Metabolism of Fructose and Galactose

Glucose is the most common monosaccharide consumed by humans. However, two other monosaccharides—fructose and galactose—occur in significant amounts in the diet (mostly in disaccharides), and make key contributions to energy metabolism. In addition, galactose is an important component of cell structural carbohydrates.

I. Fructose Metabolism

- The major source of fructose is the disaccharide sucrose, which, when cleaved in the intestine, releases equimolar amounts of fructose and glucose.
- Fructose is also found as a free monosaccharide in many fruits and in honey.
- Entry of fructose into cells is insulin independent (unlike that of glucose into certain tissues), and in contrast to glucose, fructose does not promote the secretion of insulin.

Phosphorylation of fructose

- For fructose to enter the pathways of intermediary metabolism, it must first be phosphorylated. This can be accomplished by either hexokinase or fructokinase.
- Hexokinase phosphorylates glucose in most cells of the body, and several other hexoses can be phosphorylated by this enzyme. However, it has a low affinity (i.e. high Km) for fructose. Therefore, unless the intracellular concentration of fructose becomes unusually high, the normal presence of saturating concentrations of glucose means that little fructose is converted to fructose 6-P by hexokinase.
- Fructokinase provides the primary mechanism for fructose phosphorylation. It is found in the liver (which processes most of the dietary fructose), kidney, and the small intestinal mucosa, and converts fructose to fructose 1-phosphate, using ATP as the phosphate donor. These three tissues also contain aldolase B.
Metabolism of fructose

Aldolase A is found in all tissues, whereas aldolase B is the predominant form in liver. (*, not found in liver
Cleavage of fructose 1-phosphate

- Fructose 1-phosphate is not phosphorylated to fructose 1,6-bisphosphate as is fructose 6-phosphate, but is cleaved by aldolase B to dihydroxy acetone phosphate (DHAP) and glyceraldehyde.
- DHAP can directly enter glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by a number of pathways.
- Humans express three aldolases, A, B and C, the products of three different genes. Aldolase A (found in most tissues), aldolase B (in liver), and aldolase C (in brain) all cleave fructose 1,6-bisphosphate produced during glycolysis to DHAP and glyceraldehyde 3-phosphate, but only aldolase B cleaves fructose 1-phosphate.
- The rate of fructose metabolism is faster than that of glucose because the trioses formed from fructose 1-phosphate bypass phosphofructokinase-1—the major rate-limiting step in glycolysis. Thus, high dietary fructose intake significantly elevate the rate of lipogenesis in the liver due to the rapid production of acetyl CoA.
Conversion of glucose to fructose via sorbitol

- Most sugars are rapidly phosphorylated following their entry into cells. They are thereby trapped within the cells, because organic phosphates cannot freely cross membranes without specific transporters.
- An alternate mechanism for metabolizing a monosaccharide is to convert it to a polyol (sugar alcohol) by the reduction of an aldehyde group, thereby producing an additional hydroxyl group.

1. Synthesis of sorbitol:
   - Aldose reductase reduces glucose, producing sorbitol (glucitol). This enzyme is found in many tissues, including the lens, retina, Schwann cells of peripheral nerves, liver, kidney, placenta, red blood cells, and in cells of the ovaries and seminal vesicles.
   - In cells of the liver, ovaries, and seminal vesicles, there is a second enzyme, sorbitol dehydrogenase, which can oxidize the sorbitol to produce fructose.
   - The two-reaction pathway from glucose to fructose in the seminal vesicles is for the benefit of sperm cells, which use fructose as a major carbohydrate energy source.
   - The pathway from sorbitol to fructose in the liver provides a mechanism by which any available sorbitol is converted into a substrate that can enter glycolysis or gluconeogenesis.

2. The effect of hyperglycemia on sorbitol metabolism
   - Because insulin is not required for the entry of glucose into the cells listed in the previous paragraph, large amounts of glucose may enter these cells during times of hyperglycemia, for example, in uncontrolled diabetes.
   - Elevated intracellular glucose concentrations and an adequate supply of NADPH cause aldose reductase to produce a significant increase in the amount of sorbitol, which cannot pass efficiently through cell membranes and, therefore, remains trapped inside the cell.
   - This is exacerbated when sorbitol dehydrogenase is low or absent, for example, in retina, lens, kidney, and...
nerve cells. As a result, sorbitol accumulates in these cells, causing strong osmotic effects and, therefore, cell swelling as a result of water retention.

- Some of the pathologic alterations associated with diabetes can be attributed, in part, to this phenomenon, including cataract formation, peripheral neuropathy, and microvascular problems leading to nephropathy and retinopathy.

