled outside the cell by Na\(^+\)- K\(^+\) pump which needs ATP and expel 3 Na\(^+\) against 2 K\(^+\).

  Exit all sugars from mucosal cell to the blood occur by facilitative transport through GLUT\(_2\).
It is proved that glucose and galactose are absorbed very fast; fructose and mannose intermediate rate and pentoses are absorbed slowly. Galactose is absorbed more rapidly than glucose.

**There are 2 pathways for transport of material absorbed by intestine:**

- The hepatic portal system, which leads directly to the liver and transporting water-soluble nutrients.
- Lymphatic vessels: which lead to the blood by way of thoracic duct and transport lipid soluble nutrients.
Transport of glucose, fructose, galactose, and mannose.
GLUCOSE UPTAKE BY TISSUES

Glucose is transported through cell membrane of different tissues by different protein carriers or transporters. Extracellular glucose binds to the transporter, which then alters its conformations, then transport glucose across the membrane.

- **GLUT₁**: present mainly in red cells, and retina.
- **GLUT₂**: present in liver, kidneys, pancreatic B cells, and lateral border of small intestine, for rapid uptake and release of glucose.
- **GLUT₃**: present mainly in brain.
- **GLUT₄**: present in heart, skeletal muscles, and adipose tissues. It is for insulin-stimulated uptake of glucose.
- **GLUT₅**: present in small intestine and testes for glucose and fructose transport.
- **SGLUT₁**: present in small intestine and kidneys, sodium-dependent, for active transport of glucose and galactose from lumen of small intestine and reabsorption of glucose from glomerular filtrate in proximal renal tubules.
Role of insulin in transport of glucose in adipose tissue, skeletal muscles and heart through GLUT4:

1. Insulin produces transfer of GLUT-4 from their intracellular pool to the outer membrane surface of these tissues. So, increase GLUT-4 in the cell surface of these tissues leads to increase glucose transport and uptake by these tissues.

2. Transport through the previous tissues is insulin-independent.
Insulin hormone
Intracellular signal for insulin

Intracellular location of GLUT-4
The absorbed monosaccharides are either hexoses or pentoses.

1. The absorbed pentoses are excreted in urine because the body does not deal with them.
2. The absorbed hexoses are glucose, fructose, or galactose. Fructose and galactose are converted into glucose in the liver.
Blood glucose comes from 3 main sources:
1- Absorbed glucose from diet.
2- Glcogenolysis of liver glycogen.
3- Synthesis of glucose from other substances by gluconeogenesis

The absorbed glucose has the following pathways:

1- Oxidation:
a- For provision of energy: glycolysis, and Kreb’s cycle.
b- Not for energy production:
   - HMP for synthesis of phospho-pentoses & NADPH + + H⁺.
   - Uronic acid pathway for synthesis of glucuronic acid.
2- Synthesis of other CHO substances as:

A- Mannose, fucose, neuraminic acid for glycoprotein formation.
B- Galactose and lactose in mammary gland.
C- Fructose in seminal vesicles.
E- Amino-sugar (glucosamine) for mucopolysaccharides, and glycoprotein formation.

3- Synthesis of non essential amino acids.

4- Excess glucose is stored as glycogen in liver and muscles (glycogenesis).

5- More excess glucose is stored as lipid in adipose tissue (lipogenesis).
**IMPORTANT ENZYMES IN CHO METABOLISM**

1. **Kinase**
   These are activating enzymes, which convert various metabolites into phosphorylated form in presence of ATP, Mg++. They are irreversible enzymes with few exception.
   1. Hexokinase (present in all tissues except liver) acts on any hexoses (glucose, fructose, galactose) giving 6-phosphorlyated hexose (glucose 6-P, fructose 6-P, galactose 6-P).
   2. Glucokinase (present only in liver) acts only on glucose converting it into glucose 6-P.
   3. Fructokinase (present only in liver) acts on fructose to form fructose 1-P.
   4. Galactokinase (present only in liver) acts only on galactose to give galactose 1-P.