II. Galactose Metabolism

The major dietary source of galactose is lactose (galactosyl β-1,4-glucose) obtained from milk and milk products. Lactose is digested by β-galactosidase (lactase) from the intestinal mucosal cell. Some galactose can also be obtained by lysosomal degradation of complex carbohydrates, such as glycoproteins and glycolipids, which are important membrane components. Like fructose, the entry of galactose into cells is not insulin-dependent.

**Phosphorylation of galactose**

Like fructose, galactose must be phosphorylated before it can be further metabolized. Most tissues have a specific enzyme for this purpose, galactokinase, which produces galactose 1-phosphate; using ATP as the phosphate donor.

**Formation of UDP-galactose**

- **Galactose 1-phosphate** cannot enter the glycolytic pathway unless it is first converted to UDP-galactose.

- This occurs via an exchange reaction catalyzed by galactose 1-phosphate uridylyltransferase (GALT).

- In this reaction, UDP-glucose reacts with galactose 1-phosphate, producing UDP-galactose and glucose 1-P.

- GALT is deficient in individuals with classical galactosemia. In this disorder, galactose 1-P and, therefore, galactose accumulate in cells.

- The accumulated galactose is shunted into side pathways such as galactitol production. This reaction is catalyzed by aldose reductase, the same enzyme that converts glucose to sorbitol.

- Galactitol accumulates in the eye, liver and nerve tissue leading to cataract, severe mental retardation and liver damage.

- Deficiency of galactokinase leads to non-classical galactosemia that is less severe disorder of galactosemia metabolism, although cataracts are common.
UDP-galactose as a carbon source for glycolysis or gluconeogenesis

- For UDP-galactose to enter the mainstream of glucose metabolism, it must first be converted to its C-4 epimer, UDP-glucose, by UDP hexose 4-epimerase.
- This “new” UDP-glucose (produced from the original UDP-galactose) can then participate in many biosynthetic reactions, as well as being used in the GALT reaction described above.

Role of UDP-galactose in biosynthetic reactions

UDP-galactose can serve as the donor of galactose units in a number of synthetic pathways, including synthesis of lactose, glycoproteins, glycolipids, and glycosaminoglycans.

If galactose is not provided by the diet (e.g., lactose-intolerance due to lack of β-galactosidase), all tissue requirements for UDP-galactose can be met by the action of UDP-hexose 4-epimerase on UDP-glucose, which is efficiently produced from glucose 1-phosphate.
Pathway of conversion of (A) galactose to glucose in the liver and (B) glucose to lactose in the lactating mammary gland.
Blood Glucose

Under normal condition, glucose is the only sugar present in blood. In man, glucose is equally distributed between red cells and plasma. It is freely diffusible into extracellular fluids.

**Sources and Fate of Blood Glucose**

![Diagram of glucose metabolism]

**Concentration of Blood Glucose:**

1. **Fasting blood glucose:** (FBG): FBG is measured after an overnight fast (at least 8-10 hours). Its normal value is 70-100 mg/dl (3.89-5.83 mmol/l).

2. **After a carbohydrate meal**, blood glucose reaches to 120-140 mg/dl within a period of half an hour to one hour.

3. The blood glucose then begins to decrease returning to **fasting level** after 2 hours.
Regulation and maintenance of Blood Glucose levels (BGL):

The BGL at any given time is determined by the balance between
1) The amount of glucose entering the blood stream
2) The amount leaving it.

Some tissues, such as brain and red blood cells, depend principally on glucose for energy. Most other tissues require glucose for synthetic reactions, e.g. ribose moiety of nucleotides or the carbohydrate portion of glycoproteins.

Therefore, to survive, humans must have mechanisms for maintaining BGL:

1) After a meal containing carbohydrates, blood glucose levels rise. Some of the glucose from the diet is stored in the liver as glycogen (5%) or is converted to fat (30-40%). The remainder is metabolized in muscle and other tissues e.g. for energy production.

2) After 2 or 3 hours of fasting, this glycogen begins to be degraded through glycogenolysis, and glucose is released into the blood.

3) As glycogen stores decrease, adipose triacylglycerols (fat) are also degraded, providing fatty acids as an alternative fuel and glycerol for the synthesis of glucose by gluconeogenesis. Amino acids are also released from muscle to serve as gluconeogenic precursor.

4) During an overnight fast, blood glucose levels are maintained by both glycogenolysis and gluconeogenesis. However after 18-30 hours fasting, liver glycogen stores are completely depleted and gluconeogenesis is the only source of blood glucose.

5) Blood glucose levels are maintained not only during fasting, but also during exercise when muscle cells take up glucose from the blood and oxidize it for energy. During exercise, the liver supplies glucose to the blood by the process of glycogenolysis and gluconeogenesis.

6) Muscle, although it stores glycogen, does not contribute glucose to the blood, because of the absence of glucose 6-phosphatase in muscle.

Thus, the liver plays an important role in the regulation of blood glucose, because it functions both in the removal of glucose from the blood, and in the addition of glucose to the blood.

The activity of the liver in maintaining normal blood glucose is influenced by various hormones:
Role of Hormones in the regulation of blood glucose:

I] **Insulin:** is the principal hormone affecting blood glucose levels, and an understanding of its actions is an important prerequisite to the study of diabetes mellitus. Insulin is a small protein synthesized in the beta cells of the islets of Langerhans of the pancreas. It acts through membrane receptors and its main target tissues are liver, muscle and adipose tissue.

The overall effect of insulin is to **promote cellular uptake** and storage of metabolic fuels.

1. Insulin *increases* the uptake of glucose in **muscle** and **adipose tissue**. In contrast, insulin has *no effect* on glucose uptake by **liver** cells. However, insulin activates the enzymes of **glycolysis** and **glycogenesis** in the liver.
2. It activates **hexokinase**.
3. Insulin stimulates **glycogenesis** and **lipogenesis** and inhibits **glycogenolysis**.

*Insulin*, therefore, promotes the **reduction of blood glucose** by increasing the rate of glucose utilization and decreasing the rate of delivery of glucose to the blood by the liver.

II] **Glucagon:** The hormone of the alpha cells of pancreas. Its secretion is stimulated by hypoglycemia. It *increases the blood glucose* through the following actions:

1. Glucagon accelerates **glycogenolysis** in the **liver** by activating phosphorylase. It has no effect on **muscle glycogen**.
2. Glucagon stimulates **gluconeogenesis** from amino acids and lactate.

III] **Epinephrine:** Is secreted by the adrenal medulla as a result of stressful stimuli (hypoglycemia, fear, excitement, hypoxia, etc) and leads to **glycogenolysis** in liver and muscle owing to stimulation of phosphorylase.

1. In muscle, the end product of glycogenolysis is lactate, because glucose 6-phosphatase is absent.
2. In liver, glucose is the main product of glycogenolysis, leading to increase in blood glucose.

IV] **Gluocorticoids:** (as cortisol and cortisone) are secreted by adrenal cortex.

They increase **gluconeogenesis**. This is a result of increased protein catabolism in tissues, increased **hepatic uptake of amino acids**, and increased activity of **transaminases** and other enzymes concerned with gluconeogenesis in the liver. Therefore, glucocorticoids are **antagonistic** to insulin.
The Renal Glucose Threshold (RGT):

When the blood sugar rises to high levels, the kidney exerts a regulatory effect.

a. Glucose is continuously filtered by the glomeruli, but it is normally completely reabsorbed in renal tubules by active transport and returned to the blood.
b. Since active transport is an energy dependent carrier mediated process, therefore, the capacity of the tubular system to reabsorb glucose (about 350 mg/min) is limited by its content of the responsible carrier protein.
c. When the BGL is elevated, the glomerular filtrate contains more glucose than the tubular capacity can handle, and it passes into the urine producing glucosuria.
d. In normal individuals, glucosuria occurs when the level of blood glucose exceeds 170-180 mg/dl. This is termed the Renal Threshold for glucose.

. Glucosuria may be produced in experimental animal with phlorhizin, which inhibits glucose reabsorption in the tubules. The presence of glucosuria is frequently an indication of diabetes mellitus.

Types of Glucosuria:

Normal urine contains practically no glucose. Glucosuria is the excretion of glucose in urine. There are different types of glycosuria:

A) Hyperglycemic glucosuria: This is due to an increase in blood glucose concentration above the renal threshold level i.e., 180 mg/dl.

Therefore anything which causes elevation of the blood glucose can cause glucosuria such as

1. Diabetes mellitus which is the most frequent cause of this type.
2. Increased secretion of epinephrine, during periods of excessive pain and emotional excitement (fear, anxiety, anger).
3. Alimentary glucosuria: when large amounts of carbohydrates are absorbed in the gastrointestinal tract more rapidly than can be assimilated. In this case the blood glucose rises above the renal threshold.

B) Renal glycosuria:

1. It is not associated with hyperglycemia and occurs even when blood glucose levels are normal. It is caused by defect in the renal tubules, which may be inherited and thus, it is known as "benign glucosuria" or "diabetes innocence".
2. Kidney diseases e.g., nephritis. In this case, the tubular capacity to reabsorb glucose is below the rate of glomerular filtration.
N.B. Diabetes Insipidus:
It characterized by severe polyuria (so wrongly diagnosed as DM). The volume of urine may reach 30 liter/day. This results from the deficiency of antidiuretic hormone (ADH) also known as arginine vasopressin (AVP) responsible for water reabsorption from renal tubules of kidney.
The urine is highly diluted and this accompanied by drinking of large amounts of water (polydipsia).