2. **Dehydrogenases**
   These are oxidizing enzymes that act by removal of H₂ from a substrate → the removed H₂ will be carried by special coenzymes, which are hydrogen carriers as NAD, FAD.
   The name of the dehydrogenase is derived from the name of substrate upon, which it acts as: Lactate dehydrogenase enzyme removes H₂ from lactic acids.
   The dehydrogenases are reversible enzymes.
3- Isomerases
1. These are enzymes that interconvert aldo-keto isomers. They are reversible enzymes.

\[
\text{Fructose 6-P} \xrightarrow{\text{isomerase}} \text{Glucose 6-P}
\]

4- Mutases
These are enzymes that transfer a group from carbon to another carbon in the same molecule. They are reversible enzymes.

e.g.

\[
\text{Glucose 6-P} \xrightarrow{\text{Mutase}} \text{Glucose 1-P}
\]

5- Epimerases
These are enzymes that transfer a group from a side to the opposite side of one carbon atom in the molecule. They are reversible enzymes.

e.g.

\[
\text{UDP-glactose} \xrightarrow{\text{Epimerase}} \text{UDP-glucose}
\]
6- Phosphatases

These are hydrolytic enzymes that remove a phosphate group from a phosphorylated compound by addition of $H_2O$. They are irreversible enzymes.

\[
\text{Glucose 6-P} \xrightleftharpoons[H_2O]{} \text{Glucose} + \text{Phosphate}
\]
Glycogen is the main storage form of carbohydrates in animals. It is present mainly in liver and in muscles. Glycogen is highly branched polymer of α, D-glucose. The glucose residues are united by α 1: 4 glucosidic linkages within the branches. At the branching point, the linkages are α 1: 6. The branches contain about 8-12 glucose residues.

Glycogen metabolism includes *glycogen synthesis (glycogenesis)* and *glycogen breakdown (glycogenolysis).*
**Def:** it is the formation of glycogen from glucose in muscles and from CHO and non CHO substances in liver.

**Site of location:** In the cytoplasm of every cells mainly liver and muscles.

**Steps:** as the following :-
- **Glycogen synthase enzyme** in presence of pre-existing glycogen primer or glycated glycogenin (glycogenin is a small protein that forms glycogen primer after glycosylation by UDP-glucose) adds glucose molecule from UDP-glucose through creation of α 1: 4 glucosidic link.

- When the chain has been lengthened to a minimum of 11 residues a second enzyme, **the branching enzyme** transfers a part of the 1,4 chain (minimum length of 6 glucose) to neighboring chain form α 1-6 linkage thus establishing a branching point in the molecule. The branches grow by further additions of 1,4 glycosyl unit.

The key regulatory enzyme of glycogenesis is **glycogen synthase**, which present in 2 forms:

1. Active form, which is *dephosphorylated* enzyme (GSa).
2. Inactive form, which is *phosphorylated* enzyme (GSb).
**Def.:** It is the breakdown of glycogen into glucose in liver and lactic acid in muscles.

**Site of location:** cytoplasm of many tissues mainly liver, kidney, and muscles.

**Steps:**
- **Phosphorylase is the first acting enzyme** which is the rate-limiting and key enzyme in glycogenolysis. With proper activation and in presence of inorganic phosphate (Pi), the enzyme breaks the glucosyl α-1:4 linkage and removes by phosphorolytic cleavage the 1:4 glucosyl residues from outermost chains of the glycogen molecule until approximately four (4) glucose residues remain on either side of α-1:6 branch (“limit dextrin”).
By phosphorlyase activity glucose is liberated as glucose-1-P and NOT as free glucose.

• When four glucose residues are left around the branch point, another enzyme, α-1:4 Glucan transferase transfers a “trisaccharide” unit from one side to other thus exposing α-1:6 branching point.
• The hydrolytic splitting of α-1:6 glucosidic linkage requires the action of a specific debranching enzyme. As α-1:6 linkage is hydrolytically split, one molecule of free glucose is produced.
• Fate of glucose-1-P: The combined action of phosphorlyase and other enzymes convert glycogen mostly to glucose-1-P. By the action of phosphoglucomutase enzyme glucose-1-P is easily converted to glucose-6-P as the reaction is reversible.
In liver and kidney, a specific enzyme glucose-6-phosphatase is present that removes PO₄ from glucose-6-P enabling “free glucose” to form and diffuse from the cells to extracellular spaces including blood. This is the final step in hepatic glycogenolysis, which is reflected by a rise in blood glucose.

In muscles, enzyme glucose-6-phosphatase is absent. Hence glucose-6-P enters into glycolytic cycle and forms lactate. Muscle glycogenolysis does not contribute to blood glucose directly. But indirectly, lactic acid can go to glucose formation in liver.

The key regulatory enzyme of glycogenolysis is glycogen phosphorylase enzyme which is present in 2 forms:

1. Active form (phosphorylated form) = phosphorylase a.
2. Inactive form (dephosphorylated form) = phosphorylase b.
Schematic representation of glycogenolysis (mechanism of debranching)
1-Phosphorylase enzyme is a phosphorolysis enzyme which is responsible for breaking $\alpha 1:4$ glucosidic link of glycogen in the presence of inorganic phosphorus giving G-1-P.

2-Debranching enzyme is a hydrolytic enzyme which acts on $\alpha 1:6$ glucosidic link, giving free glucose.

*NB:* The main function of muscles glycogen is to supply glucose within muscles during contraction. Liver glycogen is concerned with the maintenance of blood glucose especially between meals. After 12-18 hours of fasting, liver glycogen is depleted, whereas muscle glycogen is only depleted after prolonged exercise.
CA\textsuperscript{2+} SYNCHRONIZES THE ACTIVATION OF PHOSPHORYLASE WITH MUSCLE CONTRACTION

Glycogenolysis in muscle increases several 100-folds at the onset of contraction; the same signal (increased cytosolic Ca\textsuperscript{2+} ion concentration) is responsible for initiation of both contraction and glycogenolysis. *Muscle phosphorylase kinase*, which activates glycogen phosphorylase, is a *tetramer of four different subunits, α, β, γ, and δ*. The δ subunit is identical to the Ca\textsuperscript{2+} - binding protein *calmodulin* and binds 4 Ca\textsuperscript{2+}. The binding of Ca\textsuperscript{2+} activates the catalytic site of the δ subunit allowing activation of glycogen phosphorylase and stimulation of glycogenolysis.
REGULATION OF GLYCOGEN METABOLISM

1. Regulation of glycogen metabolism is achieved by a balance in activities between *glycogen synthase* and *glycogen phosphorylase* which are regulated reciprocally.

2. Not only "phosphorylase" enzyme is activated by a rise in concentration of phosphorylase kinase via $\uparrow$ c-AMP, but "Glycogen synthase" enzyme is at the sametime converted to "inactive" form, both effects are mediated via "cyclic -AMP-dependant protein-kinase".

3. Thus glycogenolysis is stimulated while glycogenesis is inhibited. **Both processes cannot occur simultaneously together.**

4. Dephosphorylation of "phosphorylase 'a', phosphorylase kinase 'a' and glycogen synthase 'b' is accomplished by a single enzyme of wide specificity "protein phsophatase-1", which in turn is inhibited by c-AMP dependant protein kinase via the protein "Inhibitor-1". Thus, **glycogenolysis can be inhibited and glycogenesis can be stimulated synchronously**, or vice versa, because **both processes are geared to the activity of c-AMP dependant protein-kinase.**
HORMONAL CONTROL OF GLYCOGEN METABOLISM

• **Epinephrine stimulates α1 adrenergic receptors in liver** → activation of phospholipase-C which hydrolyses phosphatidyl inositol–P2 into 1,2 diacylglycerol and inositol triphosphate → release Ca++ from its intracellular stores into the cytoplasm raising the intracytoplasmic concentration of Ca++ which reacts with calmodulin to give Ca++ - calmodulin complex → activation of Ca++ calmodulin dependent protein kinase → conversion of glycogen synthase a (active) into glycogen synthase b (inactive) and conversion of phosphorylase kinase b into phosphorylase kinase a which converts phosphorylase b (inactive) into phosphorylase a (active) → stimulation of glycogenolysis and inhibition of glycogenesis → so stimulation of glycogenolysis in liver can be cAMP independent.

• **Epinephrine** stimulate β adrenergic receptors in liver and in muscles & glucagon stimulate its receptors in liver but not in muscles → stimulation of adenylate cyclase enzyme → stimulation of cyclic AMP formation → stimulation of protein kinase A → conversion of glycogen synthase a (active) into glycogen synthase b (inactive) and conversion of phosphorylase kinase b into phosphorylase kinase a which converts phosphorylase b (inactive) into phosphorylase a (active) → stimulation of glycogenolysis and inhibition of glycogenesis.
• Insulin stimulates phosphatase enzyme so converts inactive glycogen synthase into active one and converts active phosphorylase enzyme into inactive one → stimulation of glycogenesis and inhibition of glycogenolysis. Also it stimulates phosphodiesterase enzyme → destruction of cyclic AMP.
Reaction cascades for the control of glycogen synthesis
Regulation of glyconenolysis
Allosteric Regulation of glycogen metabolism

Effect of substrate:
• In well-fed state glycogen synthase is allosterically activated by glucose-6-phosphate when present in elevated level.
• In contrast, glycogen phosphorylase is allosterically inhibited by glucose-6-phosphate and ATP.

Effect Ca^{++} ions
Phosphorylase kinase can be allosterically activated by Ca^{++2} independent of C-AMP. This mechanism is of particular importance in muscle contraction.

Effect of AMP
Muscle glycogen phosphorylase-b is active in presence of high AMP concentration which occurs in muscle under extreme condition of anoxia and ATP depletion.
### Differences between muscle and liver glycogen

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<thead>
<tr>
<th></th>
<th>Liver glycogen</th>
<th>Muscle glycogen</th>
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<tbody>
<tr>
<td><strong>Amount</strong></td>
<td>Liver has more conc.</td>
<td>Muscle has more amounts.</td>
</tr>
<tr>
<td><strong>Sources</strong></td>
<td>Blood glucose and other radicals</td>
<td>Blood glucose only</td>
</tr>
<tr>
<td><strong>Hydrolysis</strong></td>
<td>Give blood glucose</td>
<td>Due to absence of phosphatase enzyme not give free glucose but give lactic acid</td>
</tr>
<tr>
<td><strong>Starvation</strong></td>
<td>Changes to blood glucose</td>
<td>Not affected</td>
</tr>
<tr>
<td><strong>Muscular ex.</strong></td>
<td>Depleted</td>
<td>Depleted</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td>Insulin → ↑</td>
<td>Insulin → ↑</td>
</tr>
<tr>
<td></td>
<td>Adrenaline → ↓</td>
<td>Adrenaline → ↓</td>
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<tr>
<td></td>
<td>Thyroxin → ↓</td>
<td>Thyroxin → ↓</td>
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<tr>
<td></td>
<td>Glucagon → ↓</td>
<td>Glucagon → no effect due to absence of its receptors</td>
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GLYCOGEN STORAGE DISEASES

A group of diseases results from genetic defects of certain enzymes. The absence of glucose-6-phosphatase enzyme results in the classical hepatorenal glycogen storage disease Von Gierke (type I), this is characterized by:

1- It occurs in only 1 person per 200,000 and is transmitted as an autosomal recessive trait.
2- Symptoms include:
   Fasting hypoglycemia, because the liver cannot release enough glucose by means of glycogenolysis; only the free glucose from debranching enzyme activity is available.
3- Lactic academia, because the liver cannot form glucose from lactate. The increased blood lactate reduces blood pH and the alkali reserve.
4- Hyperlipidemia, because the lack of hepatic gluconeogenesis (results in increased mobilization of fat as a metabolic fuel).
5- Hyperuricemia (with gouty arthritis), due to hyperactivity of the hexose monophosphate shunt.
Other types of glycogenoses

A number of other genetic glycogen storage defects (glycogenoses) have been described. **Pompe’s** (lysosomal glucosidase deficiency), **Forb’s** (Debranching enzyme deficiency), **Andersen’s** (Branching enzyme system deficiency), **Macardle’s** (Muscle phosphorylase deficiency), **Here’s** (Liver phosphorylase deficiency) and **Taui’s** (Phosphofuctokinase deficiency).